Chapter

Detection and Management of Early Glucose Abnormalities in Cystic Fibrosis

Katerina Theocharous, Bernadette Prentice, Charles F. Verge, Adam Jaffé and Shihab Hameed

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.

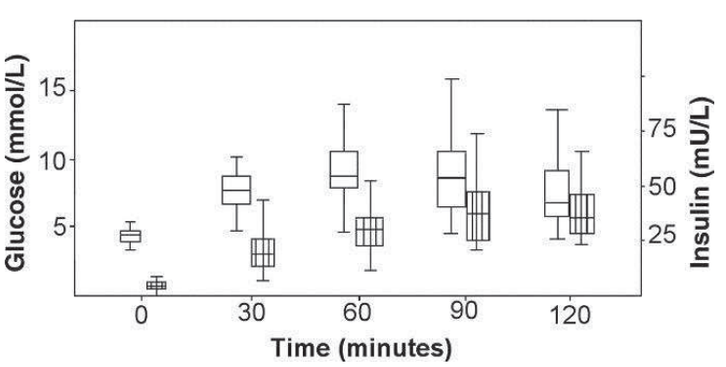

Figure 1.
Venous blood glucose (□) and insulin (▒) in 30-minutely samples over a 2-h oral glucose tolerance test, as measured in 33 children with CF aged 10–19. Boxes indicate interquartile range, horizontal lines indicate median, whiskers indicate 5th and 95th percentiles. Figure taken from Hameed et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

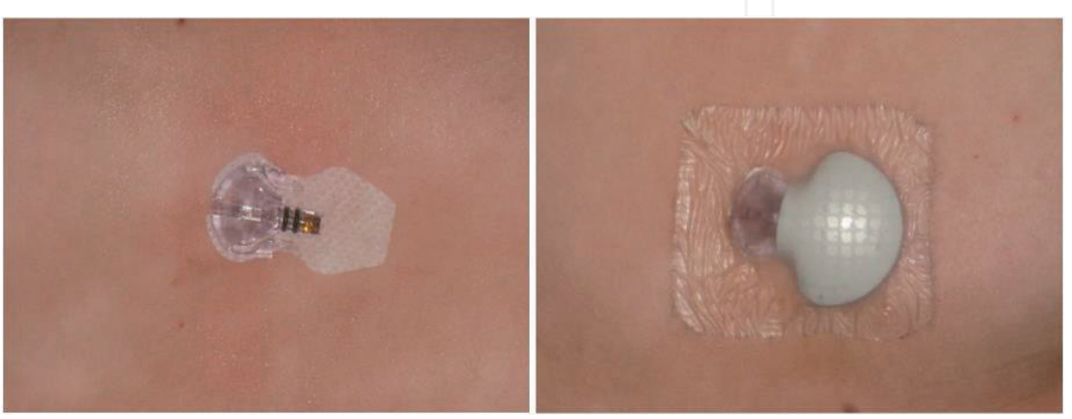

Figure 2.
Continuous glucose monitor sensor, before and after attachment of the transmitter. 'CGM set' and 'Continuous Glucose Monitor' by Sara Bassett are licensed under CC BY-NC-SA 2.0.

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.

Acknowledgements

SH, AJ and CFV have received funding from the National Health and Medical Research Council of Australia, Australasian Cystic Fibrosis Research Trust, Regional Diabetes Support Scheme, Sydney Children's Hospital Foundation, and Australasian Pediatric Endocrine Care Grant from Pfizer, and industry support from Novo Nordisk, Medtronic, and Abbott Diagnostics. BP has been awarded a fellowship from the Thoracic Society of Australia and New Zealand and Vertex, and a postgraduate scholarship from the National Health and Medical Research Council of Australia.

