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Chapter

Detection and Management of Early Glucose Abnormalities in Cystic Fibrosis

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Abstract

With advances in technology, it is now possible to detect the emergence of glucose abnormalities in cystic fibrosis with improved sensitivity, and from a very early age. These abnormalities are increasingly recognized as predictors of clinical decline, raising the possibility that early intervention may slow or prevent this deterioration. In this chapter, we will review the available literature on methods of detecting glucose abnormalities in cystic fibrosis (random and fasting glucose, HbA_{1c}, oral glucose tolerance testing, and continuous glucose monitoring), and detail their advantages and possible limitations in the interpretation of glycemic data. We will also discuss treatment outcomes of early intervention, prior to the diagnosis of diabetes as currently defined.

Keywords: cystic fibrosis-related diabetes, glucose, insulin, abnormal glucose tolerance, indeterminate glycaemia, impaired glucose tolerance, oral glucose tolerance test, continuous glucose monitoring

1. Introduction

Historically, cystic fibrosis (CF) caused fatal respiratory failure in early childhood [1, 2], but proactive multidisciplinary care has increased life expectancy to ~44 years [3]. With longer survival, co-morbidities have become more prevalent, the commonest being cystic fibrosis-related diabetes (CFRD) [4, 5]. This is associated with poorer clinical status [6–21], quality of life [22, 23], and life expectancy [16, 24, 25] relative to non-diabetic CF patients.

CFRD is distinct from other diabetes mellitus etiologies, including type 1 (T1D) and type 2 (T2D) (see **Table 1**) [4, 5]. It is caused primarily by chronic pancreatitis [26–30] with progressive insulin deficiency [9, 11, 31], particularly during first-phase insulin secretion [8, 9, 11, 19, 32–40]. Variations in peripheral insulin sensitivity also contribute to CFRD [20, 41]; hyperglycemia progressively induces insulin resistance via downregulation of glucose transporters [42–44], and insulin sensitivity decreases with inflammation, use of exogenous glucocorticoids, and puberty [45–49]. In CF, the depleted and dysfunctional pancreatic β-cells may be unable to compensate for this, producing early intermittent hyperglycemia progressing to fasting hyperglycemia [35, 44, 50].

	Type 1 diabetes	Type 2 diabetes	CFRD
Prevalence	0.2%	11%	35% (likely underestimated due to lack of testing)
Onset	Usually acute	Insidious	Insidious
Peak age of onset	Childhood or adulthood	Adulthood	Ages 18–24
Usual body habitus	Normal	Overweight	Underweight, normal, or sometimes overweight (due to CF therapy success)
Likely pathophysiology	β-cell dysfunction & destruction, primarily autoimmune with genetic & possible environmental causes	Peripheral insulin resistance & subsequent β-cell stress	β-cell destruction due to inspissated pancreatic secretions, inflammation, and replacement with fibrosis & amyloid, plus a component of β-cell dysfunction
Insulin deficiency	Nearly complete	Partial and variable	Severe but not complete
Insulin resistance	Variable	Severe	Variable depending on circumstances (e.g. glycemic control, pubertal stage, use of glucocorticoids, inflammation)
Ketoacidosis risk	High	Low	Low
Pharmacological & dietary therapy	• Insulin • Dietary monitoring to ensure appropriate insulin dosage	• Insulin or oral anti-hypoglycemics • Low-calorie, low-carbohydrate, low-fat diet	• Insulin • Continuation of CF-specific diet, designed to prevent wasting: high-calorie, high-carbohydrate, high-fat
Complications	Microvascular & macrovascular disease	Microvascular & macrovascular disease	• Decline in nutritional status & lung function, associated with early mortality • Microvascular disease
Likeliest cause of death	Macrovascular disease	Macrovascular disease	CF pulmonary disease

Table 1.
Comparison of common etiologies of diabetes. Adapted from Moran et al. [4].

CFRD is usually preceded by a spectrum of abnormal glucose tolerance (AGT) on oral glucose tolerance testing (OGTT), including impaired fasting glucose (IFG), indeterminate glucose tolerance (INDET), and impaired glucose tolerance (IGT) [4, 51]. There may be 'waxing and waning' of glucose tolerance between these categories [19, 52–55], probably due to variations in insulin sensitivity [35, 44]. Nevertheless, large prospective cohort studies report overall deterioration in CF patients' glucose tolerance over life [16, 20, 53, 54, 56]. The date of onset of CFRD is considered to be the first time a patient meets diagnostic criteria, even if glucose abnormalities subsequently resolve due to improvement in insulin sensitivity [4]. This is because studies utilizing this definition report correlations between CFRD duration, microvascular disease prevalence [57], and mortality [16, 56].

Taken together, these factors explain why CFRD becomes more common with age. Prevalence is ~1.5% in CF patients aged <10 years, but ~15% in those aged 11–17 and ~50% in those aged ≥18 [8, 16, 58]. The American Diabetes Association (ADA) recommends annual screening from age 10, using 2-h OGTT [59]. CFRD can also be diagnosed using clinical status, random blood glucose, fasting plasma

glucose, and glycated hemoglobin (HbA_{1c}) [4, 60, 61]. In clinically-stable outpatients with CF, diagnostic criteria are identical to those used for other etiologies of diabetes mellitus [4], and are shown in **Table 2**. Recently, continuous glucose monitoring (CGM) has also been used to investigate glucose abnormalities in CF patients. This method is not yet widely recommended for diagnosis of diabetes, but it is often used to monitor glycemic control or assist insulin dosage [62]. Moreover, CGM often detects even earlier CF-related glucose abnormalities than OGTT, in the form of intermittent postprandial glucose excursions [63].

