Cystic Fibrosis–Related Diabetes

Objectives

- Review the epidemiology of glucose abnormalities in cystic fibrosis (CF)
- Understand the associations of glucose intolerance and insulin secretion abnormalities with outcomes in CF
- Review clinical guidelines for screening and treatment of CF-related diabetes (CFRD)
- Summarize methods of evaluating glycemic status
- Review basic aspects of insulin secretion and glucose regulation, and abnormalities that occur in patients with CF
- Explore the potential mechanisms underlying CFRD development and its role in worse CF outcomes

VERTEX

CFRD Is Common and Distinct From Type 1 and Type 2 Diabetes

CFRD Differs from Type 1 and Type 2 Diabetes

- Despite some shared features with type 1 and 2 diabetes, CFRD is a distinct clinical entity

Parameter	CFRD	Type 1 Diabetes	Type 2 Diabetes
Prevalence in population	35% of CF	0.2%	11%
Peak age of onset	20 to 24 years	Childhood, adolescence	Mid to late adulthood
Usual body weight	Normal to underweight	Normal	Obese
Insulin deficiency	Severe but not complete	Complete	Partial, variable
Insulin resistance	Modest, fluctuates with infection	Modest	Severe
A1C	Unpredictable relation to mean blood glucose	Related to mean blood glucose	Related to mean blood glucose
Microvascular complications	Yes	Yes	Yes
Cause of death	Lung disease	Cardiovascular	Cardiovascular

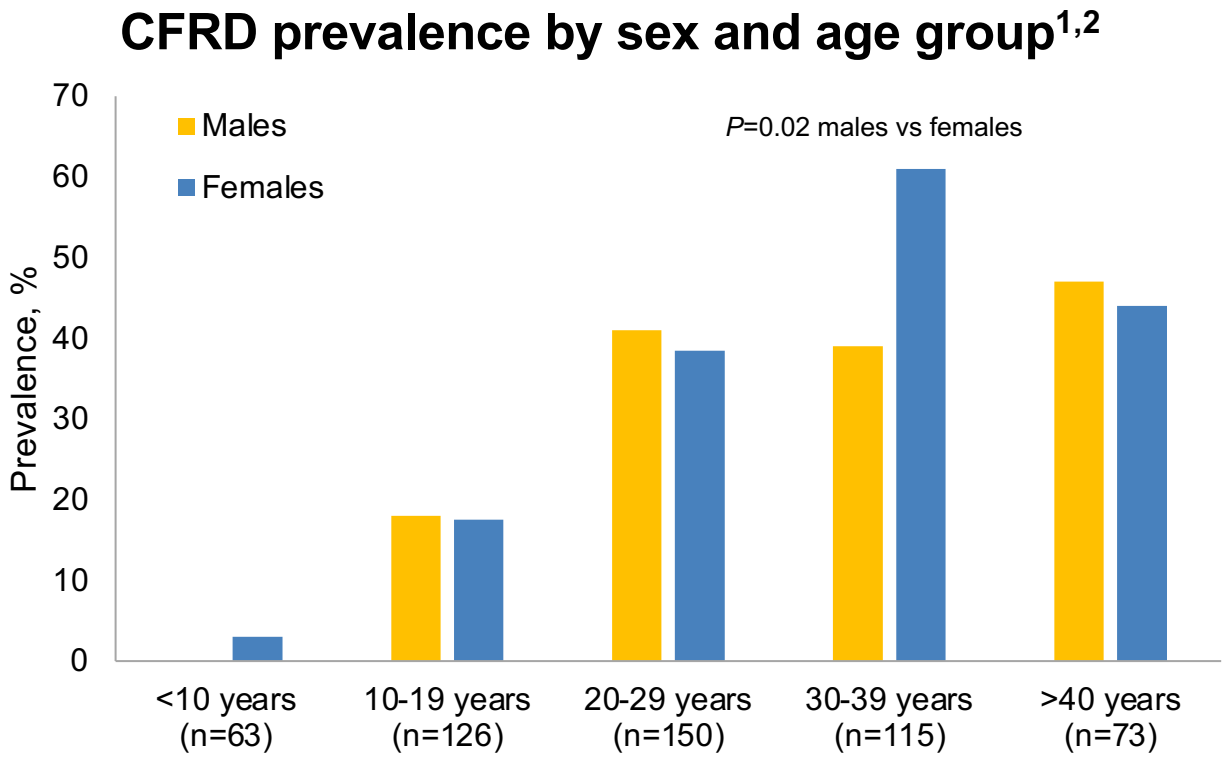
Moran A et al. *Diabetes Care*. 2010;33(12):2677-2683.

Definition of CFRD by OGTT

OGTT: Screening and Diagnostic Criteria for CFRD	2-h PG mg/dL (mmol/L)	1-h PG mg/dL (mmol/L)
NGT	<140 (<7.8)	<200 (<11.1)
IGT	140-199 (7.8-11)	
CFRD	≥200 (≥11.1)	
INDET	<140 (<7.8)	≥200 (≥11.1)

IGT, impaired glucose tolerance; INDET, indeterminate glucose tolerance; NGT, normal glucose tolerance; OGTT, oral glucose tolerance test; PG, plasma glucose.
Kelly A, Moran A. *J Cyst Fibros.* 2013;12(4):318-331.

Prevalence of CFRD Increases With Age

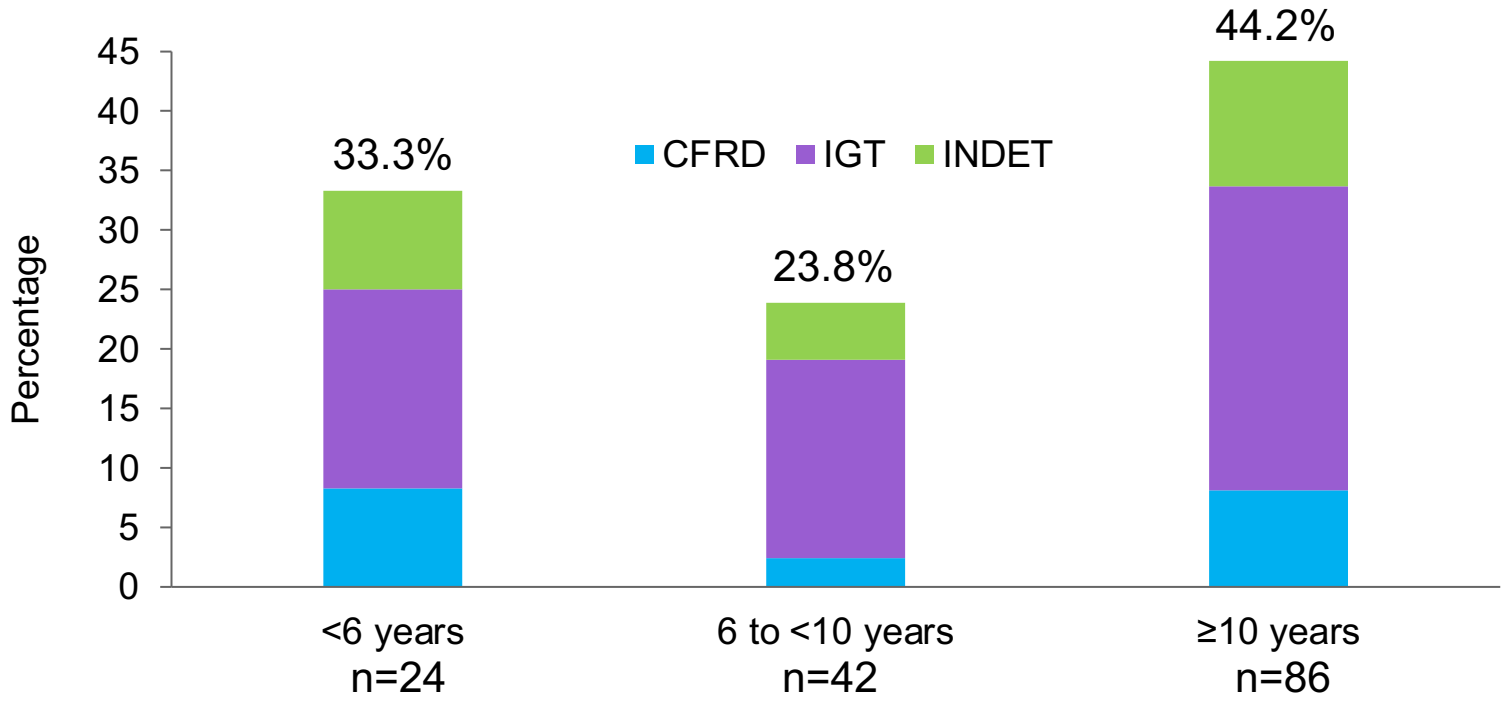


- CFRD prevalence in adolescents with CF: ~15%[2]
- Diabetes (type 1 or 2) prevalence in people aged <20 years without CF: ~0.25%[3,4]

1. Moran A et al. *Diabetes Care*. 2009;32(9):1626-1631. 2. Ode KL, Moran A. *Lancet Diabetes Endocrinol.* 2013;1(1):52-58. 3. Centers for Disease Control and Prevention. National Diabetes Statistics Report, 2014 https://www.cdc.gov/diabetes/pdfs/data/statistics/national-diabetes-statistics-report.pdf. Accessed April 2020. 4. Wild S et al. *Diabetes Care*. 2004;27(5):1047-1053.

Glucose Abnormalities May Occur Early in CF

Prevalence of glucose derangements in children with CF according to age group[1]



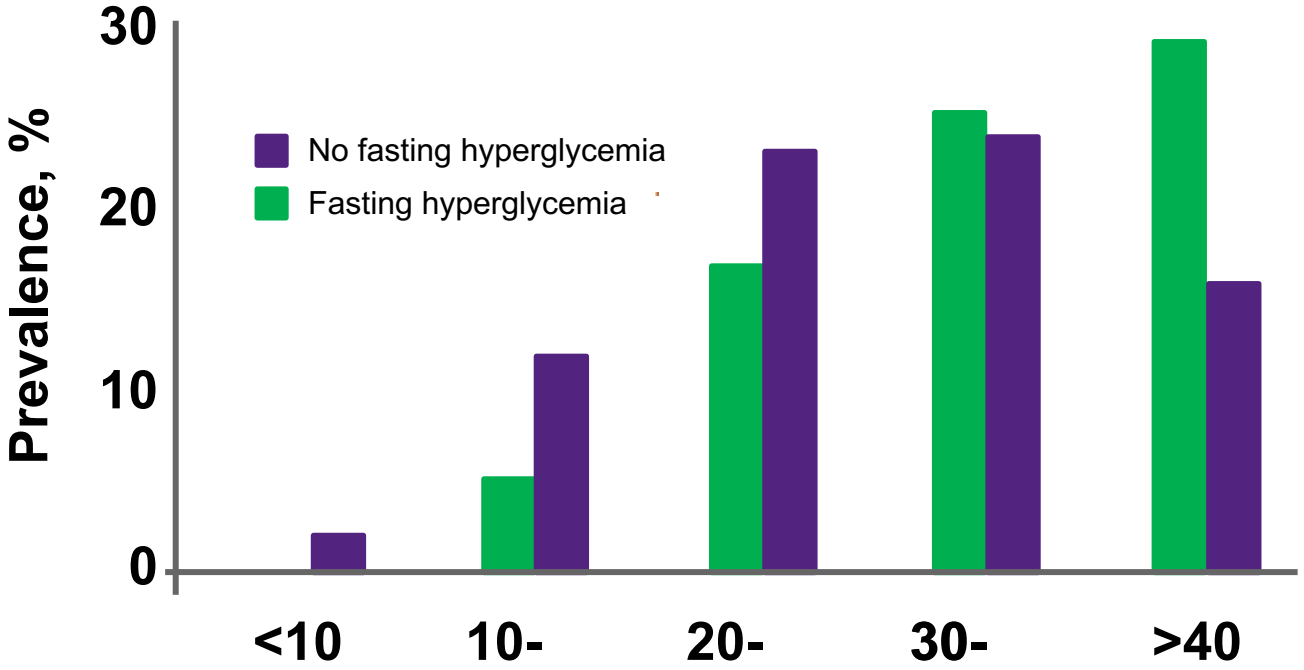
- AGT was detected at the first visit in 39% (9/23) of children with CF aged 3 months to 5 years vs 0 of 9 control children (*P*=0.03) in a prospective study[2]
  - One had INDET, 6 had IGT, and 2 met criteria for CFRD

AGT, abnormal glucose tolerance (IGT or CFRD without fasting hyperglycemia).

1. Mozzillo E et al. *Diabetes Care*. 2012;35(11):78. 2. Yi Y et al. *Am J Respir Crit Care Med*. 2016 Jul 22. doi: 10.1164/rccm.201512-2518OC.