Author details

Katerina Theocharous[1], Bernadette Prentice[1,2], Charles F. Verge[1,3], Adam Jaffé[1,2] and Shihab Hameed[1,3,4]*

1 School of Women's and Children's Health, Faculty of Medicine, The University of New South Wales, Sydney, NSW, Australia

2 Department of Respiratory Medicine, Sydney Children's Hospital, Randwick, NSW, Australia

3 Department of Endocrinology, Sydney Children's Hospital, Randwick, NSW, Australia

4 Faculty of Medicine, University of Sydney, Sydney, NSW, Australia

*Address all correspondence to: s.hameed@unsw.edu.au

References

[1] Bridges N, Rowe R, Holt RIG. Unique challenges of cystic fibrosis-related diabetes. Diabetic Medicine. 2018;**35**(9):1181-1188

[2] Reid DW, Blizzard CL, Shugg DM, Flowers C, Cash C, Greville HM. Changes in cystic fibrosis mortality in Australia, 1979-2005. The Medical Journal of Australia. 2011;**195**(7):392-395

[3] Keogh RH, Szczesniak R, Taylor-Robinson D, Bilton D. Up-to-date and projected estimates of survival for people with cystic fibrosis using baseline characteristics: A longitudinal study using UK patient registry data. Journal of Cystic Fibrosis. 2018;**17**(2):218-227

[4] Moran A, Pillay K, Becker D, Granados A, Hameed S, Acerini CL. ISPAD clinical practice consensus guidelines 2018: Management of cystic fibrosis-related diabetes in children and adolescents. Pediatric Diabetes. 2018;**19**:64-74

[5] Kayani K, Mohammed R, Mohiaddin H. Cystic fibrosis-related diabetes. Frontiers in Endocrinology. 2018;**9**:20

[6] Kerem E, Viviani L, Zolin A, MacNeill S, Hatziagorou E, Ellemunter H, et al. Factors associated with FEV1 decline in cystic fibrosis: Analysis of the ECFS patient registry. The European Respiratory Journal. 2014;**43**(1):125-133

[7] Brodsky J, Dougherty S, Makani R, Rubenstein RC, Kelly A. Elevation of 1-hour plasma glucose during oral glucose tolerance testing is associated with worse pulmonary function in cystic fibrosis. Diabetes Care. 2011;**34**(2):292-295

[8] Bismuth E, Laborde K, Taupin P, Velho G, Ribault V, Jennane F, et al. Glucose tolerance and insulin secretion, morbidity, and death in patients with cystic fibrosis. The Journal of Pediatrics. 2008;**152**(4):540-545

[9] Hameed S, Morton JR, Jaffé A, Field PI, Belessis Y, Yoong T, et al. Early glucose abnormalities in cystic fibrosis are preceded by poor weight gain. Diabetes Care. 2010;**33**(2):221-226

[10] Marshall BC, Butler SM, Stoddard M, Moran AM, Liou TG, Morgan WJ, et al. Epidemiology of cystic fibrosis-related diabetes. The Journal of Pediatrics. 2005;**146**(5):681-687

[11] Elder DA, Wooldridge JL, Dolan LM, D'Alessio DA. Glucose tolerance, insulin secretion, and insulin sensitivity in children and adolescents with cystic fibrosis and no prior history of diabetes. The Journal of Pediatrics. 2007;**151**(6):653-658

[12] Lanng S, Thorsteinsson B, Nerup J, Koch C. Influence of the development of diabetes mellitus on clinical status in patients with cystic fibrosis. European Journal of Pediatrics. 1992;**151**(9):684-687

[13] Lanng S, Thorsteinsson B, Nerup J, Koch C. Diabetes mellitus in cystic fibrosis: Effect of insulin therapy on lung function and infections. Acta Paediatrica. 1994;**83**(8):849-853

[14] Moreau F, Weiller MA, Rosner V, Weiss L, Hasselmann M, Pinget M, et al. Continuous glucose monitoring in cystic fibrosis patients according to the glucose tolerance. Hormone and Metabolic Research. 2008;**40**(7):502-506

[15] Suratwala D, Chan JS, Kelly A, Meltzer LJ, Gallagher PR, Traylor J, et al. Nocturnal saturation and glucose tolerance in children with cystic fibrosis. Thorax. 2011;**66**(7):574-578

[16] Moran A, Dunitz J, Nathan B, Saeed A, Holme B, Thomas W. Cystic fibrosis-related diabetes: Current trends in prevalence, incidence, and mortality. Diabetes Care. 2009;**32**(9):1626-1631