This chapter compiles research on use of each glucose measurement method in CF patients, with special focus on pre-diabetic patients. The benefits and limitations of each method will be explored to help ascertain when their usage might be appropriate. In the process, we will examine correlations between early glucose abnormalities and clinical decline. Finally, we will review preliminary evidence of improved long-term outcomes with insulin treatment of early glucose abnormalities, supporting their detection and management in routine practice.

Glucose measurement method	**Diagnostic criteria**		
	Normal ranges	**Pre-diabetic ranges**	**Diabetic ranges**
Clinical status	Classical symptoms of hyperglycemia, including polyuria, polydipsia, and hyperglycemic crisis, may assist diagnosis of diabetes when combined with other positive diagnostic tests. Some CF-specific definitions also consider unexplained decline in lung function & nutritional status to be classical symptoms.		
HbA_{1c}	≤5.6% (38 mmol/mol)	5.7–6.4% (39–46 mmol/mol)	≥6.5% (48 mmol/mol)
Random blood glucose	—	—	≥11.1 mmol/L (200 mg/dL)
Fasting plasma glucose	<5.6 mmol/L (100 mg/dL)	**IFG:** ≥5.6 mmol/L (100 mg/dL), <7.0 mmol/L (126 mg/dL)	≥7.0 mmol/L (126 mg/dL)
2-h OGTT	*0 min:* <5.6 mmol/L (100 mg/dL) *2 h:* <7.8 mmol/L (140 mg/dL)	All categories constitute **AGT** **IFG:** *0 min:* ≥5.6 mmol/L (100 mg/dL), <7.0 mmol/L (126 mg/dL) *2 h*: N/A **INDET:** *0 min:* <7.0 mmol/L (126 mg/dL) *OGTT midpoints:* ≥11.1 mmol/L (200 mg/dL) *2 h:* <7.8 mmol/L (140 mg/dL) **IGT:** *0 min:* <7.0 mmol/L (126 mg/dL) *2 h:* ≥7.8 mmol/L (140 mg/dL), <11.1 mmol/L (200 mg/dL)	*0 min:* ≥7.0 mmol/L (126 mg/dL) *AND/OR* *2 h:* ≥11.1 mmol/L (200 mg/dL)
CGM	Usually <7.8 mmol/L (140 mg/dL)	Elevations ≥7.8 mmol/L (140 mg/dL) are referred to as **glucose excursions**, but there are no standardized criteria correlating them with AGT or diabetes.	

HbA_{1c} = glycated hemoglobin. OGTT = oral glucose tolerance testing. IFG = impaired fasting glucose. AGT = abnormal glucose tolerance. INDET = indeterminate glucose tolerance. IGT = impaired glucose tolerance. CGM = continuous glucose monitoring.

Table 2.
Diagnostic criteria of glucose measurement methods commonly used in CF. Diagnosis must occur during clinical stability, defined as no pulmonary exacerbations during the past 6 weeks and no current systemic glucocorticoids. It is also recommended that any positive fasting plasma glucose, HbA_{1c}, or OGTT is repeated at a later date. Non-CGM diagnostic criteria are from the American Diabetes Association [59, 64]. CGM diagnostic criteria are from the Juvenile Diabetes Research Foundation Continuous Glucose Monitoring Study Group [65].

2. Benefits and limitations of conventional methods used to diagnose glucose abnormalities in CF

2.1 Clinical status and/or random blood glucose

The ADA allows diagnosis of CFRD following one random blood glucose measurement ≥11.1 mmol/L, provided that it is combined with polyuria, polydipsia, or hyperglycemic crisis [59]. However, symptomatic hyperglycemia or hyperglycemic crisis is extremely rare in CFRD [4]. In Lanng et al.'s seminal 5-year prospective cohort study of 191 CF patients receiving annual OGTT, only 33% of those diagnosed with CFRD had polyuria or polydipsia [54]. Moreover, in a cross-sectional study of all 60 patients aged ≥10 years at a Brazilian CF center, age at diagnosis was significantly lower for patients diagnosed using OGTT as opposed to clinical criteria (13.5 years vs. 22.3 years), implying much earlier detection of disease [66].

Some centers compensate by accepting unexplained decline in lung function or nutritional status as classical symptoms of hyperglycemia (see Section 3) [67]. In one cross-sectional study of 91 CF patients not known to be diabetic, these modified clinical criteria detected OGTT-diagnosed CFRD with 58% sensitivity [68], which is an improvement over other studies but still suboptimal for a screening test.

2.2 HbA_{1c}

HbA_{1c}, i.e. glycated hemoglobin as a percentage of total hemoglobin, is commonly used to monitor glycemic control in diabetes mellitus. It usually reflects average blood glucose over the life of an erythrocyte (~3 months) [64, 69]. However, CF patients with CFRD, INDET or IGT rarely have a significantly-higher HbA_{1c} than those with normal glucose tolerance (NGT) [11, 70–73], and even statistically-significant differences tend to be of <1% magnitude [8, 34, 40, 74, 75]. Godbout et al.'s study of 13 CFRD patients also found that HbA_{1c} did not correlate with mean plasma glucose, as calculated using fingerprick self-monitoring [76].