Fasting Hyperglycemia Is Uncommon in Young Patients With CFRD

Prevalence of CFRD with and without fasting hyperglycemia by decade of age[1]



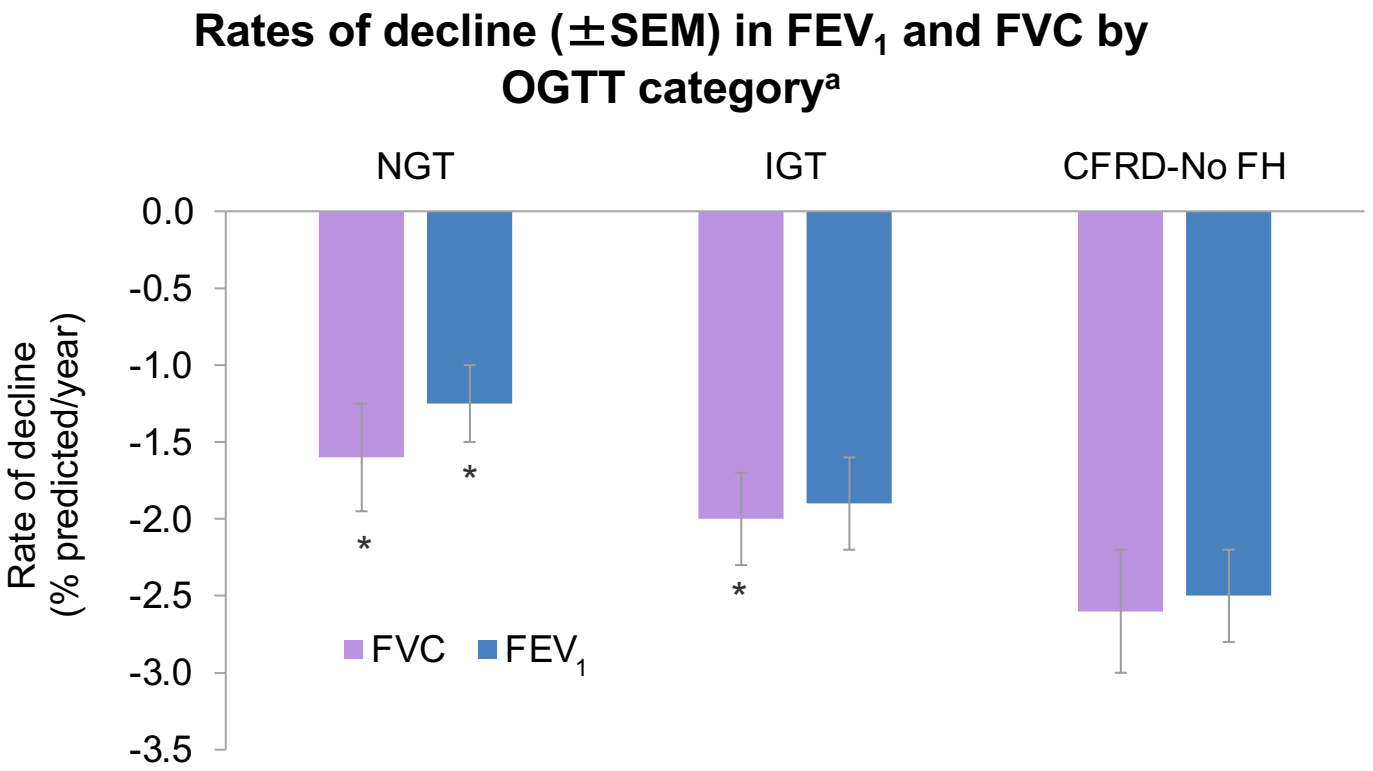
- Elevated FPG is uncommon in younger patients with CFRD but predominates in older age groups

FPG, fasting plasma glucose.
Moran A et al. *Diabetes Care*. 2009;32(9):1626-1631.

VERTEX

Associations Between CFRD and CF Outcomes

CFRD Is Associated With More Rapid Decline in Lung Function (%FVC and %FEV_1)

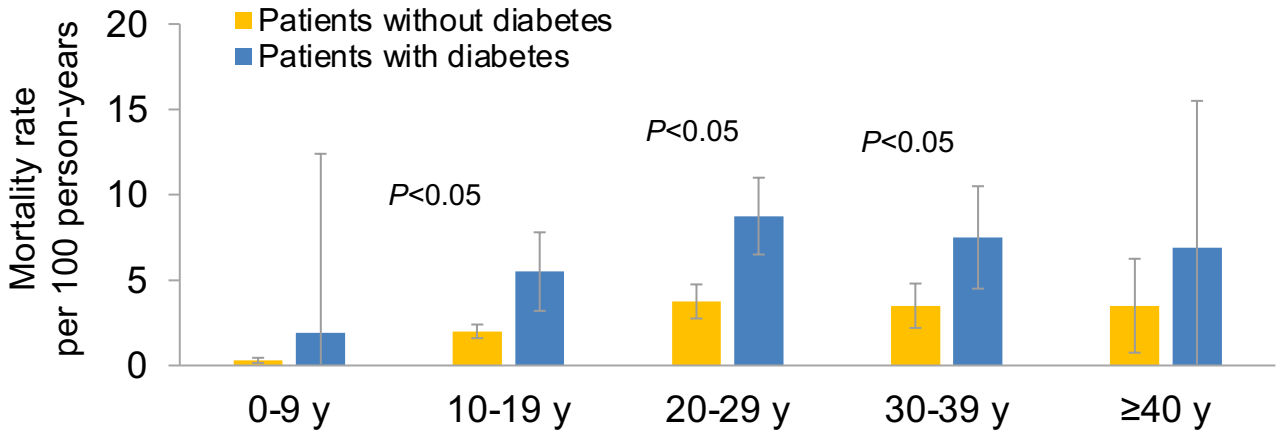


CFRD-No FH, cystic fibrosis–related diabetes without fasting hyperglycemia; FEV_1, forced expiratory volume in 1 second; FVC, forced vital capacity.
*P<0.05 for comparison of individual rates vs CFRD-No FH group.
[a]Rates were adjusted for sex and baseline age, body mass index (BMI), microbiology, use of corticosteroids, and FEV_1 level.

Milla CE et al. *Am J Respir Crit Care Med*. 2000;162(3 Pt 1):891-895.

CFRD Is Associated With Higher Mortality in CF

Mortality rates and 95% CI by age and diabetes in patients with CF[1]

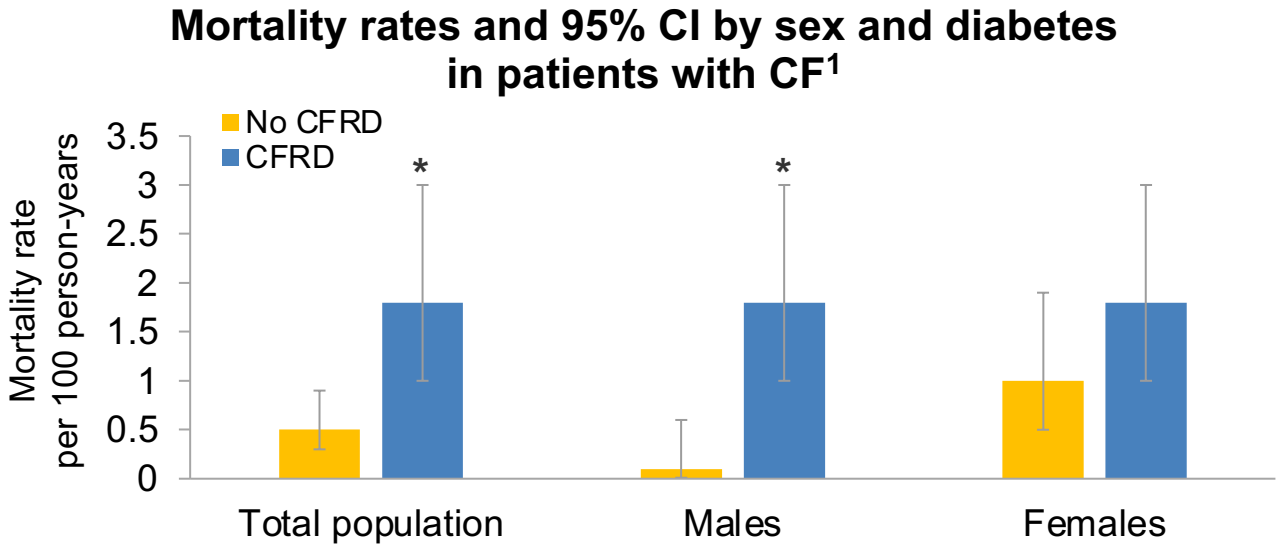


Current mortality rates per person and per 100 person-years for adults aged ≥20 years, by CFRD status[2]

	Patients (n)	Person-Years	Deaths (n)	Mortality Rate per Person (%)	*P* value	Mortality Rate per 100 Person-Years (95% CI)	*P* value
No CFRD (all)	241	831	9	4	0.0001	1.0 (0.4-2)	0.001
CFRD (all)	221	809	30	14		4.8 (3-8)	

1. Chamnan P et al. *Diabetes Care*. 2010;33(2):311-316. 2. Lewis C et al. *Am J Respir Crit Care Med*. 2015;191(2):194-200.

Protective Effect From Mortality Is Lost in Males With CFRD

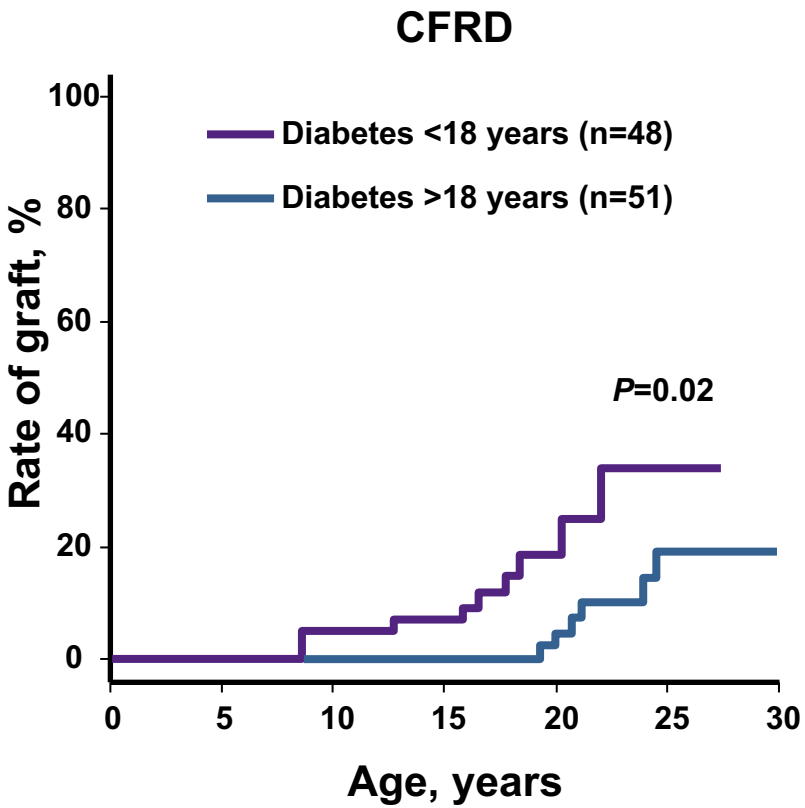


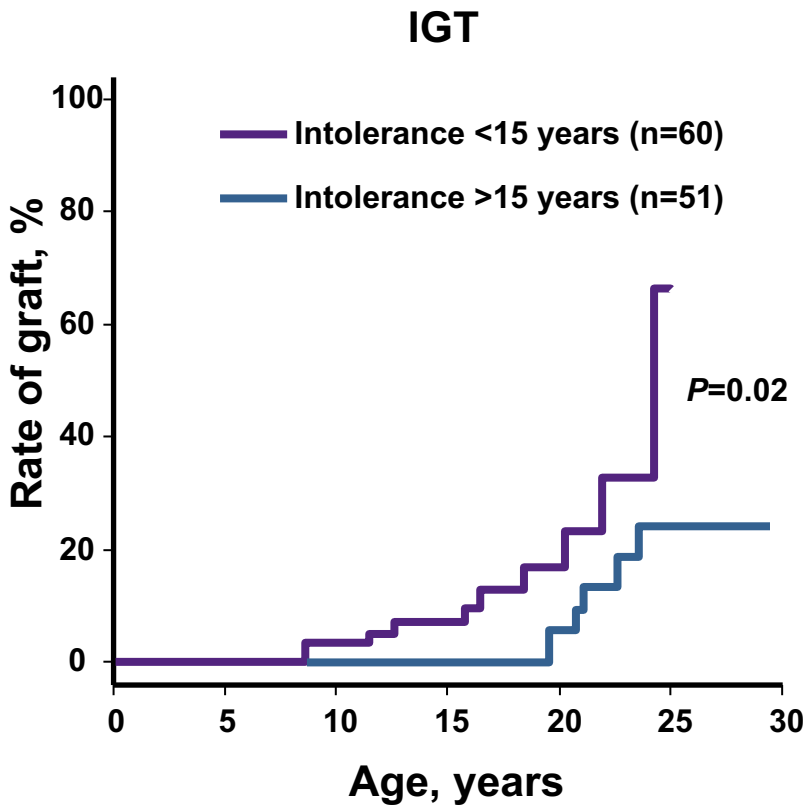
- Stratifying by sex, there were higher mortality rates among males with CFRD compared with males without diabetes
- A suggested increase in females was not statistically significant
- Male sex is protective for mortality in the CF population without CFRD (0.1 [0.01-0.6] vs 1.0 [0.5-1.9] in women)
- Increase in risk of death with CFRD was greater in men so that men and women with diabetes had an equal mortality rate (1.8 [1-3])

*Significant difference (CFRD vs No CFRD).

Lewis C et al. *Am J Respir Crit Care Med*. 2015;191(2):194-200.

Early Onset of CFRD or IGT Is Associated With Higher Rates of and Younger Age At Lung Transplantation





Reprinted from *The Journal of Pediatrics*, 152(4), Bismuth E et al, Glucose tolerance and insulin secretion, morbidity, and death in patients with cystic fibrosis, 540-545, Copyright 2008, with permission from Elsevier.
Bismuth E et al. *J Pediatr.* 2008;152(4):540-545.