[17] Rolon MA, Benali K, Munck A, Navarro J, Clement A, Tubiana-Rufi N, et al. Cystic fibrosis-related diabetes mellitus: Clinical impact of prediabetes and effects of insulin therapy. Acta Paediatrica. 2001;**90**(8):860-867

[18] Koch C, Rainisio M, Madessani U, Harms HK, Hodson ME, Mastella G, et al. Presence of cystic fibrosis-related diabetes mellitus is tightly linked to poor lung function in patients with cystic fibrosis: Data from the European epidemiologic registry of cystic fibrosis. Pediatric Pulmonology. 2001;**32**(5):343-350

[19] Milla CE, Warwick WJ, Moran A. Trends in pulmonary function in patients with cystic fibrosis correlate with the degree of glucose intolerance at baseline. American Journal of Respiratory and Critical Care Medicine. 2000;**162**(3 Pt 1):891-895

[20] Lombardo F, De Luca F, Rosano M, Sferlazzas C, Lucanto C, Arrigo T, et al. Natural history of glucose tolerance, beta-cell function and peripheral insulin sensitivity in cystic fibrosis patients with fasting euglycemia. European Journal of Endocrinology. 2003;**149**(1):53-59

[21] Limoli DH, Yang J, Khansaheb MK, Helfman B, Peng L, Stecenko AA, et al. Staphylococcus aureus and Pseudomonas aeruginosa co-infection is associated with cystic fibrosis-related diabetes and poor clinical outcomes. European Journal of Clinical Microbiology & Infectious Diseases. 2016;**35**(6):947-953

[22] Abbott J, Morton AM, Hurley MA, Conway SP. Longitudinal impact of demographic and clinical variables on health-related quality of life in cystic fibrosis. BMJ Open. 2015;**5**(5):e007418

[23] Kwong E, Desai S, Chong L, Lee K, Zheng J, Wilcox PG, et al. The impact of cystic fibrosis-related diabetes on health-related quality of life. Journal of Cystic Fibrosis. 2019;**18**(5):734-736

[24] Lewis C, Blackman SM, Nelson A, Oberdorfer E, Wells D, Dunitz J, et al. Diabetes-related mortality in adults with cystic fibrosis: Role of genotype and sex. American Journal of Respiratory and Critical Care Medicine. 2015;**191**(2):194-200

[25] Chamnan P, Shine BS, Haworth CS, Bilton D, Adler AI. Diabetes as a determinant of mortality in cystic fibrosis. Diabetes Care. 2010;**33**(2):311-316

[26] Bogdani M, Blackman SM, Ridaura C, Bellocq JP, Powers AC, Aguilar-Bryan L. Structural abnormalities in islets from very young children with cystic fibrosis may contribute to cystic fibrosis-related diabetes. Scientific Reports. 2017;**7**(1):17231

[27] Hart NJ, Aramandla R, Poffenberger G, Fayolle C, Thames AH, Bautista A, et al. Cystic fibrosis-related diabetes is caused by islet loss and inflammation. JCI Insight. 2018;**3**(8):e98240

[28] Iannucci A, Mukai K, Johnson D, Burke B. Endocrine pancreas in cystic fibrosis: An immunohistochemical study. Human Pathology. 1984;**15**(3):278-284

[29] Couce M, O'Brien TD, Moran A, Roche PC, Butler PC. Diabetes mellitus in cystic fibrosis is characterized by islet amyloidosis. The Journal of Clinical Endocrinology and Metabolism. 1996;**81**(3):1267-1272

[30] Löhr M, Goertchen P, Nizze H, Gould NS, Gould VE, Oberholzer M,

et al. Cystic fibrosis associated islet changes may provide a basis for diabetes: An immunocytochemical and morphometrical study. Virchows Archiv. A, Pathological Anatomy and Histopathology. 1989;**414**(2):179-185

[31] Mainguy C, Bellon G, Delaup V, Ginoux T, Kassai-Koupai B, Mazur S, et al. Sensitivity and specificity of different methods for cystic fibrosis-related diabetes screening: Is the oral glucose tolerance test still the standard? Journal of Pediatric Endocrinology & Metabolism. 2017;**30**(1):27-35

