screening on clinical outcomes by center: A CF patient registry study. *J Cyst Fibros* 2020;19(2):316–20.

4

Role of hyperglycemia in cystic fibrosis pulmonary exacerbations

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Background: Hyperglycemia could affect treatment response during cystic fibrosis (CF) pulmonary exacerbations (PEx). We aimed to evaluate hyperglycemia prevalence during CF PEx, associations between hyperglycemia and PEx outcomes, and feasibility of continuous glucose monitoring (CGM) during PEx.
Methods: This was an ancillary study to the STOP2 study—a multicenter randomized clinical trial evaluating the efficacy and safety of different durations of intravenous (IV) antibiotics for PEx in adults with CF [1]. Random glucose levels measured clinically during the first 7 to 10 days of PEx treatment were captured. A subset of participants at four sites also consented to undergo CGM for 5 days, beginning at IV antibiotic day 1 to 4. Associations between hyperglycemia, defined as random glucose greater than140 mg/dL, and changes in weight and lung function between baseline (initiation of IV treatment), visit 2 (day 7–10), and visit 3 (14 days after completion of IV treatment) were evaluated using linear regression after adjustment for confounders.
Results: Random glucose measurements were available for 182 STOP2 participants (18.6% of 982 randomized in STOP2). Of these participants, 37% had CF-related diabetes (CFRD), 27% were taking insulin, mean ± SD age was 31.6 ± 10.8 years, and mean ± SD baseline percentage predicted forced expiratory volume in 1 second (FEV1pp) was 53.6 ± 22.5. Hyperglycemia was detected in 44% of these participants, and 61% of those with hyperglycemia had a diagnosis of CFRD. Table 1 shows the mean estimated differences in changes in FEV1pp and weight from baseline to visit 2 and visit 3 between those with and without hyperglycemia and taking and not taking insulin. No differences were detected according to hyperglycemia or insulin use at visit 2 or visit 3. Ten participants who were not taking insulin or oral hypoglycemic agents in the 4 weeks before study underwent CGM. Mean ± SD age was 30.1 ± 6.5 years, 70% were female, and mean ± SD baseline FEV1pp was 48.9 ± 21.0 L. Mean time at greater than 140 mg/dL was 24.6 ± 12.5%, and 9/10 participants spent more than 4.5% of the time at more than 140 mg/dL.
Conclusions: Hyperglycemia identified using random glucose testing was prevalent during CF PEx in patients with and without CFRD, but we did not detect an association between hyperglycemia and changes in lung function or weight with treatment. CGM is feasible and may be a useful tool in the inpatient setting.
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Reference

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5

Comparison of meal-time dosing of rapid-acting insulin using carbohydrate counting versus fixed doses using continuous glucose monitoring in patients with cystic fibrosis–related diabetes

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Background: Optimizing prandial bolus insulin dosing is essential for cystic fibrosis (CF)-related diabetes (CFRD) management but the traditionally high-calorie diet prescribed to maintain ideal body mass index and the demands of close glucose monitoring make this difficult. This study leveraged continuous glucose monitoring (CGM) to compare fixed meal dosing with carbohydrate count–based insulin dosing.
Methods: People with CFRD treated with meal-time rapid-acting insulin were recruited. A dietician provided carbohydrate counting education, and insulin carbohydrate ratio was determined according to total daily insulin dose at the study start. Abbott Freestyle Flash Libre continuous glucose monitors were worn for 14 days. Participants used fixed mealtime insulin dosing for the first 7 days (fixed dosing week, FDW) and carbohydrate counting–based insulin dosing for the second 7 days (carbohydrate count week, CCW) using the 'rule of 500' to calculate insulin-to-carbohydrate ratio. We also compared the frequency and duration of hypo- and hyperglycemia of the two insulin delivery methods.
Results: Six (3 female, 3 male; aged 65 ± 7.7; 2 F508del homozygous, 2 F508del heterozygous, 2 with unknown mutation status) of the nine recruited participants had complete data (3 dropped out or had CGM malfunction). All subjects were on triple modulator therapy for at least 12 months. Average CFRD duration was 8.6 ± 2.9 years, glycosylated hemoglobin was 7.3 ± 0.5%, and weight was 55 ± 5.4 kg. Insulin to carbohydrate ratio ranged from 1:10 grams to 1:17 grams Average sensor glucose was not significantly different between FDW (7.27 ± 0.83 mmol/L) and CCW (7.04 ± 0.88 mmol/L) ($p = 0.8$). There were no differences in time in range (CCW, 984 ± 86 minutes; FDW, 919 ± 110 minutes; $p = 0.6$) or number of low-glucose events (FDW, 11; CCW, 9; $p = 0.6$).
Conclusions: Few studies have compared the efficacy of carbohydrate counting for dosing mealtime insulin with that of fixed pre-meal insulin doses. Larger studies that use CGM to optimize insulin to carbohydrate-