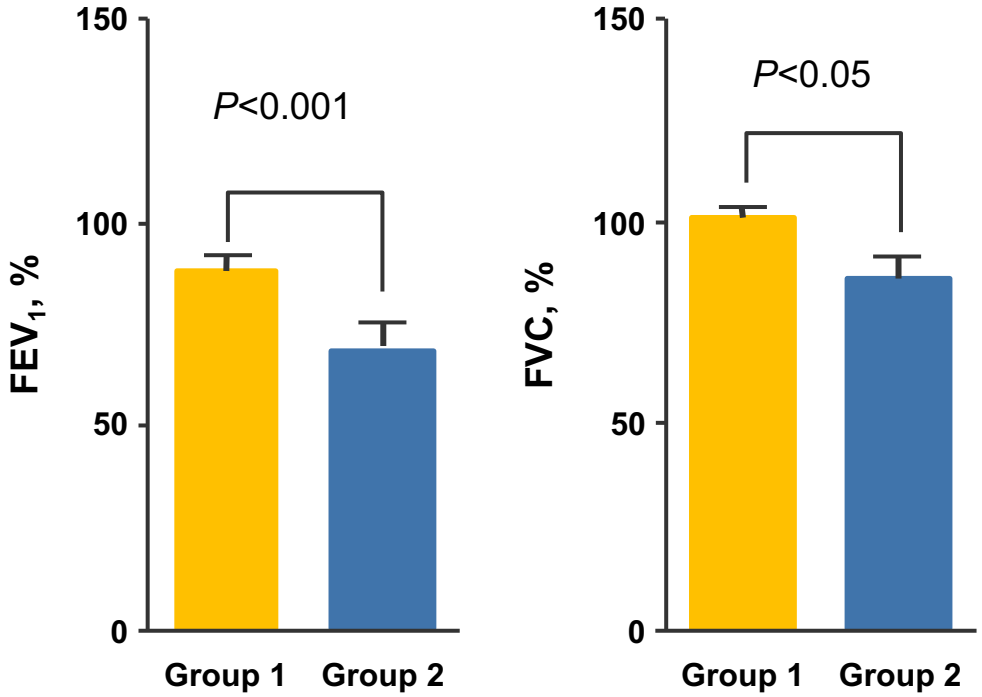
Glucose and Insulin at 1 Hour During OGTT Are Correlated With BMI and Lung Function

	Median Glucose[a]			Median Insulin[b]		
	Low	**High**	***P*-value**	**Low**	**High**	***P*-value**
BMI, kg/m^2	21.7	21.7	0.766	21.0	22.4	0.003
% predicted FEV_1	76.1	70.0	0.025	69.8	76.7	0.022

[a]Low: <11.0 mmol/L (198 mg/dL); high: ≥11.0 mmol/L (198 mg/dL).
[b]Low: <43.4 mU/mL; high: ≥43.4 mU/mL.
Coriati A et al. *Acta Diabetol.* 2016;53(3):359-366.

Abnormal Glucose on CGM Associated With Worse Lung Function in Patients With Normal OGTT

Indices of lung disease in patients with CF, abnormal glucose during CGM and normal OGTT (2-h)



P. aeruginosa Colonization		
Group 1	44.0%	*P*=0.076
Group 2	83.3%	

Group 1: No interstitial glucose value >11 mmol/L (>198 mg/dL) during CGM

Group 2: ≥1 interstitial glucose value >11 mmol/L (>198 mg/dL) during CGM

CGM, continuous glucose monitoring.

Leclercq A et al. *J Cyst Fibros.* 2014;13(4):478-484.

Screening for CFRD

OGTT Is the Preferred Method to Test for Glucose Abnormalities in CF

OGTT[1,2]
- Assessment of choice for CFRD[2]
- Sampling: Fasting and 2 hour, consider 1 hour

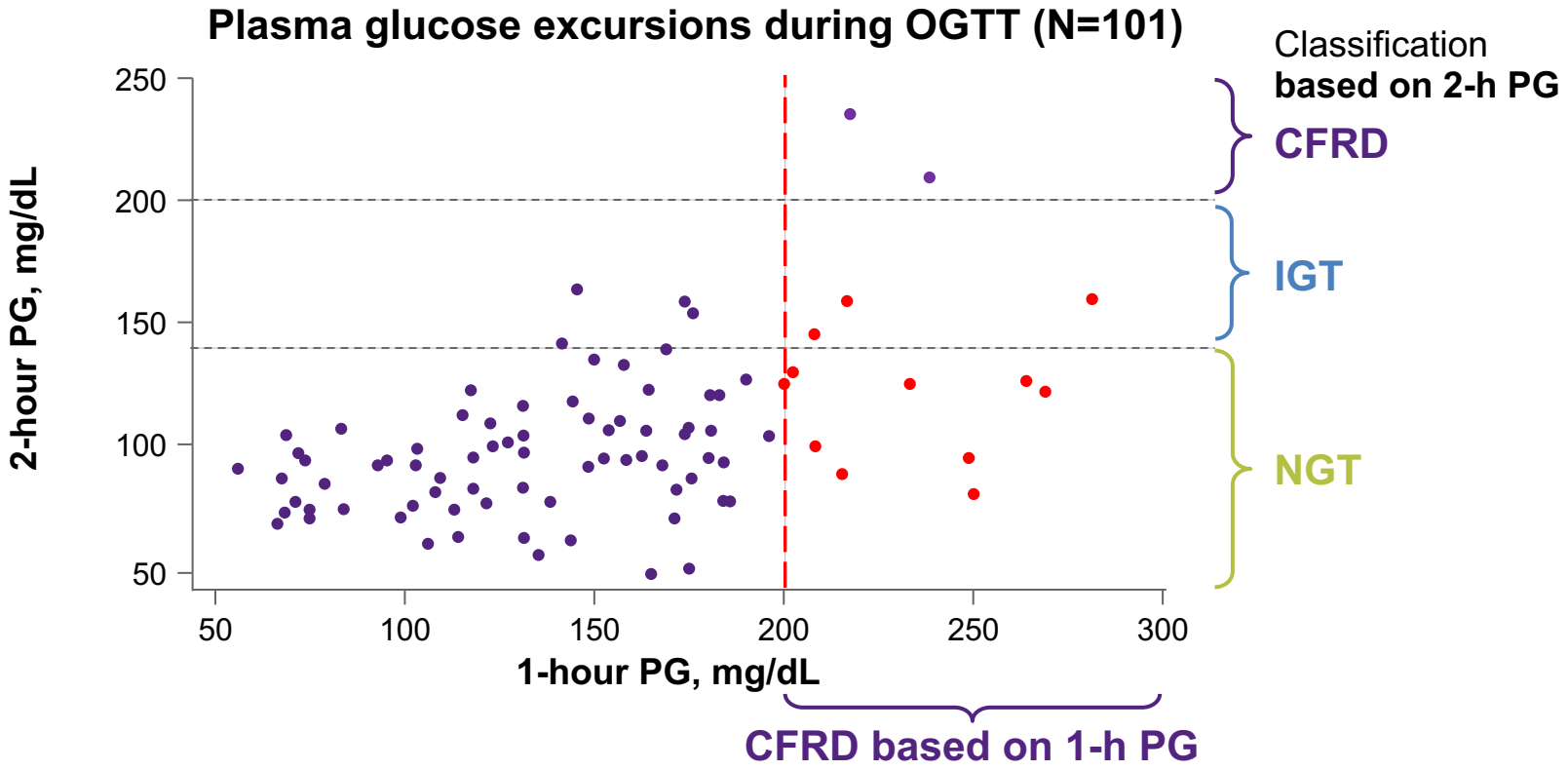
FPG[1]
- Only elevated late in CF disease course, so not good for screening for CFRD

Hemoglobin A1c (HbA1c)[1,2]
- Levels of ≥6.5% are consistent with CFRD
- Lower levels do not rule out CFRD

- Screening is recommended for patients receiving continuous enteral feedings by measuring mid-feeding and immediate post-feeding blood glucose[3]

1. National Institute of Diabetes and Digestive and Kidney Diseases. Comparing Diabetes Blood Tests. https://www.niddk.nih.gov/health-information/diabetes/overview/tests-diagnosis Accessed April 2020. 2. Kelly A, Moran A. *J Cyst Fibros.* 2013;12(4):318-331. 3. Moran A et al. *Pediatr Diabetes.* 2014;15(Suppl 20):65-76.

Early Glucose Abnormalities Can Be Detected in Patients With CF and Normal 2-Hour OGTT

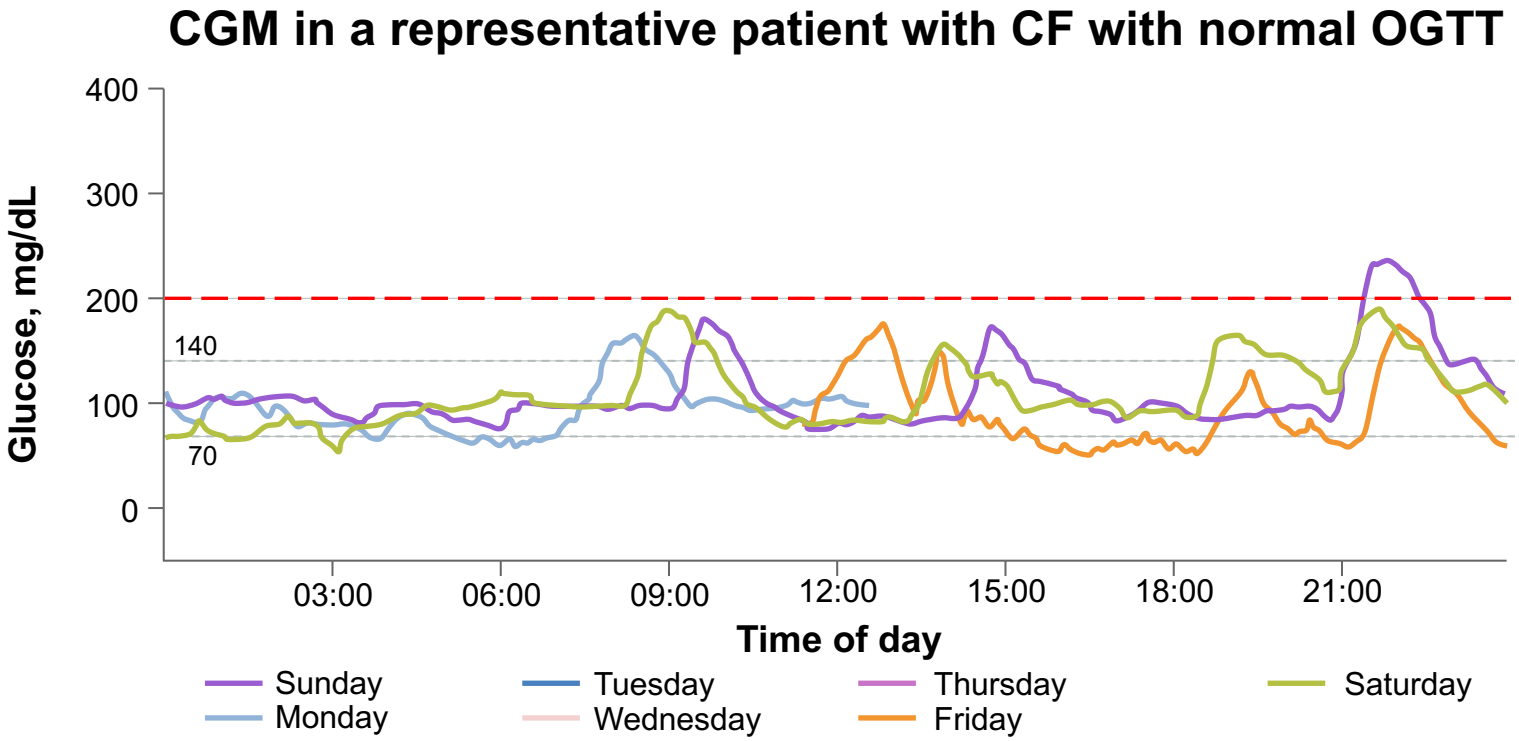


- Of 101 patients who underwent OGTT, 14 (14%) had 1-h PG ≥200 mg/dL. Of the 14
  - Nine (64%) had normal 2-h PG and would have been labeled as NGT
  - Two had CFRD, 3 had IGT

Brodsky J et al. *Diabetes Care*. 2011;34(2):292-295.