Numerous hypotheses have been espoused to explain HbA_{1c}'s relatively poor correlation with glucose tolerance in CF. These include insufficient duration of transient CF-related post-prandial hyperglycemia, which is often limited to the early phase of insulin secretion; alteration of hemoglobin glycation by hypoxia; iron deficiency, which is a common comorbidity of CF; and increased erythrocyte turnover in the context of chronic inflammation [1, 4, 5, 76, 77]. This implies that HbA_{1c} may vary with degree of inflammation [78], and that *trends* in HbA_{1c} may be more useful for predicting deterioration in glucose tolerance. Supporting this, Lanng et al.'s 5-year prospective cohort study found significant differences in median HbA_{1c} between patients who consistently had NGT (5.2%), patients who varied between NGT and IGT (5.3%), patients who developed CFRD during the study (5.8%), and patients who entered the study with a diagnosis of CFRD (6.5%) [54].

It has also been hypothesized that poor correlation between mean plasma glucose and HbA_{1c} may be confounded by use of fingerprick tests to measure glucose, since these can easily miss CF-related hyperglycaemic peaks due to their relative infrequency [76]. In two studies of CF and CFRD patients, mean plasma glucose was estimated using 2–7 days of CGM rather than fingerprick self-monitoring, and strongly correlated with HbA_{1c} (r = 0.86–0.89) [75, 79].

These findings have regenerated interest in potentially using HbA_{1c} to screen for CF-related glucose abnormalities, especially because it is much more convenient than OGTT. However, computing HbA_{1c} thresholds suitable for CFRD screening has proved challenging. Some studies do report almost 100% sensitivity for OGTT-defined CFRD using HbA_{1c} thresholds of 6.0–7.5% [40, 80–82], but all have small

sample sizes, and most either did not calculate sensitivity to CF-related AGT [81] or report low values, ~20–50% [80, 82]. Therefore, HbA_{1c} may not detect CFRD and its complications until late. Moreover, most evidence suggests that the diagnostic threshold for CFRD, HbA_{1c} ≥6.5%, has poor sensitivity compared to OGTT [54, 83–85].

Lowering the diagnostic threshold for HbA_{1c} abnormalities does increase sensitivity to both CFRD and AGT, but the thresholds required to achieve sufficient sensitivity for screening generally have unacceptably low specificity [60]. There is also wide variation in the sensitivities and specificities reported by different studies using the same HbA_{1c} threshold; this may be due to differences in type of HbA_{1c} assay [74, 86] and timing of the studies relative to the institution's routine OGTT screening [87]. Yung et al., conducting a cross-sectional study of 91 CF patients not known to be diabetic, but also not previously routinely screened, found that HbA_{1c} ≥6.1% had 83% sensitivity for OGTT-diagnosed CFRD [68]. However, more recent studies with similar designs report only 30–50% sensitivity [39, 82, 88, 89].

Given this uncertainty, the current advice from the ADA is that HbA_{1c} should not be used to screen for CF-related glucose abnormalities [59]. HbA_{1c} is still recommended for monitoring glycemic control in CFRD, although normal results must be interpreted with caution [4, 78]. It has also been suggested that HbA_{1c} might be a useful adjunct to OGTT in screening, as its results may fluctuate less and hence, may more accurately predict long-term risk of glucose abnormalities. In a recent 6-year retrospective cohort study of 50 NGT adults with CF followed up with annual OGTT, HbA_{1c} ≥5.6% had OR 3.49 for development of IGT or CFRD [90].

2.3 Fasting glucose

In 2003, the ADA briefly sanctioned fasting plasma glucose as an alternative to OGTT in CFRD screening, because there were insufficient data supporting insulin therapy for CFRD without fasting hyperglycemia [91]. However, subsequent studies have demonstrated similar insulin-induced clinical improvements in patients with and without fasting hyperglycemia [16, 92], and treatment of CFRD without fasting hyperglycemia is now standard practice [4]. Only 16–25% of patients diagnosed with CFRD on OGTT have fasting hyperglycemia [8, 54, 68, 81].

Use of fasting glucose to detect pre-diabetic stages on the glucose tolerance spectrum remains somewhat contentious in CF. Most studies report that fasting plasma glucose does not significantly differ between CF patients with NGT, INDET or IGT [39, 72, 93]. The ADA does use fasting glucose to define one pre-diabetic glucose tolerance category, IFG (5.6–6.9 mmol/L), and suggested in 2003 that screening OGTTs could be limited to IFG patients [94]. A prospective cohort study of 1128 CF patients aged 10–64 found that this approach would reduce number of OGTTs by 67%, but miss 17.8% of CFRD and IGT [94]. In a cross-sectional analysis of 73 children with CF, IFG had 100% sensitivity for CFRD, but only 25% sensitivity for IGT [11].

Finally, like HbA_{1c}, there is debate regarding the utility of IFG as an adjunctive test for predicting long-term risk of CFRD. Frohnert et al. found no significant relationship [95], but Schmid et al. found that IFG generated OR 2.72 for CFRD [96].

