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Cystic Fibrosis-Related Diabetes – An Update

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The prevalence of cystic fibrosis-related diabetes (CFRD) has increased in parallel with the improved survival of patients with CF.¹ Although initially thought to be benign,² the emergence of microvascular complications, as well as an association with declining pulmonary function and increased mortality has shifted the assessment of CFRD. This issue of *Endocrinology Rounds* describes the classification, diagnosis, pathogenesis, epidemiology, and natural history of this entity. Evidence regarding management, including screening, is reviewed and the most recent recommendations are summarized.

Classification and diagnosis

The Canadian Diabetes Association (CDA) classifies CFRD under "Other specific types; Diseases of the pancreas;"³ however, the Cystic Fibrosis Foundation Consensus Conference Report recognizes 4 categories of glucose tolerance (Table 1).⁴ Employing the same diagnostic criteria of various professional bodies, including the CDA,³ the report makes a distinction between CFRD with and without fasting hyperglycemia. The consensus committee recognized that although these criteria are associated with microvascular complications in type 1 and type 2 diabetes (T1- T2DM), this is yet unknown in CFRD.

Pathogenesis

Mutations in the CF transmembrane regulator (CFTR) result in structural and, subsequently, functional abnormalities in the exocrine and endocrine pancreas. These are compounded by various other factors unique to CF that also have an impact on glucose metabolism.

Structural abnormalities

Mutations in the CFTR, a chloride channel, result in viscous secretions throughout the body. In the pancreas, these mutations cause ductal obstruction with progressive fatty infiltration and fibrosis;⁵ further, amyloid deposition produces a destruction and derangement of islet architecture and composition,⁶ with a reduction in both alpha and beta cells, but a relative increase in delta cells.⁷⁻⁹

Functional abnormalities

Insulin deficiency: In parallel with structural islet disruption, pancreatic insulin secretion and beta-cell function are impaired. Insulin deficiency arises not only from the reduced beta-cell mass of islet destruction, but also from reduced beta-cell function. Even CF patients with normal glucose tolerance have delayed and reduced peak insulin levels compared with healthy controls.¹⁰ Both impaired glucose tolerance (IGT) and CFRD are characterized by decreased first-phase insulin secretion;¹¹ however, patients with IGT maintain normal total insulin secretion (via prolonged secretion), while those with CFRD have reduced total insulin secretion.¹²

Histological studies demonstrate that the reduction in islet number is correlated with the degree of insulin secretion;⁸ however, it is not correlated with the clinical appearance of CFRD.⁶ This suggests that there is an involvement of other etiologic factors in the progression from normal glucose tolerance (NGT) to CFRD, eg, insulin resistance.

Insulin resistance: Insulin resistance is increased in patients with CFRD,¹³⁻¹⁵ but the evidence is less clear in those with NGT and IGT. Some studies,^{11,15,16} but not all,¹³ demonstrate insulin resistance in patients with both IGT and NGT. One possible explanation is the dependence of insulin sensitivity on various factors, such as ongoing inflammation and infection; for example, erythrocyte sedimentation rate (ESR; an index of inflammation) correlates positively with glycated hemoglobin (HbA_{1c}) and negatively with insulin sensitivity.¹¹ In addition, insulin resistance measured by hyperinsulinemic euglycemic clamp may have underestimated the degree of



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Table 1: Classification of glucose tolerance in patients with CF, based on a maximum 75-g oral glucose tolerance test (OGTT)

Category	Fasting plasma glucose (mmol/L)	2-hour plasma glucose (mmol/L)
Normal glucose tolerance	<7.0	<7.8
Impaired glucose tolerance	<7.0	7.8-11.1
CFRD without fasting hyperglycemia	<7.0	≥11.1*
CFRD with fasting hyperglycemia	≥7.0**	OGTT not necessary

* or casual glucose ≥11.1 mmol/L on ≥2 occasions with symptoms
 ** on ≥2 occasions, or on 1 occasion with a casual glucose ≥11.1 mmol/L
 CFRD = cystic fibrosis-related diabetes

insulin resistance in those with CF because hepatic glucose production had not been completely suppressed.¹³

Other factors affecting glucose metabolism

Given the multisystemic nature of CF, numerous factors contribute to this complex glycemic picture, such as: malnutrition, malabsorption, abnormal intestinal transit time, increased work of breathing, elevated energy expenditure, glucagon deficiency, acute and chronic infection, medications (eg, glucocorticoid therapy), as well as liver dysfunction.