VERTEX

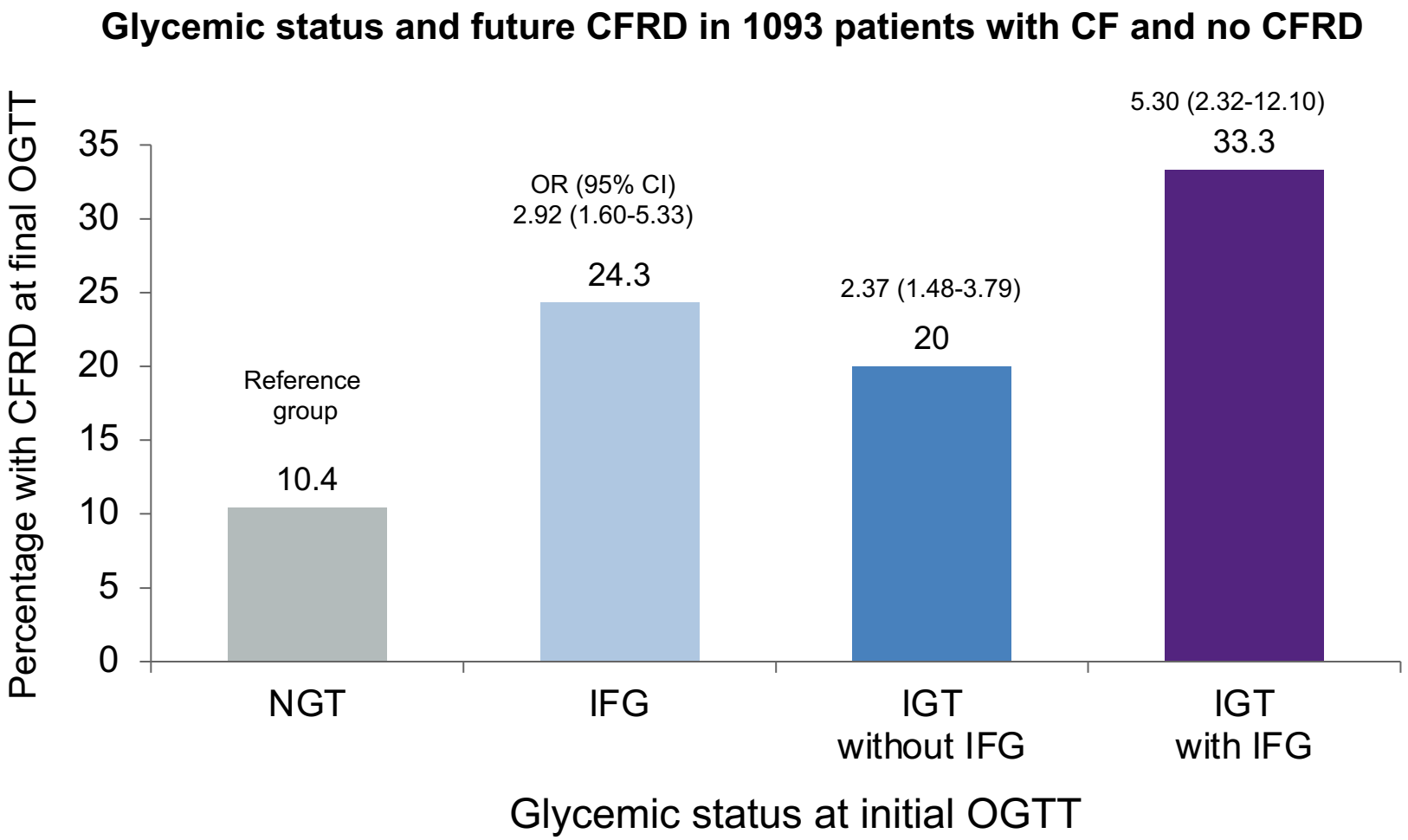
CGM Shows Glucose Abnormalities in Patients With CF With Normal OGTT



- Thirty-eight patients with CF underwent both OGTT and CGM
- Twenty-six had normal glucose using both tests
- Twelve (32%) had glucose >11 mmol/L (>200 mg/dL) at least once during CGM

Reprinted from *Journal of Cystic Fibrosis*, 13(4), Leclercq A et al, Early assessment of glucose abnormalities during continuous glucose monitoring associated with lung function impairment in cystic fibrosis patients, 478-484, Copyright 2014, with permission from Elsevier.
Leclercq A et al. *J Cyst Fibros.* 2014;13(4):478-484.

Glycemic Status Is a Predictor of CFRD in CF



IFG, impaired fasting glucose; OR, odds ratio.
Schmid K et al. *J Cyst Fibros.* 2014;13(1):80-85.

CFRD With Fasting Hyperglycemia Is Associated With Microvascular Complications

	Duration of Diabetes, y			
	<5	**5-10**	**>10**	**All**
No fasting hyperglycemia				
% with ↑ $U_{alb:cr}$ (n tested)	0 (36)	0 (23)	0 (20)	0 (79)
% with retinopathy (n tested)	0 (23)	0 (18)	0 (16)	0 (57)
With fasting hyperglycemia				
% with ↑ $U_{alb:cr}$ (n tested)	0 (22)	4 (25)	14 (36)[a]	7 (83)[a]
% with retinopathy (n tested)	0 (20)	0 (28)	16 (37)[a]	7 (84)[a]

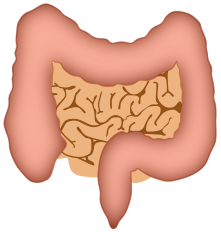
- Microvascular complications are common in individuals with type 1 and type 2 diabetes and represent a significant source of morbidity and mortality
- A significant percentage of patients with CFRD with fasting hyperglycemia showed signs of microvascular complications compared with those without fasting hyperglycemia

$U_{alb:cr}$, annual spot urine microalbumin-to-creatinine ratio. Microalbuminuria = 30 to 299 µg/mg creatinine.
[a]$P<0.05$ (fasting vs no fasting hyperglycemia).
Schwarzenberg S et al. *Diabetes Care.* 2007;30(5):1056-1061.

VERTEX

Overview of Insulin Secretion and Glucose Regulation Abnormalities in CF

Glucose Concentrations Are Tightly Regulated in Healthy Individuals



Nutrient absorption (carbohydrates, protein, fat)

↑ Blood glucose[1]

Incretin secretion (GLP-1, GIP)[3]

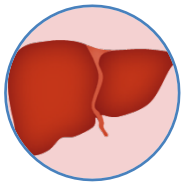
- Incretins increase pancreatic insulin secretion[1]
- "Incretin effect" may account for ~70% of total insulin secretion[2]

Pancreas

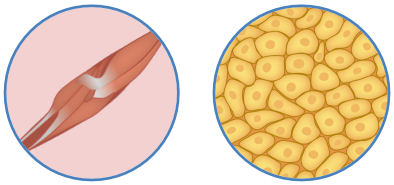
↑ Insulin secretion[1]

Suppression of protein, carbohydrate, fat catabolism[1]

↑ Glucose storage[1]



↑ Glucose uptake in muscle and fat[1]



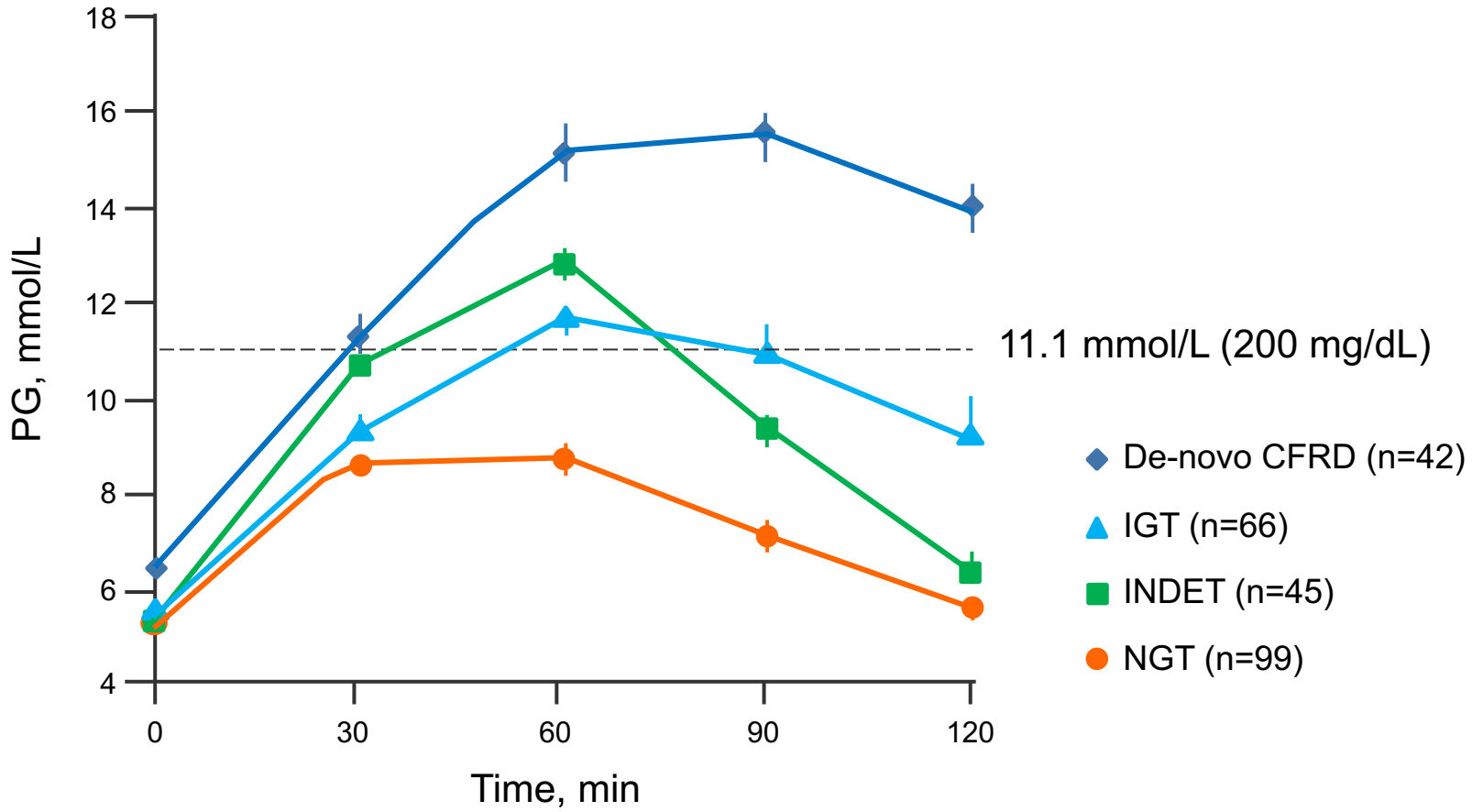
Blood glucose normalization[3]

GIP, glucose-dependent insulinotropic polypeptide; GLP-1, glucagon-like peptide-1.

1. Nussey S, Whitehead S. Chapter 2. The endocrine pancreas. In: *Endocrinology: An Integrated Approach*. Oxford: BIOS Scientific Publishers; 2001. 2. Nauck M et al. *Diabetologia*. 1986;29(1):46-52. 3. Aronoff SL et al. *Diabetes Spectrum*. 2004;17(3):183-190.

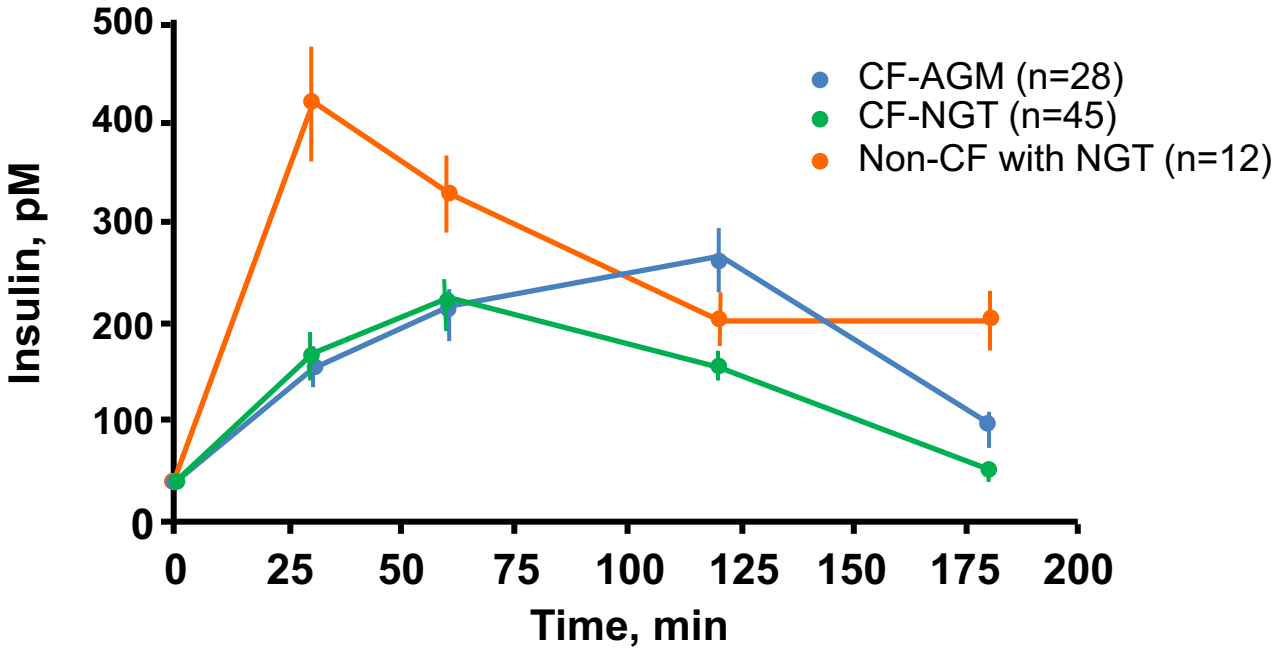
PG Is Inappropriately Elevated During Glucose Challenge in Patients With CF Prior to CFRD Development

PG levels (OGTT) in patients with CF without CFRD at baseline



Reprinted from *Journal of Cystic Fibrosis*, 15(1), Coriati A et al, Characterization of patients with cystic fibrosis presenting an indeterminate glucose tolerance (INDET), 127-132, Copyright 2016, with permission from Elsevier.
Coriati A et al. *J Cyst Fibros.* 2016;15(1):127-132.