2.4 Oral glucose tolerance testing

As discussed above, other conventional diagnostic tests have <100% sensitivity for CFRD compared to OGTT. Therefore, OGTT remains the recommended screening test in CF. It is also the only test with standardized definitions of multiple pre-diabetic glucose abnormalities, all demonstrated to predict development of CFRD [96].

Nevertheless, there are several issues with the 2-h OGTT. It may be more inconvenient and resource-intensive than other glucose measurement methods, which is

of particular concern in CF because patients and clinics already face a high treatment burden from other aspects of CF care [97]. It also requires patient co-operation, which can be difficult when assessing children [93]. Patients are expected to consume at least 150 g (600 kcal) of carbohydrates for 3 days before an OGTT, then fast for 8 h overnight and be tested early the next morning [59]. They must drink a solution containing a 1.75 g/kg glucose load, preferably within 5 min, then lie or sit quietly for 2 h [64]. In a standard OGTT, venous blood is sampled twice: immediately before ingestion of the load, and at 120 min (BG_{120}). Many CF centers also take hourly or 30-minutely samples to detect post-prandial hyperglycemia that resolves before 2 h [59]. As described earlier, these transient post-prandial glucose excursions are very common in CF, due to selective impairment of early insulin secretion. Our group previously performed OGTT with 30-minutely sampling in 33 children with CF aged 10–19, and found that peak venous insulin concentration was delayed until 90–120 min, producing an early venous glucose peak at 60–90 min [9] (**Figure 1**).

The inconvenience of OGTT may contribute to poor patient uptake of CFRD screening [98–100]. In 2018, the Cystic Fibrosis Foundation Patient Registry reported that the average CF center was screening just 61.3% of adolescents and 32.8% of adults [100]. Rates of utilization of other glucose measurement methods, such as HbA_{1c} and fasting glucose, were much higher (92.3% for adolescents and 89.6% for adults), suggesting that the main barrier to screening is the OGTT itself [100]. Suggested solutions include shortening the OGTT to 60 or 90 min [83] or replacing it with the 50-g non-fasting 1-h glucose challenge test [89, 101], which is currently used to screen for gestational diabetes mellitus in healthy women [101]. These modified OGTT protocols are not standard recommended practice [4].

There are also other issues with the OGTT that likely cannot be resolved by simply shortening it. Its diagnostic thresholds are not specific to CF and may be insensitive to CF-related clinical decline (see Section 3). OGTT results also frequently fluctuate in CF, with a large multicenter prospective cohort study finding a variability coefficient 1.5–1.8 times higher than in the general population [55]. Similarly, in two 4–5 year prospective cohort studies, 18–58% of AGT patients demonstrated overall improvement in glucose tolerance category, while only 14–22% demonstrated deterioration [19, 54].

Finally, even with venous sampling at additional timepoints, the peak blood glucose measurements recorded during OGTT may poorly reflect peak blood glucose achieved by CF patients in daily life [4, 60, 61]. After all, the OGTT's 1.75 g/kg load contains less glucose than most CF patients' everyday meals [61, 98]. This has prompted research into CF-related glucose abnormalities using CGM, a technology that can screen for glucose excursions over a longer interval of everyday life and high calorie CF diet.

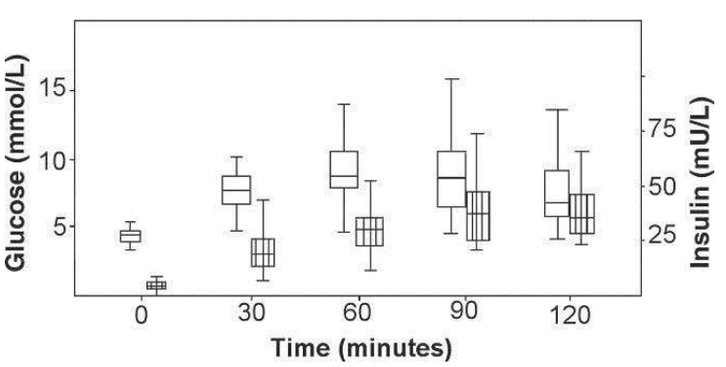

Figure 1.
Venous blood glucose (□) and insulin (▒) in 30-minutely samples over a 2-h oral glucose tolerance test, as measured in 33 children with CF aged 10–19. Boxes indicate interquartile range, horizontal lines indicate median, whiskers indicate 5th and 95th percentiles. Figure taken from Hameed et al. [9].

2.5 Continuous glucose monitoring

Most CGM systems consist of two parts: a sterile sensor, worn subcutaneously for up to 14 days, and a transmitter attached to the sensor that measures interstitial fluid glucose every 30 s, recording an average every 5 min [97] (**Figure 2**). Some systems do not require a separate sensor, instead measuring interstitial fluid glucose via an electrical current applied across intact skin, but issues have been reported with skin reactions and inaccuracy [102]. Interstitial fluid glucose reflects capillary glucose with a 4–20 min delay [103].