In summary, progressive pancreatic insult and subsequent beta-cell destruction result in a progressive defect in insulin secretion, which, although initially compensated, may be unmasked by increases in insulin resistance from infection, medications, or other unknown etiologic factors.

Epidemiology

Prevalence

The prevalence estimates of CFRD vary according to data source, with registry data likely underestimating the prevalence compared with prospectively screened populations. The Cystic Fibrosis Foundation Patients Registry Annual Data Report 2006¹ identifies an overall prevalence of CFRD and glucose intolerance of 19.5%, which rises with increasing age (Figure 1a).

The prevalence of CFRD in prospectively screened populations is even greater; for example, a large CF centre in the United States (US) reported diabetes prevalence rates of 9%, 26%, 35%, and 43% in patients aged 5-9, 10-19, 20-30, and >30 years, respectively.¹⁷ Most recent estimates, from a French centre (Figure 1b) are even higher.¹¹

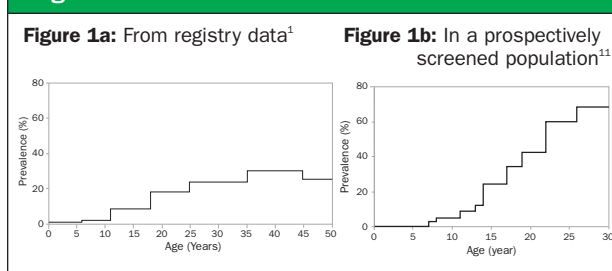
Incidence

Similarly, incidence increases with age. Patients aged 10 years and 20 years have annual rates of 5% and 9.3%, respectively, and the average annual incidence rate is 3.8%. Diabetes is diagnosed at a median age of 21, with the earliest at age 3 and oldest at age 40.¹⁸

Risk factors

In addition to increasing age, female sex and pancreatic insufficiency may be risk factors for CFRD. Girls were found to have an earlier age of onset than boys (17 years vs 21 years),¹⁸ and may generally have a higher risk for diabetes.¹⁹⁻²¹ Those with pancreatic insufficiency, defined by the

Figure 1: Prevalence estimates of CFRD



use of pancreatic enzymes, had a higher prevalence of CFRD than those without (15.0% vs 5.7%).²⁰

Clinical presentation

The clinical presentation of CFRD is insidious; at the initial diagnosis of diabetes, symptoms of hyperglycemia were present in only 33% of patients;¹⁸ in addition, CFRD symptoms and signs, other than polyuria and polydipsia, mimic those of CF. These symptoms include poor weight gain, poor growth velocity, delayed progression of puberty, and an unexplained chronic decline in pulmonary function;¹³ in fact, the latter has been observed to occur for years prior to the diagnosis of CFRD. Diabetic ketoacidosis is rare and, presumably, is secondary to residual insulin secretion and glucagon deficiency; only 2 cases were found in the literature in patients who had concurrent T1DM, despite hyperglycemic levels of up to 64 mmol/L.^{2,22} Finally, although there is a theoretical concern about susceptibility to hypoglycemia, severe hypoglycemia is rare²³ and recovery from insulin-induced hypoglycemia is normal (the poor glucagon response is compensated for by an increased catecholamine response).¹²

Progression of glucose intolerance

CFRD is characterized by intermittent hyperglycemia between periods of normoglycemia; for example, 58% of subjects diagnosed with IGT on an oral glucose tolerance test (OGTT) had NGT at the next annual test.¹⁸ However, those with IGT had a 5.6-fold greater risk of developing diabetes than those with NGT.¹⁸ Similarly, subjects with CFRD will eventually progress to fasting hyperglycemia; the percentage of CFRD patients with fasting hyperglycemia increases from <30%, to 45%, 60%, and 100% with the increasing duration of diabetes (<2 years, 2-5 years, 5-10 years, and >14 years, respectively).²⁴