Insulin Secretion in Response to Glucose Is Impaired in Patients With CF Without CFRD



- Shown are insulin levels following glucose load in children and adolescents with CF at a single center[1]
- Lack of early-phase insulin secretion and lower overall insulin in patients with CF vs healthy controls[1,2]
- Abnormalities more pronounced with worsening glycemic status[2]
- Insulin clearance may also be increased[3,4]

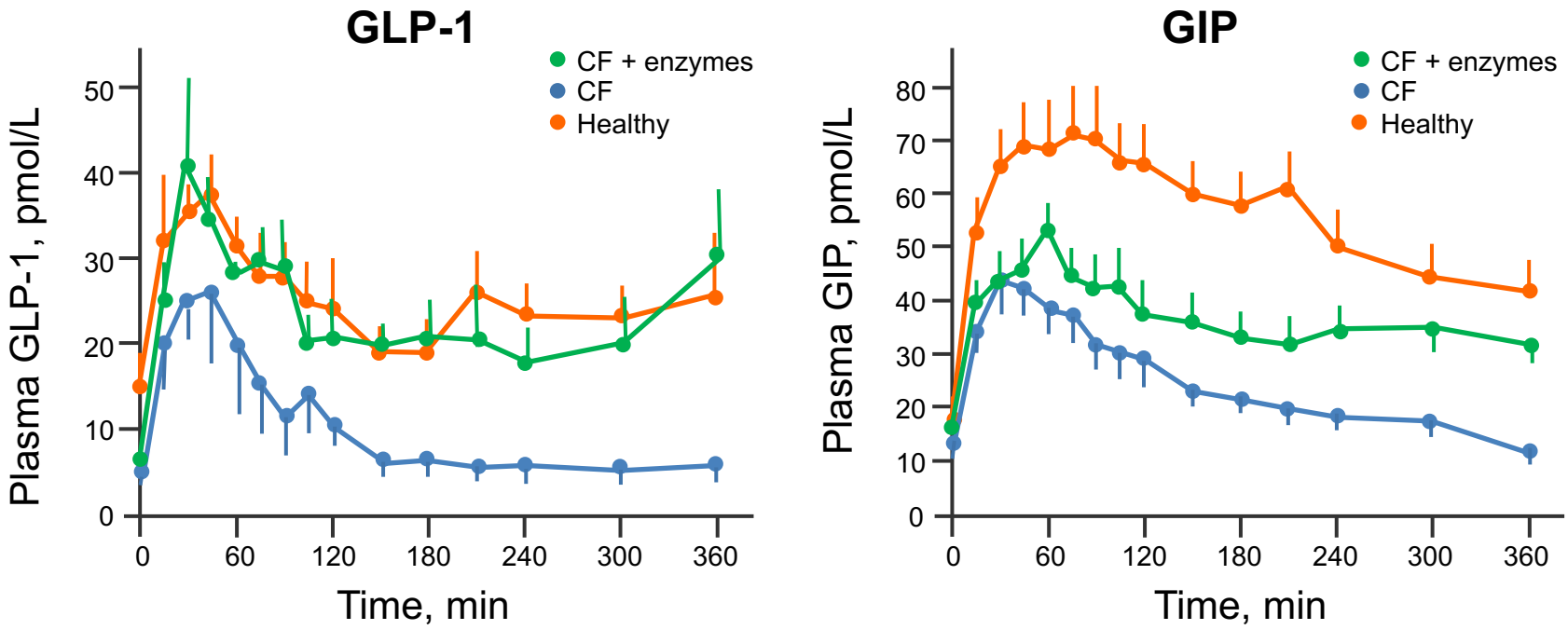
AGM, abnormal glucose metabolism, including IFG, IGT, IGT/IFG, and diabetes.
Reprinted from *The Journal of Pediatrics*, 151(6), Elder DA et al, Glucose tolerance, insulin secretion, and insulin sensitivity in children and adolescents with cystic fibrosis and no prior history of diabetes, 653-658, Copyright 2007.

1. Elder DA et al. *J Pediatr*. 2007;151(6):653-658. 2. Kelly A, Moran A. *J Cyst Fibros*. 2013;12(4):318-331. 3. Battezzati A et al. *J Clin Endocrinol Metab*. 2015;100(8):2963-2971. 4. Lanng S et al. *Clin Endocrinol (Oxf)*. 1994;41(2):217-223.

VERTEX

Incretin Secretion Is Impaired in Patients With Pancreatic Insufficient CF and Improved With Pancreatic Enzyme Therapy

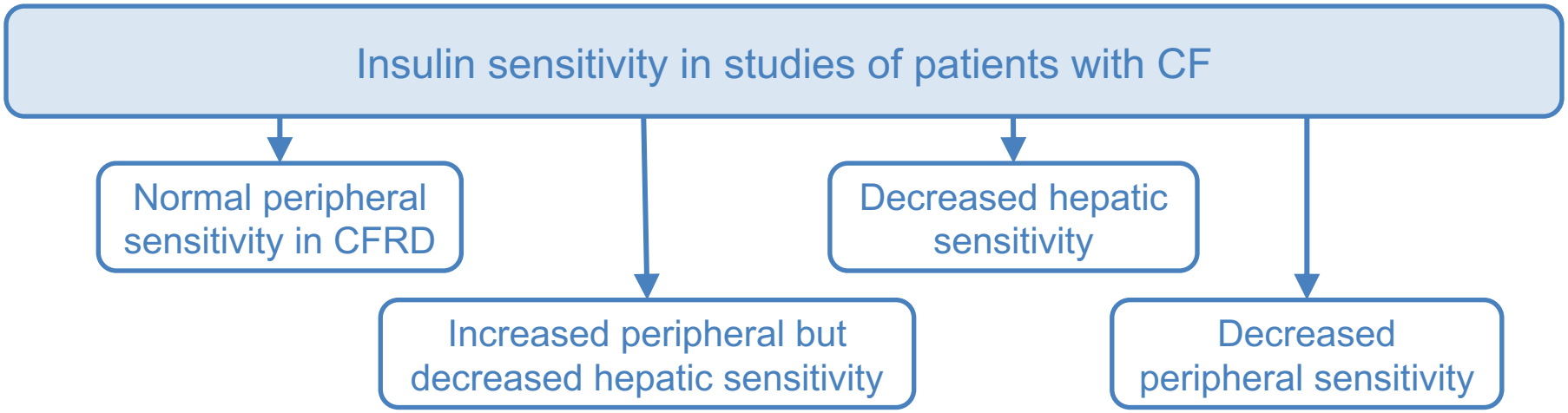
Plasma incretin levels in healthy subjects and pancreatic insufficient patients with CF



- Pancreatic enzyme supplementation normalizes GLP-1 secretion and improves GIP secretion in patients with CF and pancreatic insufficiency, indicating the importance of pancreatic enzyme replacement therapy in CF

Kuo P et al. *J Clin Endocrinol Metab.* 2011;96(5):E851-E855.

Evidence for Decreased Insulin Sensitivity in CFRD Is Inconsistent

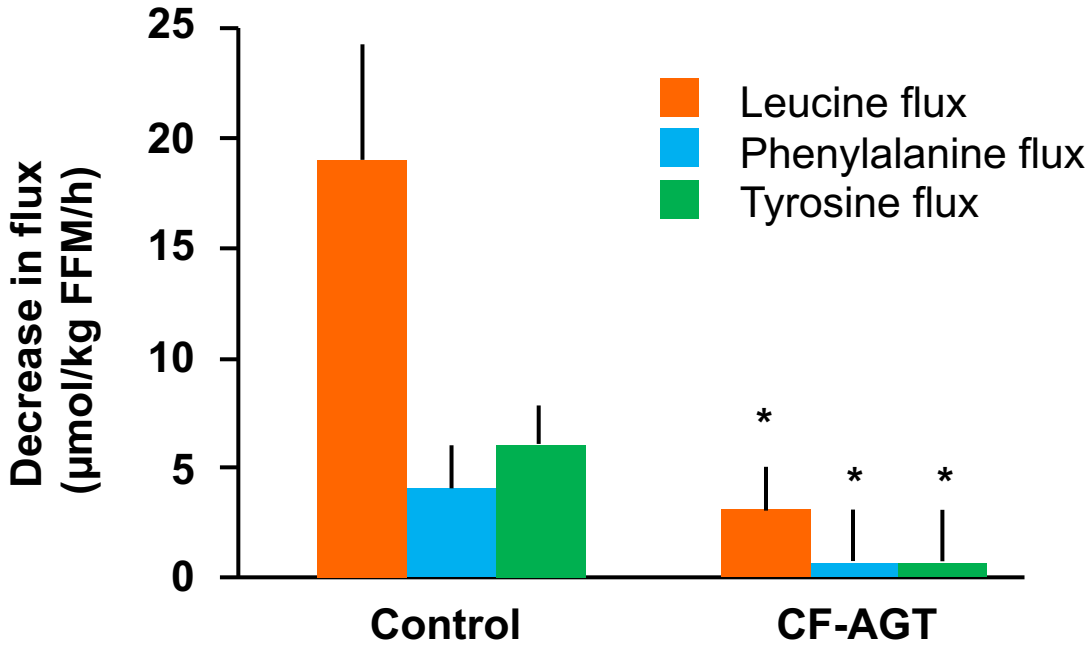


"Insulin sensitivity": Glucose uptake in tissues and decreased hepatic glucose production in response to insulin

- Variability in findings reflects between-study differences
  - Methods, glucose categorization, overall patient health
- Overall: Normal insulin sensitivity in patients with CF without CFRD, and modest insulin resistance in CFRD

Kelly A, Moran A. *J Cyst Fibros.* 2013;12(4):318-331.

Suppression of Proteolysis by Insulin Is Reduced in Patients With CF and Abnormal Glucose Tolerance

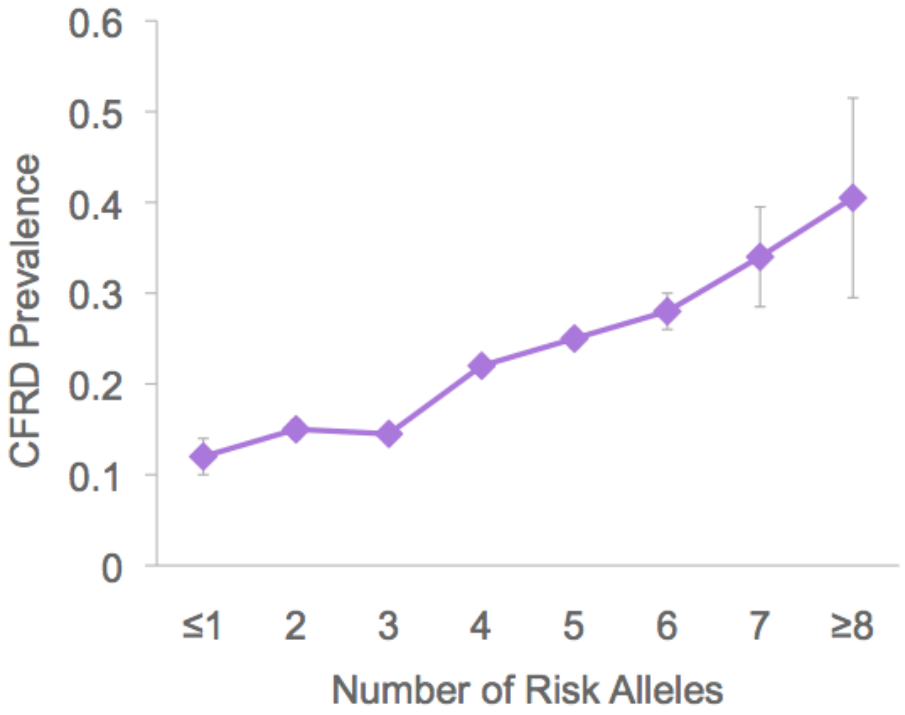


- Leucine, phenylalanine, and tyrosine are not synthesized in the human body, they must come from protein breakdown or ingestion, so they can be used as a marker of protein breakdown in the fasted state[1]
- Fasting insulin levels and rates of protein breakdown at baseline were not different between groups[1]
- Suppression of fat breakdown by insulin is also reduced by about 50% in patients with CF and IGT, but differences were not statistically significant[2]

FFM, fat free mass.
*P<0.001 vs control.
1. Moran A et al. *Diabetes*. 2001;50(6):1336-1343. 2. Moran A et al. *Metabolism*. 2004;53(11):1467-1472.

Modifier Genes Are Associated With CFRD in CF

Impact of modifier genes on CFRD: Combined effect on CFRD prevalence of modifier alleles at 5 loci



Genes with modifications (SNPs) associated with CFRD

Gene	Potential Mechanism
SLC26A9	Anion transporter that interacts with CFTR and may modify CF phenotype
TCF7L2	Known susceptibility for type 2 diabetes
CDKAL1	
CDKN2A/B	
IGF2BP2	

SNP, single nucleotide polymorphism.

Blackman SM et al. *Diabetes.* 2013;62(10):3627-3635.