CGM has been validated against OGTT in children with CF of all glucose tolerance categories [104] and non-diabetic adolescents and adults with CF [105]. A subsequent study of this latter group found that they differed significantly from healthy controls in mean CGM glucose (+14.1%) and presence of CGM peaks ≥11.1 mmol/L (+33%), but not in the conventional diagnostic measures of fasting glucose, BG_{120}, and HbA_{1c} [106]. Moreover, 70% of CF patients undertaking simultaneous CGM and OGTT had their CGM peak *outside* OGTT [106]. This was the beginning of a substantial body of evidence demonstrating the superior sensitivity of CGM to CF-related glucose excursions above OGTT diagnostic thresholds, with numerous studies finding CGM glucose peaks ≥7.8 or 11.1 mmol/L in 71–93% of patients classified as NGT on recent OGTT [14, 31, 85, 98, 107, 108]. In a 5-year prospective cohort study of 21 adults with CF, 83% had their CGM peak and BG_{120} fall in different diagnostic categories, and for 93% the CGM-identified category was worse. Again, this suggests the superior sensitivity of CGM over OGTT [98].

Most of this evidence, particularly in children, is limited by small sample sizes [14, 85, 98, 107, 108] and lack of non-CF controls [14, 85, 98, 108]. However, it is logical that the increased duration and frequency of glucose monitoring facilitated by CGM, and the opportunity to incorporate the patient's usual diet and physical activity, facilitates more sensitive detection of glucose excursions [109]. CGM is also generally easier and better tolerated than OGTT [78]. While sensors and transmitters are expensive, and staff do require training on their usage, they have become more user-friendly, smaller and cheaper over time [73, 110]. The newest devices can be inserted rapidly during a clinic appointment, do not require calibration against fingerpricks, and can be removed by patients or carers without medical supervision [97].

CGM does have one major disadvantage compared to OGTT. The clinical significance of the mild glucose excursions that it detects are still being determined; consequently, there is no standardized system for recognizing and describing clinically relevant CGM findings, and no universally accepted threshold for initiation

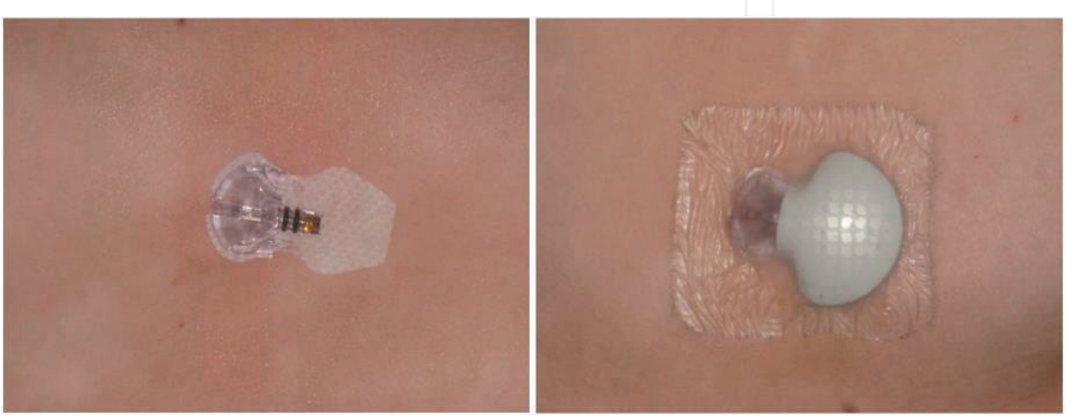

Figure 2.
Continuous glucose monitor sensor, before and after attachment of the transmitter. 'CGM set' and 'Continuous Glucose Monitor' by Sara Bassett are licensed under CC BY-NC-SA 2.0.

of treatment [97]. Common variables computed by CGM software include average sensor glucose, maximum glucose, area under the curve of glucose per day ($AUC_{glucose}$/day), percentage time spent above thresholds (e.g. 7.8 or 11.1 mmol/L), number of excursions ≥11.1 mmol/L, and measures of glycemic variability, such as standard deviation of average sensor glucose [103]. All these parameters have been correlated with HbA_{1c} in CF patients [75], and many have been correlated with clinical outcomes. However, these studies report heterogeneous findings and rarely include substantial prospective follow-up (see Section 3) [84].

Given all these factors, CGM is not yet widely recommended for CFRD diagnosis or screening [4]. However, it is used in some centers for diagnosis and screening, follow-up of borderline diagnostic tests, and investigation of patients who cannot or refuse to undergo OGTT [31, 111, 112]. Like HbA_{1c}, it may also be useful as an adjunctive test for predicting long-term risk of CF-related glucose abnormalities. In a prospective cohort study of 17 children with CF, all those who had glucose excursions ≥11.1 mmol/L on CGM developed either CFRD or IGT with INDET over a period of 2.5 years, irrespective of their glucose tolerance at baseline [107].

3. Clinical significance of early glucose abnormalities in CF, as detected using various glucose measurement techniques

3.1 Defining clinically significant sequelae of CFRD: the importance of lung function & nutritional status

CFRD is well-understood to have a differing profile of sequelae as compared to T1D or T2D. Macrovascular disease is uncommon outside of case reports [1, 4, 5, 113], and although screening for microvascular disease should be routinely undertaken [59], microvascular complications are uncommon until at least 5–10 years of CFRD with fasting hyperglycemia [57, 114, 115]. Therefore they are substantially predated by declines in lung function [6–21, 116–118] and nutritional status [7, 9–12, 14, 117], both of which are significant predictors of early mortality in CF [10, 11, 16, 18, 25, 56, 119]. Four large cohort studies also report higher annual frequency in diabetic vs. non-diabetic CF patients of pulmonary exacerbations requiring intravenous antibiotics or hospitalization [10, 21, 39, 120], and it was recently demonstrated that diabetic CF patients have reduced recovery of baseline forced expiratory volume in 1 sec as a percentage of predicted (FEV_1%) following pulmonary exacerbations [116].