Table 1. (abstract 4):
Mean estimated difference (95% confidence interval) in changes in lung function and weight from baseline to visit 2 and visit 3 according to hyperglycemia and insulin use

	Change in ppFEV1 at visit 2	P value	Change in ppFEV1 at visit 3	P value	Change in weight at visit 2	P value	Change in weight at visit 3	P value
Hyperglycemia vs. no hyperglycemia	1.34 (-1.39, 4.08)	0.37	-1.15 (-4.01, 1.71)	0.43	0.33 (-0.11, 0.78)	0.15	0.34 (-0.31, 0.99)	0.31
On insulin vs. no insulin	0.41 (-2.33, 3.14)	0.77	-1.71 (-4.36, 0.94)	0.2	0.27 (-0.21, 0.75)	0.27	0.05 (-0.70-0.80)	0.89

based dosing are needed to compare the glycemic benefit of this approach with the additional patient burden of carbohydrate counting.

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6

Decline in HbA1c during the first year on elexacaftor/tezacaftor/ivacaftor in the Danish cystic fibrosis population

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Background: In cystic fibrosis (CF), elexacaftor/tezacaftor/ivacaftor has a remarkable effect on lung function, but whether it affects glucose tolerance, including CF-related diabetes (CFRD) is not clear. We aimed to study both the effect of elexacaftor/tezacaftor/ivacaftor (ELX/TEZ/IVA) on glycosylated hemoglobin (HbA1c) in the Danish national CF population and changes in use of insulin in a CFRD subpopulation during the first year of treatment.

Methods: The entire Danish CF population is followed in either of two CF centers that measure HbA1c at baseline and 3, 6, 9 and 12 months after initiation of ELX/TEZ/IVA. All treated individuals aged 12 and older with a baseline sample and one or more follow-up samples were included in the study. During consultations with individuals with CFRD before and 12 months after initiation of treatment, information was obtain on use of insulin, hypoglycemic events, and if available, continuous glucose monitoring (CGM) from the past 30 days. Change in HbA1c 3 and 9 months after treatment initiation was assessed according to age group (12–25, 26–35, 36–45, 46–80), sex, glucose tolerance status (normal: <7.8 mM, impaired: 7.8–11.0 mM, CFRD: >11.0 mM 2-hour glucose), and previous modulator treatment (naïve, first-generation modulator) in mixed models using splines. The models included interaction between the concerned covariate and treatment time and were adjusted for the above-mentioned covariates. Changes in use of insulin and CGM parameters (covariance, average blood glucose, time below (<3.9 mM) and above (>10.0 mM) normal range) were assessed in paired Wilcoxon signed-rank tests.

Results: For 298 individuals with CF, average HbA1c was 43.3 mmol/mol at baseline, 1.9 mmol/mol (95% CI, −1.3 to −2.4 mmol/mol, $p < 0.001$) lower after 3 months of treatment, and 2.7 mmol/mol (95% CI, −2.2 to −3.1 mmol/mol, $p < 0.001$) lower after 9 months of treatment. In all age, sex, glucose tolerance, and previous treatment groups HbA1c had declined significantly after 3 months and even more after 9 months. The youngest individuals seemed to have the smallest decline in HbA1c (12–25 years: −1.8 mmol/mol, 95% CI, −0.7 to −3.0 mmol/mol, $p < 0.001$), whereas the decline was more pronounced in individuals aged 36 to 45 (−3.4 mmol/mol, 95% CI, −1.6 to −5.2 mmol/mol, $p < 0.001$) after 9 months. The decline was independent of glucose tolerance status (normal: −2.4 mmol/mol, 95% CI, −1.3 to −3.5 mmol/mol, $p < 0.001$; CFRD: −2.8 mmol/mol, 95% CI, −1.8 to −3.8 mmol/mol, $p < 0.001$) (Figure 1). In 26 individuals with CFRD, HbA1c declined, but we did not see a significant change in insulin use after 12 months (long-acting insulin: −2.0 international units (IE)/day, 95% CI, −5.0 to 3.5 IE/day, $p = 0.21$; short-acting insulin: −4.3 IE/day, 95% CI, −12.0 to 0.0 IE/day, $p = 0.05$). Neither the weekly number of hypoglycemic events (0.2, 95% CI, −3.2 to 1.8, $p = 0.81$) nor the CGM parameters (covariance, average blood glucose, time above and below range) changed.