Treatment Guidelines for CFRD
From the International Society for Pediatric and Adolescent Diabetes

- Insulin is the treatment of choice[1]
- Oral diabetes agents are not recommended[1]
- Patients with CFRD receiving insulin should perform blood glucose monitoring ≥3 times daily[1]
  - HbA1c quarterly to guide insulin therapy decisions
- Treatment goals are to maintain glucose levels in accordance with ADA guidelines for diabetes (postprandial: <180 mg/dL [10.0 mmol/L] for adults and adolescents, <200 mg/dL [11.1 mmol/L] for children)[1,2]
- Adherence to CFF nutritional guidelines and moderate aerobic exercise are recommended[1]

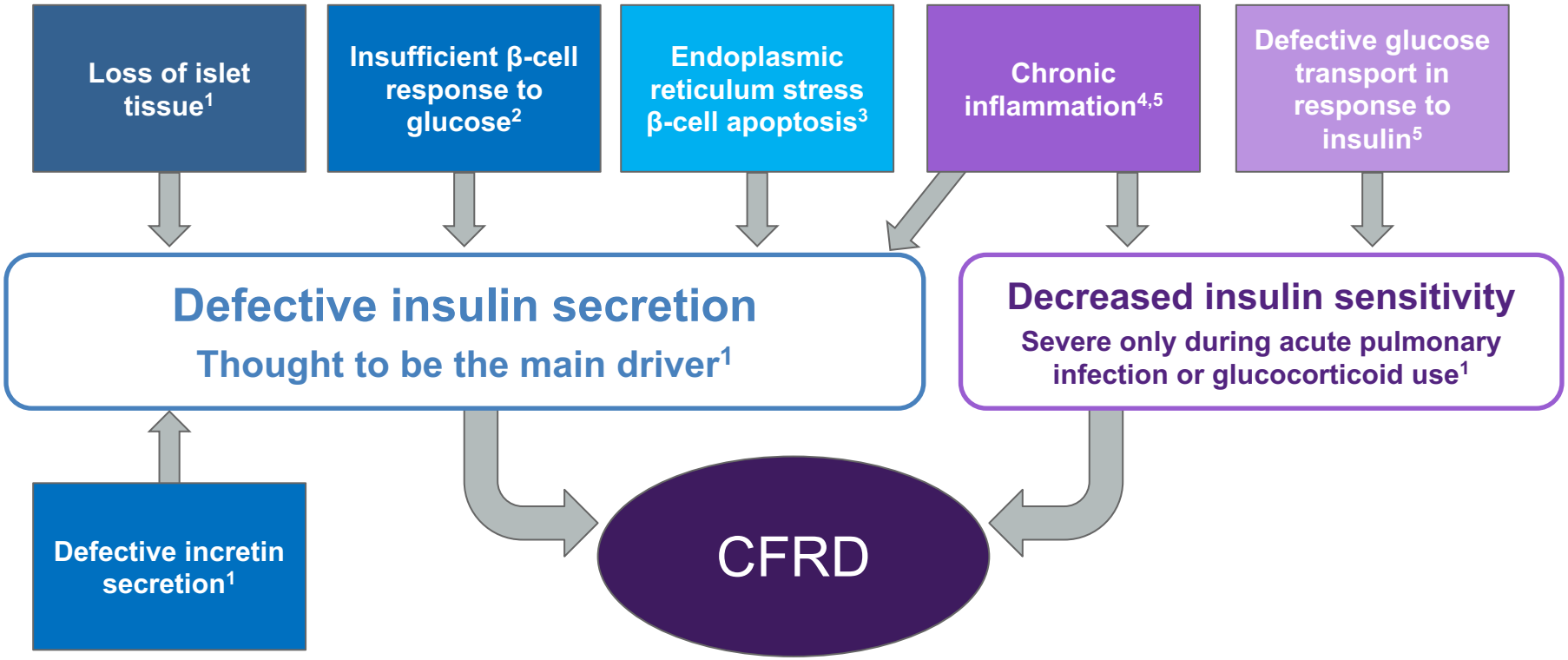
ADA, American Diabetes Association; CFF, Cystic Fibrosis Foundation.

1. Moran A et al. *Pediatr Diabetes.* 2014;15(Suppl 20):65-76. 2. Moran A et al. *Diabetes Care.* 2010;33(12):2697-2708.

VERTEX

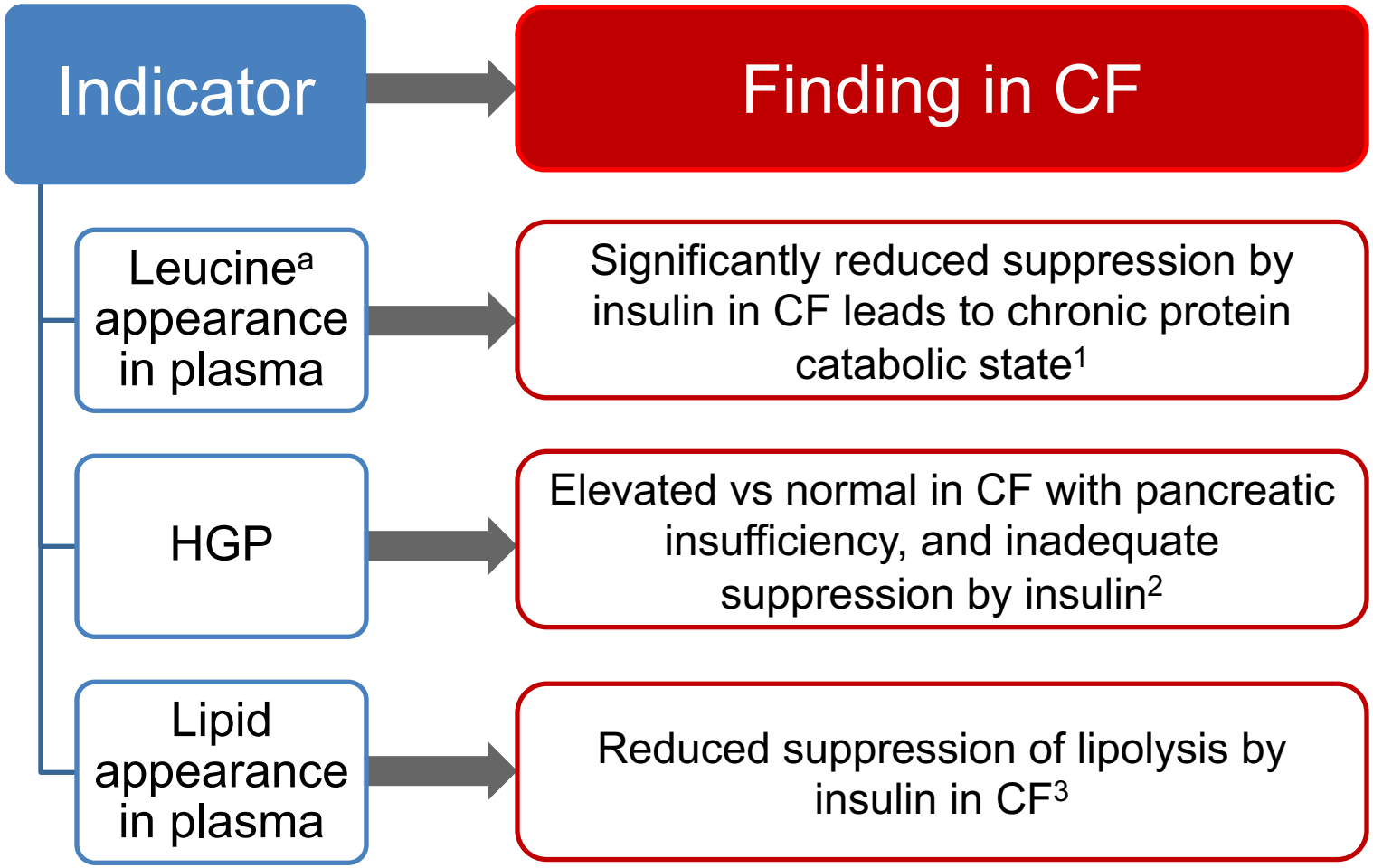
Pathophysiology of CFRD

Overview of Potential Mechanisms Contributing to CFRD in CF



1. Barrio R. *Eur J Endocrinol*. 2015;172(4):R131-R141. 2. Guo JH et al. *Nat Commun*. 2014;5:4420. 3. Ali BR. *Med Hypotheses*. 2009;72(1):55-57. 4. Galli F et al. *Biochim Biophys Acta*. 2012;1822(5):690-713. 5. Hardin DS et al. *Am J Physiol Endocrinol Metab*. 2001;281(5):E1022-E1028.

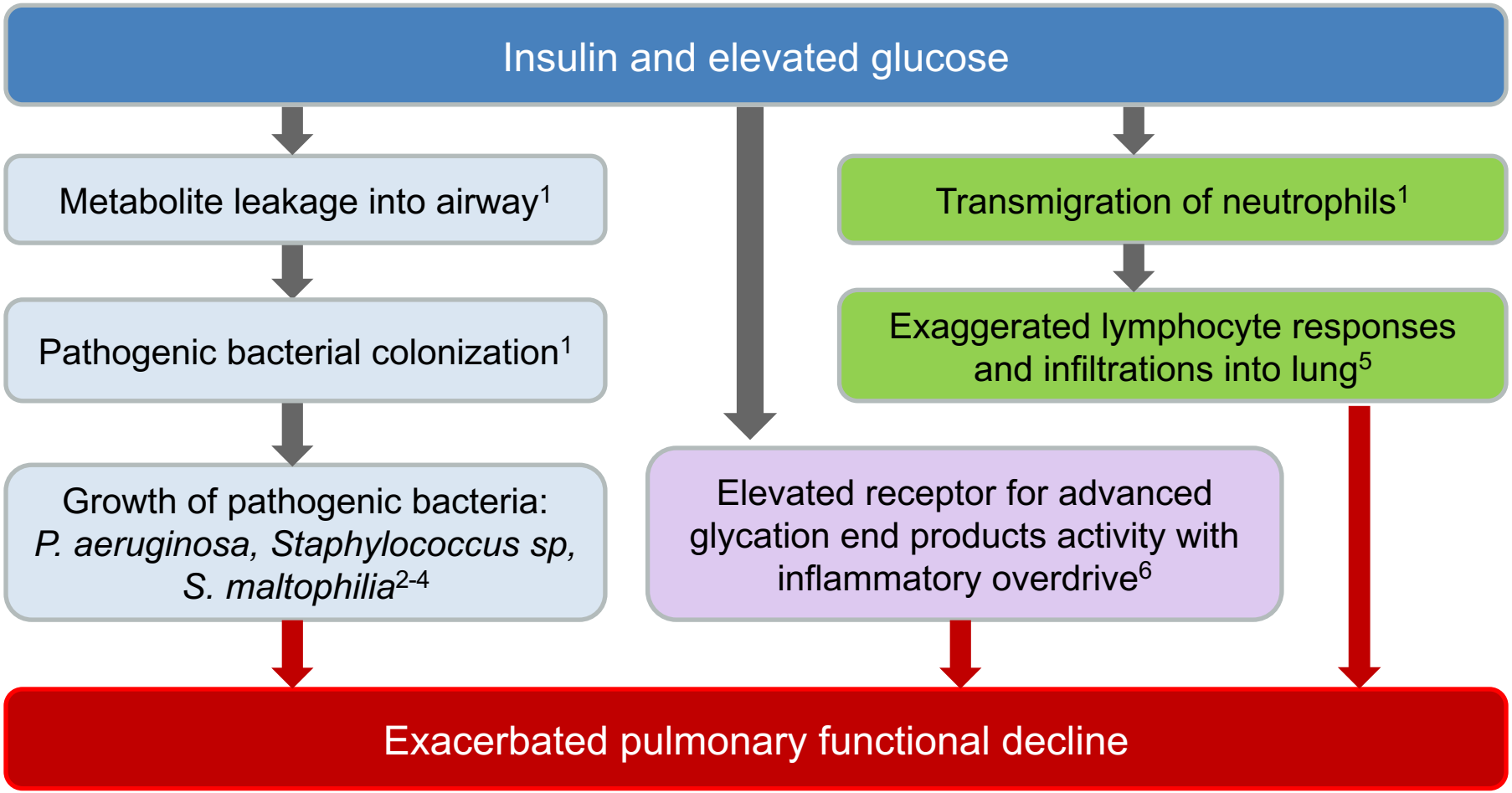
Defective Peripheral Insulin Action in CF, Even With Normal Peripheral Glucose Disposal



HGP, hepatic glucose production.
[a]Also tyrosine and phenylalanine; appearance in plasma under experimental conditions indicates protein breakdown.[1]

1. Moran A et al. *Diabetes*. 2001;50(6):1336-1343. 2. Moran A et al. *Diabetes*. 1994;43(8):1020-1026. 3. Moran A et al. *Metabolism*. 2004;53(11):1467-1472.

Potential Links Between Defects in Glucose Metabolism and Lung Function



1. Molina SA et al. NACFC 2015. Abstract 150. 2. Hameed S et al. *Curr Opin Pediatr.* 2015;27(4):525-533. 3. Fothergill JL. ECFC 2015. Abstract ePS06.1. 4. Garnett JP et al. *PLoS One.* 2013;8(10):e76283. 5. Ziai S et al. *Diabetes Res Clin Pract.* 2014;105(1):22-29. 6. Mulrennan S et al. *Sci Rep.* 2015;5:8931.

Summary

- CFRD is distinct from type 1 and 2 diabetes
- Glucose abnormalities begin at a young age and are common
- CFRD is associated with worse lung function, worse nutritional status, increased mortality, and microvascular complications
- Screening for CFRD with OGTT is recommended by age 10 years
- Insulin is the treatment of choice in CFRD
- CFRD arises from defects in insulin secretion, impaired incretin responses, and abnormal insulin responses

VERTEX

Interactive Question 1

- The current treatment of choice for CFRD is
  - A. Oral hypoglycemics (eg, metformin)
  - B. Insulin
  - C. GLP-1 agonists
  - D. DPP-IV inhibitors

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Interactive Question 2

- Which of the following is the preferred method of screening for glucose abnormalities in patients with CF?