A causative relationship between CFRD, impaired lung function, and poor nutritional status is implied by the clinical improvements seen following insulin therapy [13, 92, 120–122], and is also biologically plausible on several accounts. Insulin is a powerfully anabolic hormone, therefore insulin deficiency combined with CF's increased metabolic requirements promotes catabolism with nutritional decline [9, 93, 123, 124]. Regarding lung function and pulmonary exacerbations, hyperglycemia is known to promote respiratory tract infections (RTIs) both systemically, via pro-inflammatory and immunosuppressive effects [125, 126], and locally, via glucose leakage into airway secretions, which could promote pathogen growth [125, 127–130]. Several cohort studies report higher prevalence in diabetic vs. non-diabetic CF patients of certain RTIs, including *Pseudomonas aeruginosa* [10, 19, 117, 131], *Staphylococcus aureus* [132, 133], and *Burkholderia cepacia* [10, 117, 132].

Finally, hyperglycemia can also impair lung function through non-infective pathways. It has been associated with restrictive lung disease in T1D and T2D (via non-enzymatic glycation of collagen and elastin) [134], and with inflammatory and proteolytic lung destruction in CFRD [135–137]. Lung proteolysis may be exacerbated

by protein catabolism [19, 122], which can furthermore weaken respiratory muscles [138, 139] and impair immunoprotein synthesis during RTIs [61]. This may explain why lung function in CF also correlates with nutritional status [6, 7, 140–142].

3.2 Decline in clinical status prior to diagnosis of CFRD

Numerous cohort and case-control studies examining the 1–5 years before CFRD diagnosis report decline in lung function [19, 35, 38, 92, 143–146] and nutritional status [19, 35, 38, 92, 143, 144] in pre-diabetic patients, or significantly reduced values compared to non-diabetic CF controls [12, 17]. This suggests that pre-diabetic glucose abnormalities are clinically significant. Two case-control studies focusing specifically on pediatric populations also report that pre-diabetic children with CF have significantly lower height and weight velocities than non-diabetic CF controls [145, 146], with one study demonstrating differences up to 11 years before CFRD diagnosis [146]. These differing velocities produce steadily-widening gaps in height-for-age and weight-for-age, reaching statistically-significant sizes after CFRD diagnosis, usually around ages 15–19 [18, 146]. Importantly, this growing disparity seems to occur even if aggressive insulin therapy is commenced at diagnosis [144], and although it may narrow with prolonged therapy, it may not fully correct [18, 144, 147]. Therefore, optimizing clinical outcomes in CFRD may require treatment of pre-diabetic abnormalities, highlighting the importance of glucose measurement systems that can sensitively predict clinical decline.

3.3 Clinically significant pre-diabetic markers detectable using OGTT

Traditional OGTT diagnostic thresholds are not specific to CF – in fact, they were originally designed to predict T2D-associated microvascular disease in Pima Native Americans [148]. This may explain their apparent insensitivity to CF clinical outcomes. A few studies do report poorer lung function or nutritional status in IGT vs. NGT CF patients [37, 72], and several more identify IGT as a significant risk factor for substantial decline in FEV_1% over 4–5 years [19, 149]. However, most studies attempting to correlate IGT with contemporary lung function and nutritional status find no significant relationship [19, 33, 34, 39, 53, 70–73, 150–152].

A more successful non-conventional OGTT parameter is the additional glucose tolerance category of INDET, defined as blood glucose ≥11.1 mmol/L at an OGTT midpoint – most commonly 60 min (BG_{60}) – as opposed to 0 or 120 min [4]. BG_{60} has been shown to inversely correlate with BMI in children with CF, and correlates with FEV_1% and forced vital capacity as a percentage of predicted (FVC%) in both children [7] and adults [150]. In a subsequent study, INDET patients had mean FEV_1% comparable to CFRD patients, representing a significant reduction compared to NGT and IGT patients [71]. INDET has also been confirmed to predict development of CFRD (OR 2.81 over ~3.5 years) [93, 96].

Other OGTT parameters shown to predict FEV_1% in non-diabetic CF patients include higher peak glucose (BG_{max}) [9, 33, 72, 153], higher $AUC_{glucose}$ [124, 153], and reduced insulin secretion [34, 35, 72, 124]. Finally, a few studies have correlated FEV_1% with trajectories of deterioration in glucose tolerance [41, 154]. One prospective cohort study recruited 152 non-diabetic CF patients, and stratified them according to whether their glucose tolerance on OGTT improved, deteriorated or remained stable over 2 years [41]. While all patients experienced a decline in FEV_1%, the extent of decline only reached statistical significance in patients of stable or deteriorating glucose tolerance, and those of deteriorating glucose tolerance also had a much larger drop than those of stable glucose tolerance (−6.1% vs. −1.6%) [41].

