Predictive Value of 1-Hour Glucose Elevations during Oral Glucose Tolerance Testing for Cystic Fibrosis-Related Diabetes

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Introduction

- Outcomes for cystic fibrosis (CF) have improved in recent years, illustrated by an increased median predicted survival.
- With increased longevity, the prevalence of cystic fibrosis-related diabetes (CFRD) and diabetes-related complications are expected to increase.
- Current CFRD screening cut-offs are based on the oral glucose tolerance test (OGTT) 2-hour glucose (2hG) in people with CF (PwCF) and are the same as for other types of diabetes.
- Elevations in 1-hour glucose (1hG) have been described to represent early glucose intolerance, but studies on the predictive value of 1hG are limited.

Methods

- Single CF center, retrospective study
- Data collected via chart review from patients seen between 2/2010 - 6/2019
- Inclusion Criteria:
  - absence of CFRD at first OGTT,
  - at least one OGTT between 2/2010 and 6/ 2019, and
  - a baseline OGTT in this time frame that included the 1hG
- Data collected:
  - Age, sex, CF genotype
  - Hemoglobin A1c and OGTT results
  - Body mass index (BMI) %tile
  - Pulmonary function testing (PFT)
- Statistical Analysis – 2 cohorts:
  - Group 1 cross-sectional cohort with all participants
    - Mixed effect models: whether baseline glucose predicts trajectories of BMI %ile and PFTs
  - Group 2 longitudinal cohort with participants with ≥2 OGTTs
    - Kaplan Meier: likelihood of progression to CFRD
    - Cox proportional hazard models: whether baseline glucose predicts time to development of CFRD

Results

Table 1. Demographics and baseline variables

	Cross-sectional Cohort	Longitudinal Cohort
	n=243	n=177
Male, n (%)	120 (49%)	94 (53%)
Race		
Caucasian, n (%)	194 (80%)	142 (80%)
Age (years)	12.7 ± 3.0	12.4 ± 2.6
Fasting OGTT (mg/dL)	89 ± 8	89 ± 8
1-hour glucose (mg/dL)	163 ± 45	162 ± 45
2-hour glucose (mg/dL)	117 ± 33	116 ± 33
BMI %ile	18.8 ± 3.0	19.0 ± 3.1
HbA1c (%)	5.5 ± 0.4	5.5 ± 0.4
Genotype, n (%)		
2 Minimal function mutations	213 (88%)	159 (90%)
ppFEV1	91.6 ± 16.9	90.7 ± 15.7
ppFVC	99.1 ± 15.0	98.3 ± 13.7
FEV1/FVC	0.9 ± 0.1	0.9 ± 0.1
CFTR Modulator Use Baseline, n (%)		
Yes	42 (17%)	21 (12%)
Started Modulator During F/U, n (%)		
Yes	90 (37%)	79 (45%)

Note: Data presented as n (%) or mean±SD as indicated.

Abbreviations: BMI body mass index, CFTR cystic fibrosis transmembrane conductance regulator, F/U follow-up, OGTT oral glucose tolerance test, ppFEV1 percent predicted forced expiratory volume in the first second, ppFVC percent predicted forced vital capacity

Cross-sectional Cohort:

- Mean duration of follow-up:
  - 3.2 years ± 1.4 years
- Mixed-effect models:
  - Baseline 1hG not predictive of trajectories of BMI %ile nor PFTs ($p > 0.05$)
  - Baseline 2 hG predicted decline in ppFEV1 ($p = 0.01$), ppFVC ($p = 0.03$), as well as FEF 25–75% ($p = 0.001$).

Longitudinal Cohort:

- Mean duration of follow-up:
  - 3.2 years (range 0.6 – 7.3 years)
- Over the study period:
  - 28 participants (16%) developed CFRD
- Cox proportional hazard models:
  - Hazard ratio (HR) for development of CFRD of **1.1 (95% CI 1.01, 1.2)** for every 10 mg/dL increase in baseline 1hG
  - HR of **1.08 (95% CI 0.97, 1.21)** for every 10 mg/dL increase in baseline 2hG

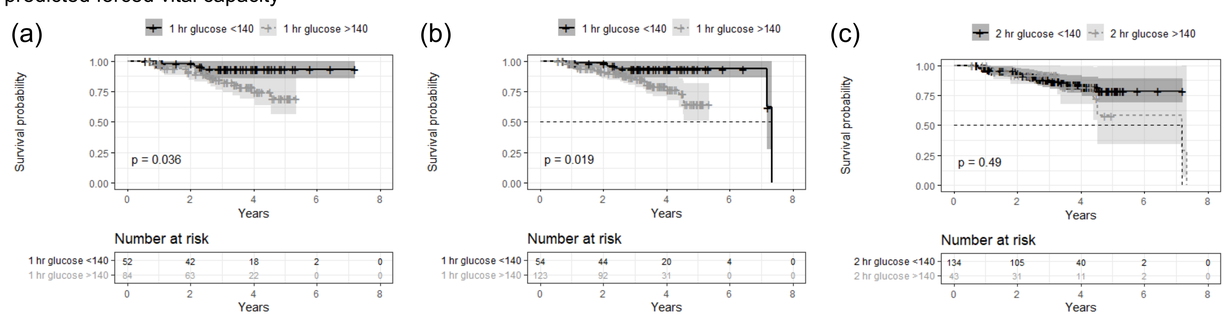

Figure 1: Kaplan–Meier survival curves comparing baseline glucose and the likelihood of developing diabetes between (a) patients with elevated 1 hG (≥140 mg/dL) with normal glucose tolerance (2 hG < 140 mg/dL) to low 1 hG (<140 mg/dL) with normal glucose tolerance, (b) patients with elevated 1 hG (≥140 mg/dL) including those with impaired glucose tolerance (2 hG ≥ 140 mg/dL) to low 1 hG (<140 mg/dL) including those with impaired glucose tolerance, and (c) patients with elevated 2 hG (≥140 mg/dL) to low 2 hG (<140 mg/dL), regardless of 1 hG concentrations.

Discussion

- Findings highlight the unique strengths of 1hG and 2hG for clinical decision-making:
  - 1hG appears to be useful for predicting future CFRD risk and identifying individuals at high vs. low risk for developing diabetes, and
  - 2hG better predicted clinical declines.
- Despite the clinical value of the OGTT, annual CFRD screening remains a significant challenge for many patients and CF centers:
  - A more feasible screening approach supported by our findings, would be to use the 1 hG to identify individuals at low risk for CFRD who might benefit from reduced screening frequency (for example, every 3-5 years instead of annually).
- Our data were examined prior to the widespread adoption of the latest triple combination CFTR modulator:
  - Long-term impacts of modulator therapy on CFRD progression are unknown.
  - Prospective, multicenter studies in this new era are needed.

References

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