14

Preservation of body composition in adolescents and young adults with cystic fibrosis

S. Sheikh[1], R. Gallop[2], B. Zemel[3], R. Rubenstein[4], A. Kelly[5]. *[1]Division of Pulmonary Medicine, Department of Pediatrics, Children's Hospital of Philadelphia, Philadelphia, PA; [2]Department of Biostatistics, University of Pennsylvania, School of Medicine, Philadelphia, PA; [3]Division of Gastroenterology, Hepatology and Nutrition, Department of Pediatrics, Children's Hospital of Philadelphia, Philadelphia, PA; [4]Division of Allergy and Pulmonary Medicine, Department of Pediatrics, Washington University School of Medicine, St. Louis, MO; [5]Division of Endocrinology and Diabetes, Department of Pediatrics, Children's Hospital of Philadelphia, Philadelphia, PA*

Background: In people with cystic fibrosis (PwCF), pulmonary function has traditionally been positively correlated with body mass index (BMI) and negatively associated with a diagnosis of diabetes. The literature indicates that lean body mass (LBM) mediates the association between BMI and percentage predicted forced expiratory volume in 1 second (FEV_1pp). We hypothesized that adolescents and young adults with CF have deficits in LBM accrual that are worse with glucose intolerance.

Methods: Body composition was measured using whole-body dual-energy X-ray absorptiometry in PwCF without diabetes and sex-, age- and BMI-matched healthy controls (HCs) who participated annually in three study visits between May 2016 and January 2022. A 75-gram oral glucose tolerance test (OGTT) was performed in PwCF. LBM, appendicular LBM, and fat mass indices (LBMI = LBM/height^2, ALBMI = appendicular LBM/height^2, FMI = FM/height^2) were calculated. Mixed-effects models were used to estimate accrual of body composition indices in groups adjusted for sex and age and using an interaction term for group and time. The association between body composition indices and OGTT glucose were also tested using mixed-effects models, again adjusted for sex and age.

Results: Twenty-six PwCF (median age 19.8, range 16.5–23.2; 14 male; 20 pancreatic insufficient; median FEV_1pp 98% (71–130%); BMI 25.1 kg/m^2, range 18.0–34.3 kg/m^2) and 24 HCs (median age 20.8, range 16.6–23.1; 12 male; BMI 24.1 kg/m^2, range 19.9–33.8 kg/m^2) were followed for 25.5 (0–40.2) and 24.1 months (0–39.7), respectively. Follow-up data were available for 24 PwCF and 18 HCs. At baseline, fasting blood glucose (FBG) was 91 mg/dL (80–112 mg/dL), OGTT 1-hour glucose was 175 mg/dL (97–329 mg/dL), and OGTT 2-hour glucose 107 mg/dL (36–162 mg/dL). Glucose tolerance worsened for seven PwCF, two of whom developed CFRD, were

Table 1 (abstract 14):
Subject characteristics at baseline

Subject characteristics at baseline	HC (N=24)		CF (N=26)	
	MALES (N=12)	FEMALES (N=12)	MALES (N=14)	FEMALES (N=12)
Study participation, months	24 (0-36)	18 (0-40)	35 (0-39)	26 (14-40)
Age, years	21.3 (16.6-23.1)	18.4 (16.8-22.1)	20.8 (16.6-23.2)	18.4 (16.6-22.7)
Height, meters	1.78 (1.63-1.87)	1.60 (1.56-1.78)	1.75 (1.63-1.85)	1.61 (1.49-1.69)
Weight, kg	85.6 (51.4-103.3)	64.4 (51.8-78.8)	72 (58.2-107.5)	62.1 (50.6-72.8)
BMI, kg/m²	25.6 (18.0-34.3)	24.9 (20.5-27.7)	23.7 (19.9-33.8)	24.9 (20.2-28.4)
LBMI, kg/m²	18.1 (13.7-24.2)	14.3 (12.6-18.2)	17.2 (15.5-23.7)	14.9 (13.7-16.9)
Appendicular LBMI, kg/m²	8.2 (5.9-11.5)	5.8 (5.3-7.8)	7.5 (6.3-10.3)	5.9 (5.4-7.4)
FMI, kg/m²	5.7 (3.3-9.3)	8.8 (5.7-12.8)	5.0 (3.3-9.6)	8.1 (6.0-12.3)
FBG, mg/dL	-	-	91 (80-112)	92 (80-104)
OGTT 1-hr glucose, mg/dL	-	-	171 (118-234)	178 (97-329)
OGTT 2-hr glucose, mg/dL	-	-	125 (36-162)	107 (70-137)
FEV1%-predicted	-	-	91 (71-120)	110 (73-129)

Data are median (range)

initiated on insulin therapy, and then censored from analyses. Fifteen PwCF were treated with a CF transmembrane conductance regulator modulator during the study (4 on elexacaftor/tezacaftor/ivacaftor). At baseline, LBMI (15.8 kg/m^2, range 13.7–23.7 kg/m^2 vs 15.5 kg/m^2, range 12.6–24.2 kg/m^2; $p = 0.7$), ALBMI (6.9 kg/m^2, range 5.4–10.3 kg/m^2 vs 6.8 kg/m^2, range 5.3–11.5 kg/m^2; $p = 0.7$), and FMI (6.4 kg/m^2, range 3.1–12.3 kg/m^2 vs 7.5 kg/m^2, range 3.2–12.8 kg/m^2; $p = 0.5$) did not differ between PwCF and HCs. Over the study period, LBMI ($p = 0.8$), ALBMI ($p = 0.2$), and FMI ($p = 0.1$) did not change in the study population. LBMI accrual, adjusted for sex and baseline age, was similar for PwCF and HCs ($p = 0.6$), as was ALMBI accrual ($p = 0.5$). Similarly, no group differences in FMI accrual were found ($p = 0.3$). Further adjustment for BMI did not result in group differences in indices. In male and female PwCF, LBMI over time was not associated with increasing FBG ($p = 0.8$), OGTT 1-hour glucose ($p = 0.9$), or OGTT 2-hour glucose ($p = 0.9$). ALBMI and FMI accrual were not associated with FBG or OGTT 1- or 2-hour glucose, either ($P > 0.1$ for all). Use of a CFTR modulator was not associated with changes in LBMI, ALBMI, or FMI in PwCF ($P > 0.1$ for all).