It is rarer for studies to report correlations between OGTT parameters and nutritional status [33–35, 41, 71, 72, 154], possibly because intensive dietician

management of CF mitigates nutritional decline [133, 154]. Nevertheless, one seminal prospective cohort study inversely correlated age-adjusted height and BMI with $AUC_{glucose}$ [8], and a recent cross-sectional study found that lower-than-median insulin secretion at 60 min is independently associated with worse BMI [150]. In children, BMI (calculated as weight in kg divided by the square of height in meters) may be a less sensitive measure of nutritional status than weight-for-age, as poor linear growth may mask decline [146]. Nevertheless, Wooldridge et al. report a direct correlation between $AUC_{insulin}$ and BMI z-score in 146 NGT children with CF aged 5–20 [123], and our group has found that $AUC_{glucose}$ inversely correlates with age-adjusted weight, height and BMI in children aged ≤10 years [153]. Furthermore, in an earlier cohort study of 33 children aged 10–19, we found that higher BG_{max} was associated with decline in weight z-score, FEV_1% and FVC% over the past 12 months, and BG_{max} ≥8.2 mmol/L had 87% sensitivity and 70% specificity for a clinically significant decline in weight z-score [9]. By contrast, BG_{120} was no better than chance at detecting decline in weight z-score, and the conventional diagnostic threshold of 11.1 mmol/L had only 10% sensitivity [9]. These findings led us to propose an alternative system for classifying CF-related glucose abnormalities on OGTT, the Cystic Fibrosis Insulin Deficiency (CFID) stages (**Table 3**) [9].

3.4 Clinically significant pre-diabetic markers detectable using CGM

Six main studies have explored the clinical significance of CGM-based measures of CF-related early glucose abnormalities [9, 98, 111, 152, 155, 156]. Their results are compelling but heterogeneous. Taylor-Cousar et al. conducted a 5-year prospective cohort study of 17 originally non-diabetic CF patients, 7 of whom developed CFRD during observation [98]. In this subgroup, there was significant inverse correlation between peak glucose and BMI, and a trend towards correlation with FEV_1% [98]. Leclercq et al. also examined peak glucose, stratifying 38 NGT CF patients according to whether they had any peaks ≥11.1 mmol/L during 72-h CGM [155]. In the 'yes' group, there was significantly lower FEV_1% and FVC%, and increased risk of colonization with *P. aeruginosa* [155].

In the aforementioned study undertaken by our research group in 33 children with CF aged 10–19, we also showed that percentage time ≥7.8 mmol/L on CGM predicted 12-month rate of decline in weight z-score, FVC%, and FEV_1%. Similarly, on receiver operator characteristic (ROC) analysis, ≥4.5% time at ≥7.8 mmol/L on CGM was a sensitive and specific predictor of clinically significant decline in weight z-score and FVC% [9]. Frost et al. subsequently used these parameters to interpret the CGM results of 59 adults being investigated for CF-related glucose abnormalities [112]. They found that percentage time ≥7.8 mmol/L on CGM correlated with baseline FEV_1% and 12-month rate of decline [112].

In Chan et al.'s study of 88 children with CF aged 10–18, 12-month decline in FEV_1% and FVC% was predicted by multiple other CGM parameters: peak glucose, number of daily glucose excursions >11.1 mmol/L, mean amplitude of glycemic

Diagnostic category	o-min OGTT glucose	Max OGTT glucose	2-h OGTT glucose
CFID1	<7.0 mmol/L	≥8.2 mmol/L	<11.1 mmol/L
CFID2	<7.0 mmol/L	≥11.1 mmol/L	<11.1 mmol/L
CFID3	<7.0 mmol/L	*N/A*	≥11.1 mmol/L
CFID4	≥7.0 mmol/L	*N/A*	*N/A*

Table 3.
Cystic fibrosis insulin deficiency (CFID) classification system of CF-related glucose abnormalities, as proposed by Hameed et al. [9].

excursions, and standard deviation [152]. Brugha et al. investigated another glycemic variability measure, glucose interquartile ranges, in a 7-year retrospective cohort study [111]. On ROC analysis, ranges >1.95 mmol/L predicted CFRD with 60% sensitivity and 98% specificity, but did not correlate with BMI or FEV_1% [111].

Finally, our group recently conducted a cross-sectional study of 18 children with CF aged ≤5 years [156]. Even in this very young group, history of *P. aeruginosa* was predicted by mean glucose and percentage time at ≥7.8 mmol/L, and levels of inflammatory markers in bronchoalveolar lavage fluid were predicted by peak glucose, mean glucose, percentage time at ≥7.8 mmol/L, and standard deviation [156].

3.5 Clinically significant pre-diabetic markers detectable using other glucose measurement techniques

3.5.1 HbA_{1c} and alternative glycated proteins

Three studies report a weak inverse correlation between HbA_{1c} and lung function in non-diabetic CF patients ($r = -0.25–0.3$) [72, 73, 88], and one of these also found a direct correlation with number of infective pulmonary exacerbations per year [73]. In two more studies, $HbA_{1c} \geq 5.5–5.8\%$ predicted poorer FVC% [74] or FEV_1% [82]. Therefore HbA_{1c}, despite its insensitivity to CF-related glucose abnormalities, may be a useful harbinger of clinical decline when elevated.