Diabetes-related complications

Microvascular complications: Although initially thought to be uncommon,² the existence of microvascular disease in conjunction with CFRD is gaining increasing attention; in small studies (19-62 subjects),^{2,25-27} prevalence ranged from 5%-36% for retinopathy, 5%-16% for nephropathy, and 5%-21% for neuropathy. The largest study (n=285; mean age = 30 years, average duration of diabetes = 4.7 years) found that 22% had an elevated microalbumin-to-creatinine ratio, 19% had retinopathy, 34% had cardiac autonomic neuropathy (assessed by heart-rate variability), and 17% had somatic neuropathy (defined by decreased sensation, sural amplitude, or nerve-conduction velocity).²⁴

Gastrointestinal symptoms (including gastroesophageal reflux, gastroparesis, constipation, and nocturnal diarrhea) were found in 51%, although these symptoms can result from CF alone. Nevertheless, these complications were found only in those with fasting hyperglycemia and CFRD durations of >5 years; in addition, those with complications had significantly higher HbA_{1c} than those not developing complications (7.2% vs 5.9%). Recently, van den Berg et al²⁸ compared microvascular complications and their risk factors in CFRD and T1DM, in 79 patients, matched for sex, age (mean age=31 years), and duration of insulin therapy (mean duration = 6.6 - 6.9 years). Compared with T1DM patients, those with CFRD had significantly more microalbuminuria (21% vs 4.1%), but similar macroalbuminuria (1%), less retinopathy (10% vs 24%), and similar neuropathy on monofilament testing (2%-3%). Patients with CFRD had significantly lower total cholesterol (3.6 mmol/L vs 4.6 mmol/L), and prevalence of smoking (0% vs 32%), and slightly lower HbA_{1c} levels (6.8% vs 7.4%). Cholesterol/high-density lipoprotein (HDL) ratio, and diastolic and systolic blood pressures (BPs) were similar in both groups. While the prevalence of microalbuminuria was comparable, retinopathy and neuropathy appeared lower in the subsequent study, likely due to differences in ascertainment and definitions of retinopathy and neuropathy.

Macrovascular complications: Although macrovascular complications of CF are generally unknown (and previously thought to be reduced),²⁹ 3 case reports have emerged³⁰⁻³² of coronary artery disease in patients with CF, one of whom had CFRD.³⁰ The first case was a 41-year-old woman with CFRD complicated by gastroparesis, retinopathy, and neuropathy; after succumbing to respiratory failure, on autopsy the patient was incidentally found to have generalized atherosclerosis.³⁰ The cardiac risk factors included a total cholesterol level of 5.1 mmol/L and progressive hypertension with biopsy-proven nephrosclerosis at age 31. The second case was a 40-year-old asymptomatic man who was found incidentally to have segmental hypokinesia with grade 2 systolic function on a thallium perfusion scan performed as part of a research study.³¹ Further details regarding other cardiac risk factors were not reported. The third case was a 52-year-old man presenting with exertional dyspnea, who was found to have a reversible anteroseptal perfusion defect on thallium stress testing and confirmed by angiography, demonstrating severe and diffuse disease.³² The patient was a lifelong nonsmoker, with no diabetes (HbA_{1c} 5.1%), or dyslipidemia (total cholesterol 3.56 mmol/L, low-density lipoprotein [LDL] 2.05 mmol/L, HDL 0.77 mmol/L, and triglycerides 0.85 mmol/L).

Cardiac risk factors

Dyslipidemia: Despite high total and saturated-fat intake (representing 33.0% and 16.8% of energy intake, respectively) and enzyme supplementation, CF patients with pancreatic insufficiency had low to normal cholesterol levels.³³⁻³⁴ Mean total cholesterol ranged from 3.57-3.77 mmol/L, and mean total triglycerides ranged from 1.30-1.51 mmol/L.^{34,35} Compared with healthy controls, adults with CF had significantly lower mean total cholesterol levels (men: 3.1 mmol/L vs 4.7 mmol/L; women: 3.2 mmol/L vs 4.3

mmol/L);³⁶ however, those free of pancreatic insufficiency had serum cholesterol levels in the high normal range.