Conclusions: In the Danish CF population, HbA1c continued to decline over 9 months of ELX/TEZ/IVA treatment regardless of age and diabetes status. In 26 individuals with CFRD, we were unable to detect a significant change in CFRD treatment or regulation. We speculate that factors other than insulin secretion (e.g., reduced inflammation, more physical activity) might contribute to the reduction HbA1c.

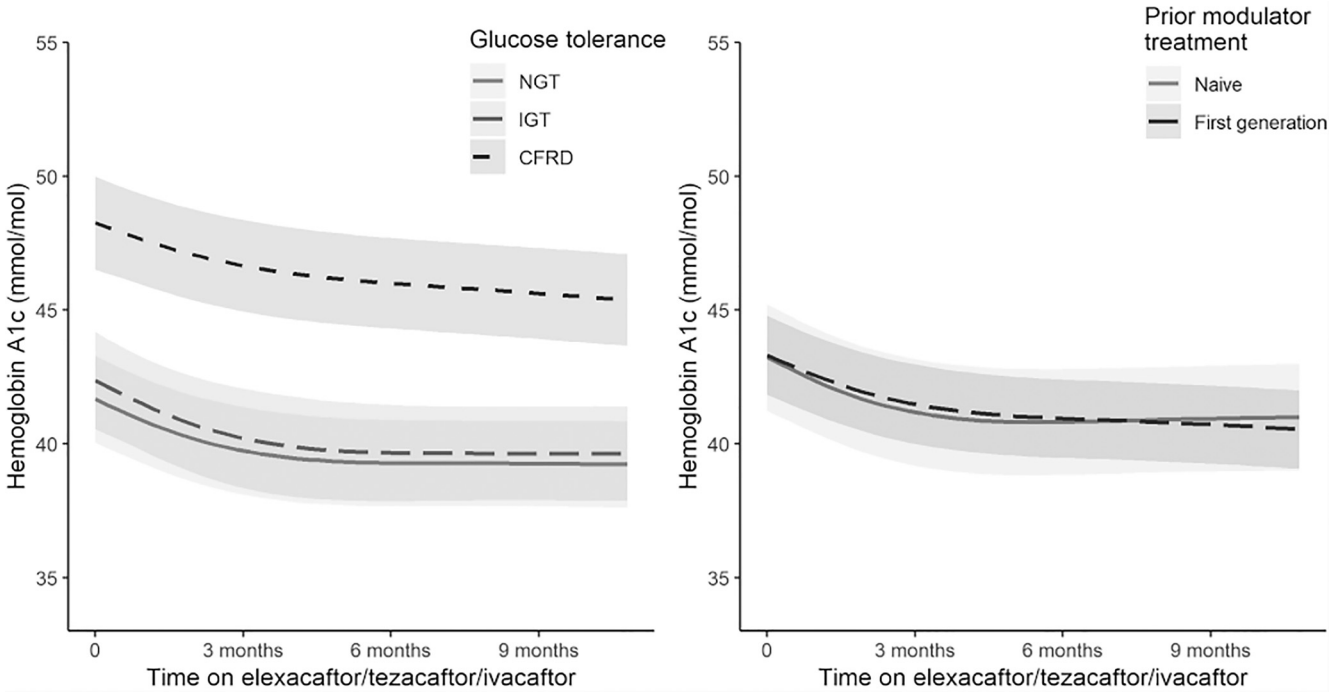

Figure 1 (abstract 6): Change in HbA1c according to glucose tolerance status and prior modulator treatment after initiation of ELX/TEZ/IVA treatment in 298 individuals with CF. Data were analyzed in mixed models with three knot splines. Covariates were fitted in interaction with treatment time and adjusted for age group, sex, glucose tolerance, and prior modulator treatment. NGT, normal glucose tolerance; IGT, impaired glucose tolerance; CFRD, cystic fibrosis–related diabetes; first generation, ivacaftor monotherapy, lumacaftor/ivacaftor, or tezacaftor/ivacaftor.