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  B. Glycated hemoglobin (A1c)

  C. Fasting plasma glucose (FPG)

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Interactive Question 2

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Interactive Question 3

- Compared with type 1 and type 2 diabetes, CFRD
  - A. Is characterized by severe insulin resistance
  - B. Has an autoimmune component
  - C. Has an unpredictable relation between HbA1C and plasma glucose
  - D. Has cardiovascular disease as the dominant cause of death

Interactive Question 3

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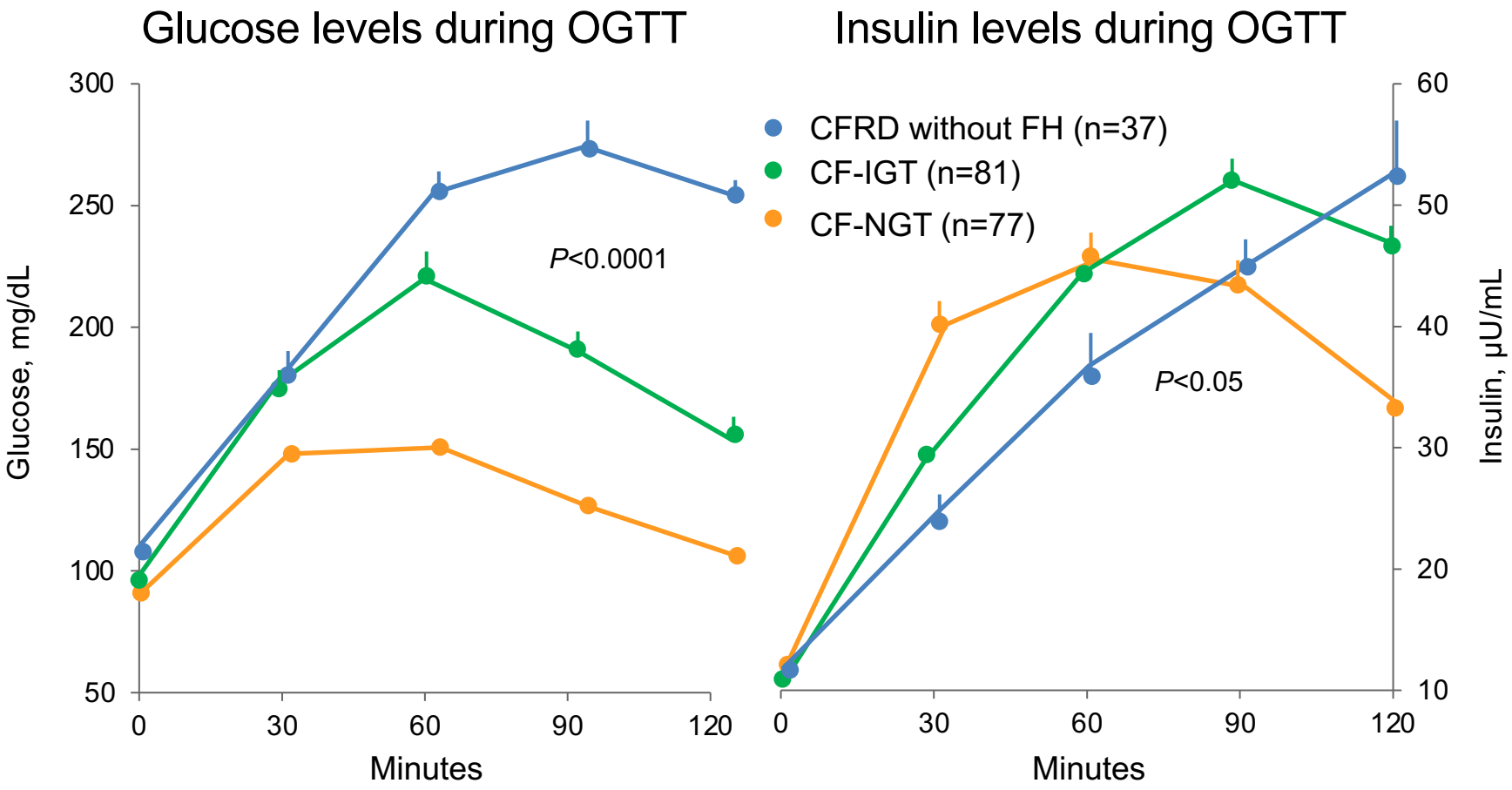
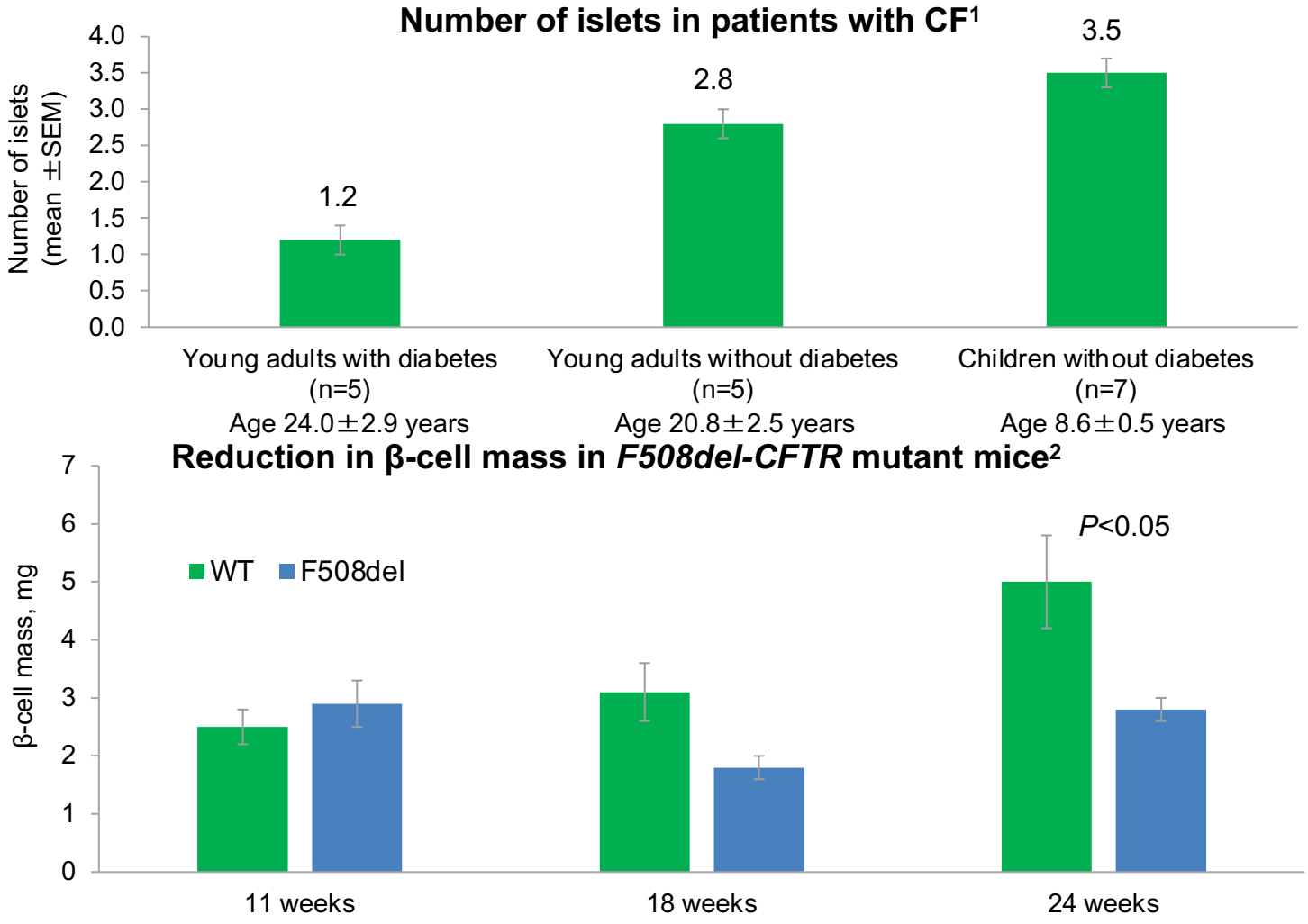
More Information

Abnormal Glucose and Insulin Levels in Patients With CF With and Without CFRD



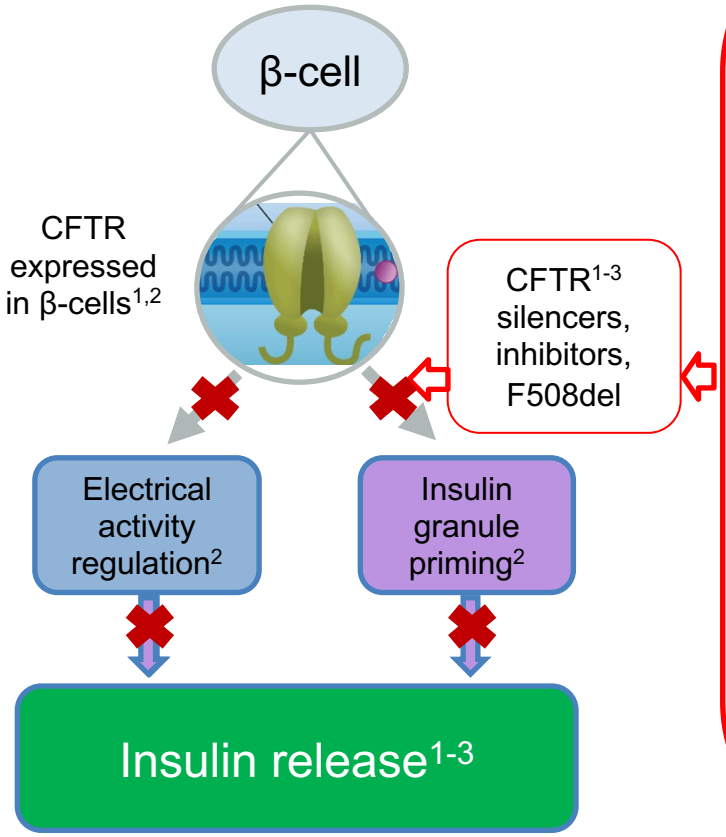
Moran A et al. *J Pediatr*. 1998;133(1):10-17.

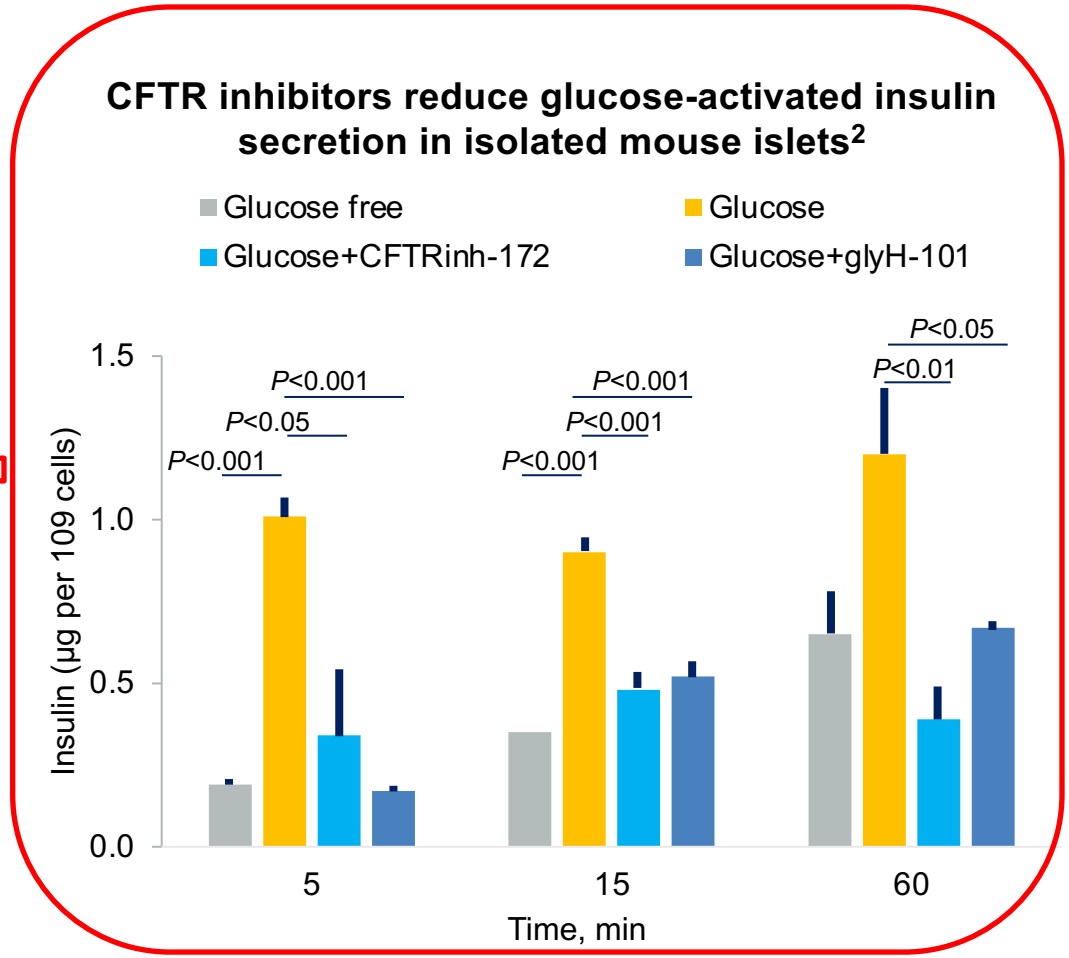
Loss of Islets and Islet Cells Contributes to Defective Insulin Secretion in CF



1. Iannucci A et al. *Hum Pathol.* 1984;15(3):278-284. 2. Fontés G et al. *Diabetes.* 2015;64(12):4112-4122.

CFTR Directly Affects β-Cell Response to Glucose, Which May Contribute to Defective Insulin Secretion



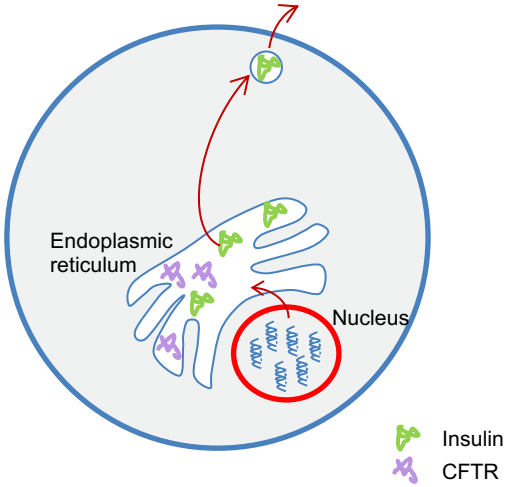


Reprinted from Guo JH et al. Glucose-induced electrical activities and insulin secretion in pancreatic islet β-cells are modulated by CFTR. *Nat Commun*. 2014;5:4420.