BP: Low BP characterizes CF and is ascribed to salt loss through perspiration secondary to the CFTR mutation. Legris et al³⁷ found that, compared with controls, those with CF had lower mean BP, further enhanced by experimental salt depletion, despite compensatory increases in plasma renin, aldosterone, and angiotensin. A subsequent study³⁸ suggested a possible gene dosage effect; compared with control subjects, carriers of a CF mutation had lower systolic BP and a slower rise in BP with age, with perspiration sodium and chloride levels highest in those CF carriers with the lowest BP.

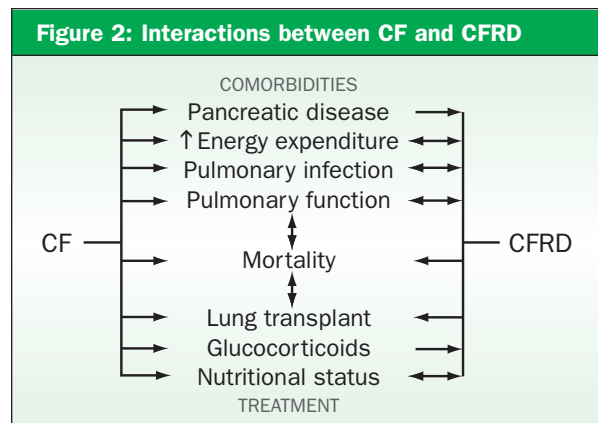
Smoking: Estimates of smoking prevalence vary from 0% to 11% in adult populations^{28,39,40} and 21% in an adolescent population.⁴¹

Chronic inflammation: CF lung disease is characterized by cycles of impaired airway clearance, chronic endobronchial infection, and exuberant inflammation, as evidenced by increased production of proinflammatory mediators including interleukin (IL)-8⁴² and tumour necrosis factor-alpha (TNF- α),¹⁵ as well as elevations in acute-phase reactants, such as ESR.¹¹ The significance of these risk factors in the development of macrovascular disease is not yet known in the CFRD population; however, as survival improves, premature macrovascular disease may become an important comorbidity in people with CFRD. Greater attention to risk factor modification and recognition of cardiac causes in the presentation of the patient with CF will be warranted as this population ages.

Impact of CFRD on CF

In addition to these typical complications, one must also consider the complex interactions between CFRD and CF (Figure 2), including the sequelae of diabetes on important CF outcomes. When considering the pathogenesis of these outcomes, the glycemic paradigm of insulin deficiency must be expanded to include the anabolic effect of insulin on lipid and protein metabolism. In the setting of a CF patient with diabetes, insulin deficiency promotes a state of chronic protein catabolism,^{43,44} resulting in reduced growth,¹¹ respiratory muscle wasting with subsequent decreased lung function, and increased mortality.

Decreased lung function: CF patients with diabetes have poorer lung function than those without diabetes.^{20,45}



The decline of pulmonary function can be seen over the 2- to 4-year period prior to the diagnosis of CFRD,^{23,46,47} and is directly proportional to the severity of glucose intolerance and the degree of insulin deficiency.⁴⁸ Patients with CFRD had more pulmonary exacerbations requiring treatment with parenteral antibiotics, compared with those without diabetes (1.55/year vs 0.78/year) and a greater prevalence of *Burkholderia cepacia* complex (10.3% vs 5.2%),²⁰ which in CF is also associated with accelerated deterioration of pulmonary function and shortened survival.⁴⁹ Significantly, observations in this population on the early appearance of impaired glucose metabolism (defined as age <15 years for IGT and <18 years for diabetic OGTT) was associated with a higher rate of lung transplantation.¹¹