Several studies have also investigated fructosamine, glycated albumin, and 1,5-anhydroglucitol as alternatives to HbA_{1c} in CF. These biomarkers are not dependent on the lifespan of erythrocytes, and have been shown to correlate with mean plasma glucose in CF as estimated using CGM [75]. However, evidence of their ability to predict glucose abnormalities and clinical decline in CF is currently mixed [11, 74, 157]. In one study, fractional serum fructosamine (FSF) ≥3.70 μmol/g predicted IGT and CFRD with 100% sensitivity and 67% specificity, and patients with elevated FSF also had significantly lower median FEV_1% (47% vs. 90%) [157].

3.5.2 Fasting glucose

Early evidence suggests that fasting glucose, including IFG, does not correlate with clinical status in CF [53, 95]. In one case-control study, IFG actually predicted *better* lung function than normal fasting glucose in some patient subgroups, particularly children with simultaneous IGT [95]. It was hypothesized that IFG may represent a physiological adaptation to CF, with hepatic glucose production upregulated to meet increased baseline metabolic requirements [95].

4. Detection protocols for early glucose abnormalities and CFRD at the Sydney Children's Hospital, Randwick

Our institute, the Sydney Children's Hospital, provides one example of integrating multiple glucose measurement methods into routine practice. Children with CF are screened annually for glucose abnormalities from age 10, using OGTT with 30-minutely sampling. CGM is used to follow up borderline OGTTs, or to investigate children with clinically-suspected glucose abnormalities who have normal OGTTs or are unable to undergo OGTT. CGM excursions ≥11.1 mmol/L over 72 h of monitoring are considered severe abnormalities that warrant further investigation for possible insulin therapy. Moreover, some pre-diabetic children on OGTT are randomized to insulin therapy via the CF-IDEA trial (ClinicalTrials.gov Identifier NCT01100892, see Section 5).

5. Management of early glucose abnormalities in CF

Ultimately, the most clinically relevant measures of CF-related early glucose abnormalities are those that alter patient management. Therefore the long-term effects of actively treating early abnormalities is an important research question. Most studies have focused on insulin therapy, as insulin is currently the only recommended pharmacotherapy for CFRD (in part because of its anabolic effects) [59]. Emerging research has also explored oral anti-hypoglycemics [158], incretin modifiers [159], and CFTR modulators [160, 161].

It is already known that earlier diagnosis and treatment of CFRD, via OGTT screening programs, improves life expectancy and resolves historical sex differences in clinical outcomes (females with CFRD previously did worse than males) [16, 24]. Seven studies were identified trialing insulin therapy for CF patients who were pre-diabetic on OGTT [92, 122, 143, 162–164]. Five report statistically-significant improvements in lung function [122, 163, 165], nutritional status [122, 143, 164, 165], or rate of decline in either variable [163, 164], either intra-individually or relative to untreated controls. Moreover, five out of six studies assessing tolerability found no significantly-increased incidence of symptomatic hypoglycemia [92, 122, 143, 162, 164, 165]. Finally, one additional study has assessed the efficacy of insulin therapy initiated based on CGM, via retrospective analysis of all non-diabetic adults at a British CF center who had a CGM ordered between 2013 and 2016 [112]. Insulin was initiated if patients spent >4.5% time at >7.8 mmol/L on CGM, and if they recorded no clear triggers for these glucose excursions in a contemporary food diary. Patients treated with insulin demonstrated statistically-significant improvements in FEV_1% and weight within 3 months of treatment, and maintained an improvement in weight and annual rate of lung function decline at 12 months [112].

All this suggests that treatment of CF-related AGT may be beneficial. However, results are difficult to generalize, due to heterogeneity in studies' inclusions criteria, types of controls, and insulin regimens [166]. Studies are also limited by small sample sizes [92, 112, 122, 143, 162–165], short durations [92, 112, 122, 143, 162, 165], and mixed analysis of pre-diabetic and diabetic patients [92, 122], highlighting the need for large long-term randomized control trials. One such trial, CF-IDEA (ClinicalTrials.gov Identifier NCT01100892), is nearing completion. To date, CF-IDEA has recruited 86 participants aged ≥5 years at 5 participating sites, all non-diabetic on OGTT with BG_{max} 8.2 mmol/L to <11.1 mmol/L (CFID1) or ≥ 11.1 mmol/L (CFID2). Participants are randomized to observation only or to a once-daily insulin detemir (Levemir) for 12 months, with starting dose 0.1 units/kg/day, blood glucose self-monitoring intensively for 10 days and twice daily thereafter, and a blood glucose target range of 4–8 mmol/L. The main outcome factors are change in weight SDS, change in lung function, and frequency of hospitalization.

6. Conclusions

As patients with CF live longer, CFRD becomes an increasingly prevalent serious co-morbidity, associated with significant decline in lung function and nutritional status. Evidence suggests that this decline may begin years earlier, in the pre-diabetic phase. Currently, OGTT is the most sensitive licensed diagnostic tool for identifying pre-diabetic CF-related glucose abnormalities, but its utility is limited by inconvenience, high variability of results, and insensitivity of traditional diagnostic categories to CF-related glucose excursions and clinical decline.

Development of standardized interpretation systems for CGM may revolutionize detection of clinically relevant early glucose abnormalities. Results of randomized controlled trials of insulin treatment prior to onset of CFRD may alter the point at which insulin is offered.

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