1. Edlund A et al. *BMC Med.* 2014;12:87. 2. Guo JH et al. *Nat Commun.* 2014;5:4420. 3. Ntimbane T et al. *Am J Physiol Endocrinol Metab.* 2016;310(3):E200-E212.

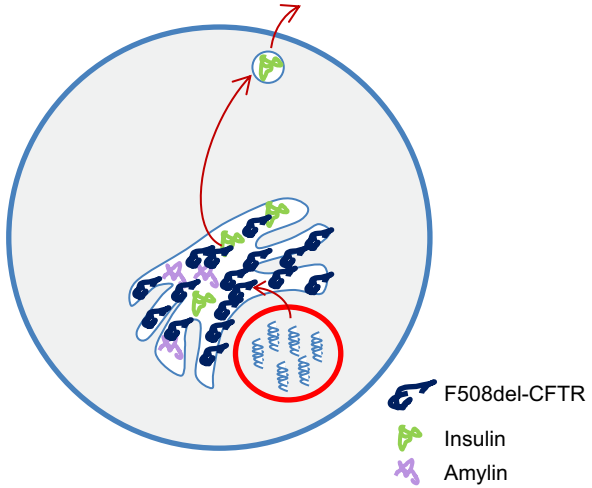
Endoplasmic Reticulum Stress With β-Cell Apoptosis May Lead to Defective Insulin Secretion in CF

Secretory β-cell



- High rate of protein synthesis
- Vulnerable to unfolded protein accumulation

Secretory β-cell with F508del-CFTR



- Misfolded F508del-CFTR accumulation
- Activation of UPR and ERAD

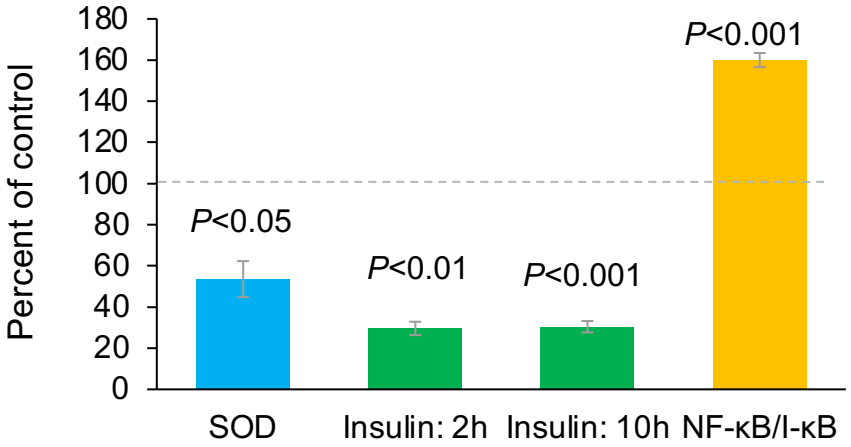
Endoplasmic reticulum stress → β-cell apoptosis

ERAD, endoplasmic reticulum–associated protein degradation; UPR, unfolded protein response.
Ali BR. *Med Hypotheses*. 2009;72(1):55-57.

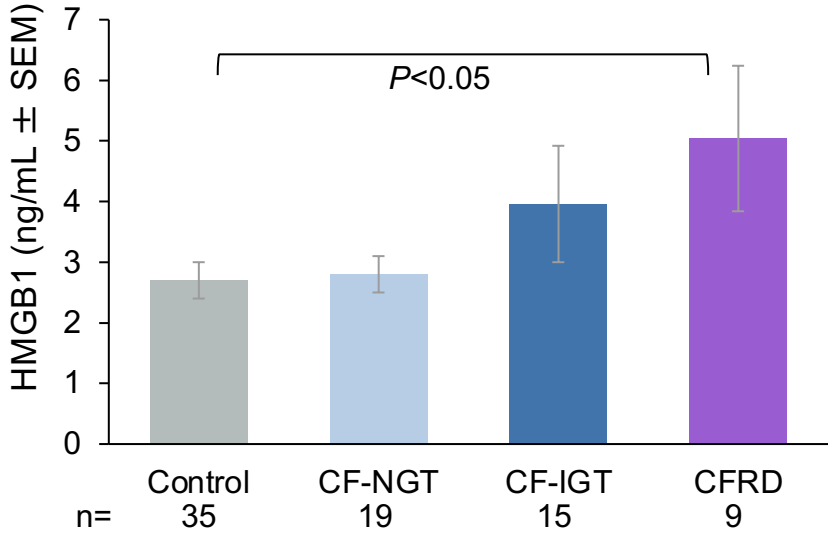
Oxidative Stress and Inflammation May Contribute to Defective Insulin Secretion

- β-cells have very low antioxidant levels, increasing risk for oxidative stress[1]
- Defective CFTR appears to cause an abnormal generation of reactive oxygen species[2]

CFTR-silenced β-cell line produces low levels of SOD and insulin, and high levels of inflammatory marker[3]



Serum HMGB1 level is elevated in CFRD[4]



- HMGB1 activates NF-kB, endothelial cells, and systemic inflammatory cells, and is elevated in CFRD[4]

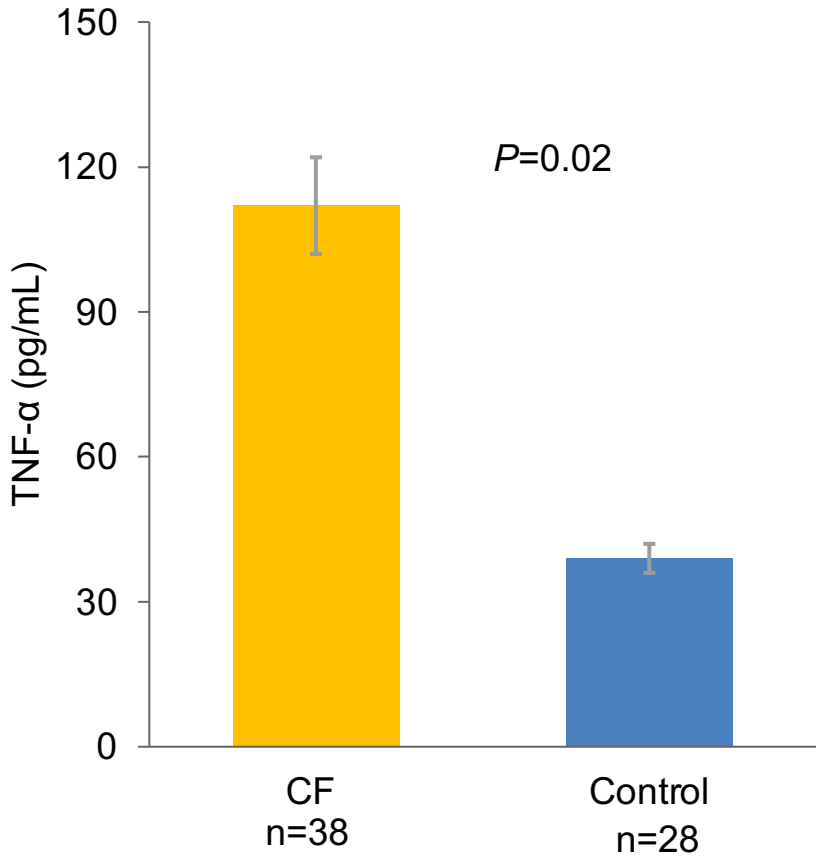
HMGB1, high mobility group box 1 protein; SOD; superoxide dismutase.

1. Pouitout V, Robertson RP. *Endocr Rev*. 2008;29(3):351-366. 2. Galli F et al. *Biochim Biophys Acta*. 2012;1822(5):690-713. 3. Ntimbane T et al. *Am J Physiol Endocrinol Metab*. 2016;310(3):E200-E212. 4. Montanini L et al. *J Clin Endocrinol Metab*. 2016;101(3):1274-1281.

Inflammation May Play a Role in Reduced Insulin Sensitivity

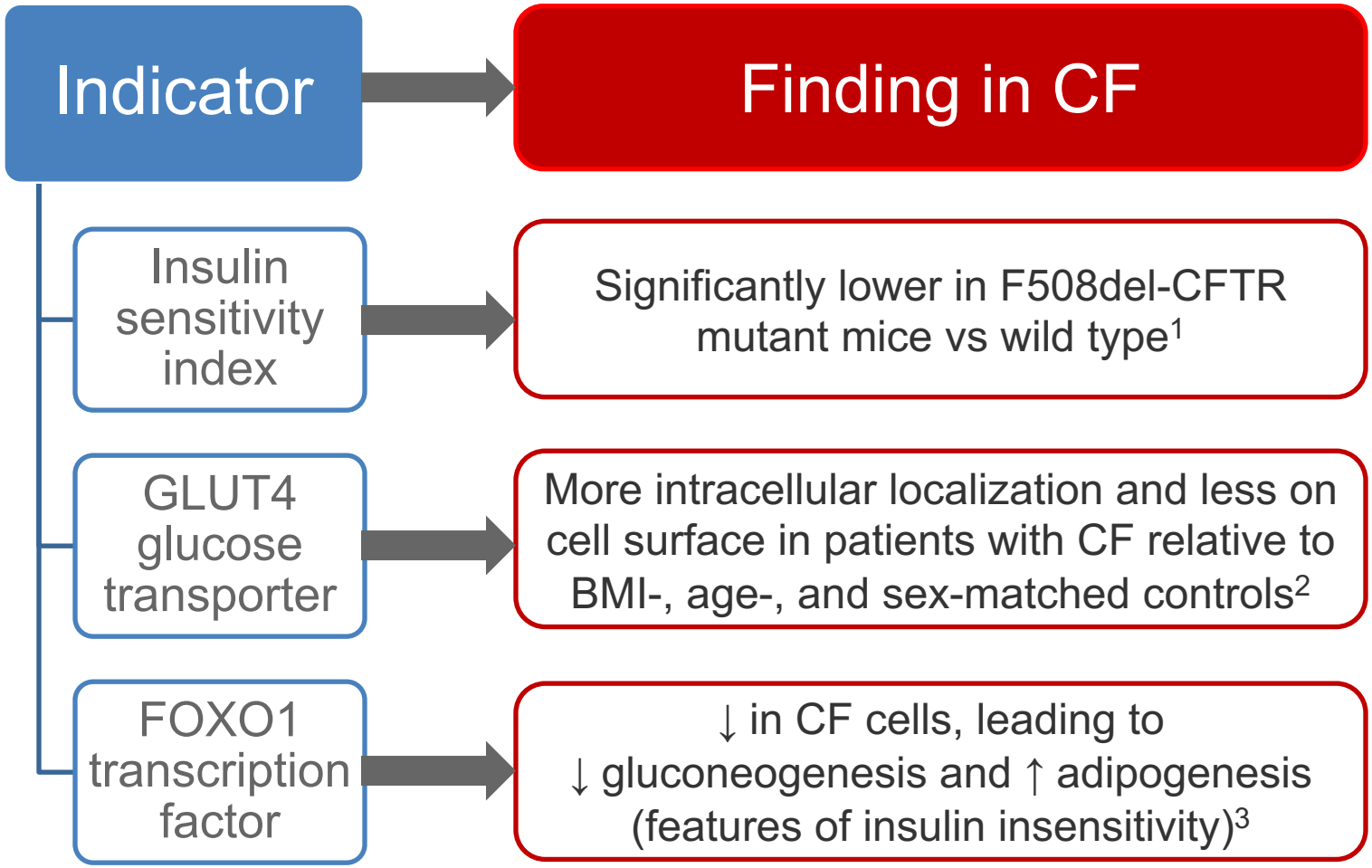
- ↑ pro-inflammatory TNF-α in insulin-resistant subjects[1]
- ↑ insulin in patients with type 2 diabetes with infusion of synthetic antibodies to TNF-α[1]
- Higher TNF-α levels in subjects with CF with IGT or CFRD than in subjects with CF with NGT (*P*=NS)[1]
- Collectively, studies indicate insulin resistance in the setting of acute pulmonary illness[2]

Serum TNF-α levels are elevated in CF[1]



1. Hardin DS et al. *Am J Physiol Endocrinol Metab*. 2001;281(5):E1022-E1028. 2. Barrio R. *Eur J Endocrinol*. 2015;172(4):R131-R141.

Some Evidence Suggests a Defective Peripheral Insulin Response in CF



1. Fontés G et al. *Diabetes.* 2015;64(12):4112-4122. 2. Hardin DS et al. *Am J Physiol Endocrinol Metab*. 2001;281(5):E1022-E1028. 3. Smerieri A et al. *Int J Mol Sci.* 2014;15(10):18000-18022.