Increased mortality: CFRD is also associated with increased mortality and decreased survival. A retrospective study of 448 patients reported that <25% of patients with CF and diabetes survived to age 30 years, contrasting with 60% in those without diabetes.⁴⁶ Interestingly, Milla et al⁵⁰ found that, compared with non-CFRD subjects, median survival of women with CFRD, but not men, was reduced (women: 47.0 years vs 30.7 years; men: 49.5 years vs 47.4 years). Patients with fasting hyperglycemia and early onset of dysglycemia are of particular concern, since in those with fasting hyperglycemia, death is 4-fold more prevalent (no sex difference).²⁴ The appearance of OGTT before age 15 and of CFRD before age 18 is associated with a lower rate of survival.¹¹ Thus, in addition to the multiple microvascular and potential macrovascular complications, the significant impact it has on important health indicators and outcomes in CF reveal CFRD as a consequential clinical entity in the assessment and management of CF.

Management

Consensus guidelines

There are no recommendations specific to CFRD from the CDA or the American Diabetes Association (ADA), nor the Canadian or American Thoracic Societies. The Cystic Fibrosis Foundation convened a consensus conference in 1998 to define standards of care for diagnosis, screening, and management of CFRD.⁴ In the absence of a reliable evidence base, many recommendations were extrapolated from the T1 and T2DM literature of the ADA, and tailored to the unique clinical characteristics of this population.

Healthcare delivery and screening

The patient with CFRD should be cared for by an experienced multidisciplinary team, including physicians (respirologist, endocrinologist, gastroenterologist, etc), diabetes nurse educators, dietitians, and social workers.⁴

The consensus report recommended screening asymptomatic individuals with an annual casual glucose measurement, followed by a fasting plasma glucose if >7.0 mmol/L, and symptomatic individuals with a 75-g OGTT.⁴ However, casual as well as fasting plasma glucose are poorly sensitive; for example, one

study found that at diagnosis of diabetes, fasting hyperglycemia (≥ 7.8 mmol/L) was seen in only 16%.¹⁸ Thus, various investigators and CF centres recommend screening with the OGTT.^{18,51-53}

Other screening tests: Although the 50-g glucose challenge test was highly sensitive (100%), it was poorly specific (50%).⁵⁴ Similarly, HbA_{1c} levels (>6.0%-6.4%) had a sensitivity of only 16%-50% when compared with a 75-g OGTT.¹⁸⁻⁵⁴

Glycemic control

Glucose targets: Large-scale epidemiologic studies to identify a threshold glycemic target for reducing complications in CFRD are lacking. However, some evidence suggests that tighter glycemic control is associated with reduced complications. In the absence of data specific to the CFRD population, the consensus report adopted the ADA glycemic goals for T1 and T2DM targeting preprandial glucose of 5-7 mmol/L, postprandial glucose of <10 mmol/L, and HbA_{1c} of <7%.⁵⁵

Monitoring: No studies have specifically examined the role of capillary blood glucose self-monitoring (SMBG) in the CFRD population. The consensus report recommends SMBG at least 3-4-times/day, including postprandial and monthly early morning assessments.⁴ HbA_{1c} measurements in those with CFRD may represent an underestimate of mean blood glucose levels, secondary to decreased red-blood-cell turnover time;⁵⁶ however, it continues to be used in clinical practice and research.

Lifestyle modification of nutrition and physical activity: Since CF is characterized by fat malabsorption, protein catabolism, and high energy expenditure, a high-fat (35%-40% of energy), high-protein (15%-20% of energy) diet of 120% of the usual recommended daily intake is suggested.⁴ In order to optimize glycemic control, complex carbohydrates should be spread evenly throughout the day⁵⁷ and salt intake is not restricted. Although aerobic exercise enhances pulmonary function,⁵⁸ there are no studies to date regarding the role of physical activity specifically in the management of CFRD.

Antihyperglycemic agents: While some CF centres use oral medications, insulin therapy is the recommended and most widely used treatment method.⁵⁹ A recent Cochrane systematic review identified an absence of randomized, controlled trials assessing both the efficacy and adverse effects of insulin and other antihyperglycemic agents in the management of CFRD, and thus the need for such a trial.⁵⁹ In the absence of data, the consensus report recommends insulin therapy be used in the management of diabetes, reserving oral agents only in the context of a controlled trial.⁴ Many practical and theoretical concerns limit the use of oral agents in the management of CFRD, including risk of lactic acidosis, binding to the CFTR, risk of hepatotoxicity, and worsening of malabsorption with the use of biguanides,⁶⁰ sulphonylureas,^{61,62} thiazolidinediones,⁶⁰ and alpha-glucosidase inhibitors,⁶³ respectively; non-sulphonylurea secretagogues such as

repaglinide have been used⁶³ with the benefit of addressing postprandial hyperglycemia.

