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Original Article

# Prevalence of hypoglycemia during oral glucose tolerance testing in adults with cystic fibrosis and risk of developing cystic fibrosis-related diabetes☆

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**Abstract**

*Background:* Hypoglycemia in cystic fibrosis (CF) patients during the oral glucose tolerance test (OGTT) has been reported; however, these patients have not been well-characterized. Few studies have examined whether hypoglycemia during the OGTT increases the risk of developing CF-related diabetes (CFRD). Objectives of this study were to describe the characteristics of CF patients with hypoglycemia during the OGTT and to determine the incidence and time to development of CFRD in those with hypoglycemia.
*Methods:* This cohort study included 466 adults with CF at the Toronto Adult CF Clinic between 1996 and 2015. Subjects were classified into two groups based on their plasma glucose (PG) level 2 h after a 75 g OGTT: hypoglycemia (PG ≤ 3.9 mmol/L) or no hypoglycemia (PG > 3.9 mmol/L). Clinical and demographic data were collected from the clinic visit closest to the OGTT. Differences between groups were assessed using Fisher's exact test or Mann-Whitney-Wilcoxon test.
*Results:* 138 patients (29.6%) experienced hypoglycemia during the OGTT. More males experienced hypoglycemia compared to no hypoglycemia (69.6% vs. 54.6% respectively; $p = 0.003$). Those who were heterozygous deltaF508 were more likely to experience hypoglycemia ($p = 0.006$). Subjects who experienced hypoglycemia were less likely to develop CFRD at ten years compared to no hypoglycemia (12.0% vs. 42.1%, respectively; $p < 0.001$).
*Conclusions:* Hypoglycemia following OGTT is common in CF however the 10 year risk of developing CFRD in these patients was low. Males and those who were heterozygous deltaF508 were at higher risk for hypoglycemia.


*Keywords:* Cystic fibrosis; Hypoglycemia; Diabetes mellitus; Glucose tolerance test

## 1. Introduction

Cystic fibrosis-related diabetes (CFRD) is one of the most important and common comorbidities in individuals with cystic fibrosis (CF), occurring in approximately 35% of adults [1]. The pathophysiology of CFRD is unclear; however, the disease is thought to be caused primarily by insulin insufficiency with a component of insulin resistance [2]. CFRD is associated with microvascular damage, decline in pulmonary function and nutritional status, and decreased survival [3–5].

Consensus guidelines recommend that individuals over the age of 10 years with CF should receive annual screening for CFRD with a 2-hour 75 g OGTT [6]. Although the OGTT is typically used to detect hyperglycemia, individuals can experience hypoglycemia following this glucose load. The

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prevalence of hypoglycemia in CF patients during the OGTT varies in the literature between 7 and 15%; however, the criteria used to define hypoglycemia differed across studies ranging from plasma glucose (PG) <2.8 mmol/L to <4.0 mmol/L [7–10]. The etiology of hypoglycemia in CF is unknown but may be caused by delayed first-phase insulin secretion together with a diminished glucagon response [11,12]. It has been hypothesized that hypoglycemia during the OGTT may denote dysregulation of insulin secretion and in fact, may represent a stage preceding the onset of CFRD. This hypothesis was not supported by Radike et al. where a hypoglycemic response to the OGTT was not associated with an increased risk of developing CFRD in the 3.5 year follow-up period [8]. It is possible that the negative results were due to the fact that the follow-up time was not long enough for CFRD to manifest itself.

Identifying individuals without autonomic or neurogenic symptoms of hypoglycemia with low PG values is clinically important because if left untreated, this can result in seizures, decreased level of consciousness, and even death [13]. The clinical characteristics of CF patients who experience hypoglycemia have not been well-defined and whether or not hypoglycemia during the OGTT increases the risk of developing CFRD in the future is controversial.

The objectives of this study were a) to describe the clinical characteristics of adult CF patients who experienced hypoglycemia during the OGTT over the past 20 years and b) to determine the incidence and time to development of CFRD in those with hypoglycemia.