Conclusions: Over a 2-year period, body composition in PwCF remained stable and was comparable with body composition of individuals without CF. This small CF cohort also demonstrated a lack of association between body composition and early glucose intolerance or CFTR modulator therapy. With overall advances in CF care and better lung function and nutritional status, a subgroup of PwCF may be less vulnerable to the traditional nutritional decline with glucose intolerance and may experience no additional gain in LBM with CFTR modulator use.

Acknowledgements: This work was supported by Public Health Service research grants National Institute of Diabetes and Digestive and Kidney Diseases K23 DK107937 (to S.S.) and UL1 TR001878 (University of Pennsylvania Centers for Human Phenomic Science).

15

Promise: Glucose excursion and insulin secretion after 12 to 18 months of highly effective modulator therapy

M. Stalvey[1], R. Walega[2], S. Rowe[3], D. Nichols[4,5], D. Stefanovski[6], A. Kelly[2,7]. *[1]Pediatrics, University of Alabama at Birmingham, Birmingham, AL; [2]Division of Endocrinology and Diabetes Children's Hospital of Philadelphia, Philadelphia, PA; [3]University of Alabama at Birmingham, Birmingham, AL; [4]Division of Pulmonary and Sleep Medicine, Department of Pediatrics, Seattle Children's Hospital, University of Washington, Seattle, WA; [5]Cystic Fibrosis Foundation Therapeutics Development Network Coordinating Center, Seattle Children's Research Institute, Seattle, WA; [6]New Bolton Center, School of Veterinary Medicine, University of Pennsylvania, Kennett Square, PA; [7]Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA*

Background: Clinical observations, case series, and registry data revealed greater glucose tolerance, better insulin secretion, and fewer cystic fibrosis (CF)-related diabetes (CFRD) diagnoses with ivacaftor. Inspired by these data, this study was designed to test the effect of clinically prescribed elexacaftor/tezacaftor/ivacaftor (ELX/TEZ/IVA) on glucose intolerance and insulin secretion and sensitivity.

Methods: Three-hour 10-sample oral glucose tolerance tests (OGTTs) were performed at baseline and 12 to 18 months at 10 designated endocrine substudy centers of *pROMISE,* a 56-center prospective, observational study of ELX/TEZ/IVA in people with CF aged 12 and older with at least one *F508del* mutation. Rapid-acting insulin was withheld for the subset treated with insulin. Glucose tolerance (GT) was defined as: normal (NGT), early glucose intolerance (EGI; 60 minutes at ≥155 mg/dL then 120 minutes at <140 mg/dL), impaired glucose tolerance (IGT; 120 minutes at ≥140 mg/dL then <200 mg/dL, CFRD (120 minutes at ≥200 mg/dL), and hypoglycemia (≤65 mg/dL). Incremental area under the curve ($iAUC_{30}$) for glucose tolerance, glycosylated hemoglobin (HbA1C), OGTT glucose (0, 60, 120 minutes), insulin sensitivity, and 0- to 30-minute glucose and insulin secretory rates (ISRs) were compared at baseline and follow-up using mixed-effects ordinal or linear models (fixed effect: visit; random effect: subject) and to further test for relationships with age, body mass index (BMI) Z-score, and percentage predicted forced expiratory volume in 1 second (FEV_1pp).

Table 1 (abstract 15):
Baseline and 12- to 18-month demographic, glucose, and insulin data

N=65; 32M/33F	Baseline Mean (95% CI)	12-18 mo post-ETI Mean (95% CI)	p-value
BMI-Z	0.02 (-0.22-*0.26)	0.27 (0.05-0.49)	<0.001
FEV1%-predicted	82.9 (77.4-88.5)	95.7 (90.5-100.9)	<0.001
HbA1C, %	5.83 (5.64-6.01)	5.53 (5.39-5.68)	<0.001
No insulin treatment (n=53)	5.57 (5.48-5.67)	5.33 (5.24-5.42)	<0.001
NGT/EGI/IGT/CFRD	8/22/23/12	8/29/17/11	0.22
Hypoglycemia *(5 had abbreviated OGTT)*	15/60	23/60	0.059
Fasting glucose, mg/dL *No basal insulin treatment (n=58)*	94 (92-96)	91 (89-93)	0.019
60-min glucose, mg/dL	200 (189-211)	201 (188-214)	0.82
120-min glucose, mg/dL	158 (141-175)	150 (132-167)	0.17
$iAUC_{30}$Glucose, (mg/dL)/min (n=51)	942 (855-1029)	957 (842-1071)	0.46
$iAUC_{30}$ISR, (pmol/L)/min (n=51)	2164 (1873-2454)	2269 (1965-2572)	0.38
$iAUC_{30}$ISR : $iAUC_{30}$Glucose, mU/mg (n=51)	0.043 (0.036-0.05)	0.045 (0.038-0.052)	0.63
SI (μU/mL)/min	8.48 (6.36-10.6)	7.37 (6.11-8.66)	0.37