Experience with insulin therapy: Not only does insulin use result in reduced postprandial glycemic excursions and HbA_{1c},⁶⁴ it may also play a role in protein metabolism affecting nutritional status and lung function. Two retrospective, longitudinal studies of 14 and 18 patients with CFRD described a reversal of the decline in body mass index (BMI) with the initiation of mixed insulin twice daily or a combination of intermediate- and short-acting insulin once or twice daily.^{23,65} Concurrent with insulin initiation and improvement in BMI, these studies also demonstrated a reversal in respiratory-function decline. A prospective study of 6 patients supported these findings, documenting a decline in BMI, forced expiratory volume in 1 second (FEV₁), and clinical score, coincident with the development of impaired first-phase insulin response; all measures were subsequently reversed with the initiation of twice-daily mixed insulin therapy.⁶⁶

The biologic mechanism for these observations is likely multifactorial, but may include the favourable effects of insulin therapy on protein metabolism and reductions in lung infection. A study of 28 patients with CFRD demonstrated a significant improvement in net protein synthesis 3 months after the initiation of insulin therapy,⁶⁷ further, the percentage of sputum examinations positive for *Haemophilus influenzae* and *Streptococcus pneumoniae* decreased in the diabetic patients.⁶⁵ Finally, the initiation or addition of the basal insulin, glargine, to a prandial short-acting insulin regimen was found to reduce the number of lung infections in 8 patients with CFRD.⁶⁸ Based on these data, some investigators suggest that insulin therapy should be started when diabetes mellitus is diagnosed.⁶⁵

Screening for complications

Microvascular complications: Due to the high prevalence of microvascular complications, investigators recommend annual screening for complications after a known diabetes duration of 5 years in patients with CFRD and fasting hyperglycemia, as well as immediate screening for new-onset diabetes of unknown duration.^{24,28} The consensus report recommends screening at the time of initial diagnosis, with examinations of the feet, annual dilated eye examinations, and annual urine albumin measurement.⁴

Macrovascular complications, cardiac risk-factor identification and modification: Adult CF patients have survived to an age where coronary artery disease becomes prevalent.¹ The case reports³⁰⁻³² suggest that coronary disease should be included in the differential diagnosis of persistent dyspnea associated with chest discomfort as in non-CF patients, paying careful attention to cardiac risk factors. Although the consensus report makes no specific recommendations regarding screening for macrovascular disease, beginning at the time of diagnosis, it recommends regular measurements of BP, as well as the baseline fasting lipid profile after metabolic control is achieved, and subsequent assess-

ments only if abnormal or in the presence of a family history of dyslipidemia or cardiovascular disease. Other than 1 case report where acetylsalicylic acid was used for stroke secondary to paradoxical embolism from an indwelling intravenous catheter,⁶⁹ there are no other studies of antiplatelet, lipid-lowering, or antihypertensive therapy in primary or secondary prevention of macrovascular disease in this population.

Summary

CFRD, resulting from progressive pancreatic damage and insulin deficiency, is an insidious but common complication of CF. It is initially characterized by intermittent glucose intolerance and progresses to overt diabetes with fasting hyperglycemia. Initially thought to be benign, the increasing lifespan has unmasked a similar prevalence of microvascular complications, the emergence of macrovascular disease, as well as a negative impact on nutritional status, lung function, and mortality. Given these implications, aggressive screening may be warranted; microvascular complications should be screened for, as in other diabetes populations, and cardiac risk factors should be identified. While insulin therapy is by consensus the standard of care, further studies are needed to elucidate its role in CF outcomes, as well as the role of oral agents. Further studies on the impact of diabetes and the development of complications will guide clinicians regarding optimal therapy.

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