## 2. Subjects and methods

This cohort study included all individuals followed at the Adult CF Clinic at St. Michael's Hospital in Toronto who had an OGTT between 1 January 1996 and 31 December 2015, inclusive. All subjects had previously been diagnosed with CF on the basis of sweat chloride testing, genotyping, or both. Demographic data as well as clinical information obtained at each clinic visit were obtained from the Toronto CF registry. Toronto CF registry data are collected prospectively in all individuals attending the CF clinic in Toronto. Informed consent was obtained from each subject for his or her information to be entered into the Toronto CF registry. The use of Toronto CF registry data for this project was approved by the Research Ethics Board at St Michael's Hospital. All ethical procedures followed were in accordance with the ethical standards of our institution.

### 2.1. Clinical characteristics of the study cohort

An OGTT is routinely carried out at times of clinical stability as per the Clinical Care Guidelines for CFRD [6]. We compared the clinical characteristics of individuals who experienced an episode of hypoglycemia and those who did not. The appropriate cut-off for hypoglycemia in non-diabetic patients is controversial [14,15]. We chose to define individuals as having hypoglycemia in the study period if they ever had a PG level at the two-hour time point during a 75 gram OGTT that was ≤3.9 mmol/L which has been used in the literature [10,16]. Subjects were classified into two groups: (i) those with hypoglycemia and (ii) individuals who never had an episode of hypoglycemia during OGTT testing, who are referred to as "no hypoglycemia". OGTTs were excluded if they occurred during pregnancy or post-transplant.

Height, weight, and forced expiratory volume in 1 s ($FEV_1$) were taken on the closest date within 1 year prior to the OGTT. BMI was classified on the basis of WHO guidelines [17]: underweight (<18.5 kg/m$^2$), normal weight (18.5–24.9 kg/m$^2$), overweight (25.0–29.9 kg/m$^2$), or obese (≥30 kg/m$^2$). $FEV_1$ was expressed as a percentage of the normal predicted values using the Hankinson equations [18]. $FEV_1$ was classified as "normal" (≥90%), "mild" (70–89%), "moderate" (40–69%), and "severe" (<40%). The number of hospital admissions was considered over the calendar year of the OGTT. Pancreatic status was determined by any of the following: pancreatic enzyme usage, 3 day fecal fat measurements, serum trypsinogen, or clinical evidence of steatorrhea. CFRD was defined as persistently elevated blood sugars and/or a positive OGTT diagnostic for CFRD on the basis of the Clinical Care Guidelines for CFRD [6]. Any OGTTs that resulted in a diagnosis of CFRD or that occurred after a diagnosis of CFRD was made were excluded. Patients are recorded as having liver disease within the Toronto CF registry if they have evidence of cirrhosis or portal hypertension on imaging. Genotype was classified as homozygous for deltaF508, heterozygous for deltaF508, other, or missing.

For those individuals who had positive sputum culture results for multiple organisms in a given year, we categorized patients based on the organism that had the worst prognosis in terms of survival. This categorization allowed us to create mutually exclusive groups to avoid combining less virulent organisms with ones associated with a worse prognosis. Patients with multiple types of bacteria cultured in a given year were categorized as follows: *Burkholderia cepacia* complex (BCC) took precedence over any other type of infection, *Pseudomonas aeruginosa* took precedence over all remaining organisms. Subjects were classified as BCC positive if they had ever provided sputum samples containing BCC prior to the OGTT and *P. aeruginosa* positive if they had ever provided a sputum sample containing *P. aeruginosa* and no evidence of BCC.

### 2.2. Statistical analysis

Subjects had multiple OGTTs over the study period. If there were multiple episodes of hypoglycemia, the first episode was used for the study. For the no hypoglycemia group, all OGTTs were assigned a random number and we randomly selected an OGTT to summarize the clinical characteristics of this population.

Categorical variables are summarized as frequency and percent. Continuous variables are summarized as median and range. The Fisher's exact test was used to examine whether there were significant associations between demographic and clinical categorical variables and hypoglycemia, and the Mann-Whitney-Wilcoxon test was used for continuous variables. Variables that showed borderline association with hypoglycemia (with a

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