[32] Yung B, Noormohamed FH, Kemp M, Hooper J, Lant AF, Hodson ME. Cystic fibrosis-related diabetes: The role of peripheral insulin resistance and beta-cell dysfunction. Diabetic Medicine. 2002;**19**(3):221-226

[33] Anzeneder L, Kircher F, Feghelm N, Fischer R, Seissler J. Kinetics of insulin secretion and glucose intolerance in adult patients with cystic fibrosis. Hormone and Metabolic Research. 2011;**43**(5):355-360

[34] Costa M, Potvin S, Hammana I, Malet A, Berthiaume Y, Jeanneret A, et al. Increased glucose excursion in cystic fibrosis and its association with a worse clinical status. Journal of Cystic Fibrosis. 2007;**6**(6):376-383

[35] Street ME, Spaggiari C, Ziveri MA, Rossi M, Volta C, Viani I, et al. Insulin production and resistance in cystic fibrosis: Effect of age, disease activity, and genotype. Journal of Endocrinological Investigation. 2012;**35**(3):246-253

[36] Cano Megías M, González Albarrán O, Guisado Vasco P, Lamas Ferreiro A, Máiz CL. Insulin resistance, β-cell dysfunction and differences in curves of plasma glucose and insulin in the intermediate points of the standard glucose tolerance test in adults with cystic fibrosis. Endocrinología y Nutrición. 2015;**62**(2):91-99

[37] Tofé S, Moreno JC, Máiz L, Alonso M, Escobar H, Barrio R. Insulin-secretion abnormalities and clinical deterioration related to impaired glucose tolerance in cystic fibrosis. European Journal of Endocrinology. 2005;**152**(2):241-247

[38] Martin-Frías M, Lamas Ferreiro A, Enes Romero P, Cano Gutiérrez B, Barrio CR. Abnormal glucose tolerance in prepubertal patients with cystic fibrosis. Anales de Pediatría (Barcelona, Spain). 2012;**77**(5):339-343

[39] Mohan K, Miller H, Dyce P, Grainger R, Hughes R, Vora J, et al. Mechanisms of glucose intolerance in cystic fibrosis. Diabetic Medicine. 2009;**26**(6):582-588

[40] De Schepper J, Dab I, Derde MP, Loeb H. Oral glucose tolerance testing in cystic fibrosis: Correlations with clinical parameters and glycosylated haemoglobin determinations. European Journal of Pediatrics. 1991;**150**(6):403-406

[41] Boudreau V, Coriati A, Hammana I, Ziai S, Desjardins K, Berthiaume Y, et al. Variation of glucose tolerance in adult patients with cystic fibrosis: What is the potential contribution of insulin sensitivity? Journal of Cystic Fibrosis. 2016;**15**(6):839-845

[42] Klip A, Tsakiridis T, Marette A, Ortiz PA. Regulation of expression of glucose transporters by glucose: A review of studies in vivo and in cell cultures. The FASEB Journal. 1994;**8**(1):43-53

[43] Vuorinen-Markkola H, Koivisto VA, Yki-Jarvinen H. Mechanisms of hyperglycemia-induced insulin resistance in whole body and skeletal muscle of type I diabetic patients. Diabetes. 1992;**41**(5):571-580

[44] Hardin DS, Leblanc A, Marshall G, Seilheimer DK. Mechanisms of insulin resistance in cystic fibrosis. American Journal of Physiology. Endocrinology and Metabolism. 2001;**281**(5):E1022-E10E8

[45] Rotter V, Nagaev I, Smith U. Interleukin-6 (IL-6) induces insulin resistance in 3T3-L1 adipocytes and is, like IL-8 and tumor necrosis factor-α, overexpressed in human fat cells from insulin-resistant subjects. The Journal of Biological Chemistry. 2003;**278**(46):45777-45784

[46] Nieto-Vazquez I, Fernández-Veledo S, De Alvaro C, Lorenzo M. Dual role of interleukin-6 in regulating insulin sensitivity in murine skeletal muscle. Diabetes. 2008;**57**(12):3211-3221

[47] Hotamisligil GS, Peraldi P, Budavari A, Ellis R, White MF, Spiegelman BM. IRS-1–mediated inhibition of insulin receptor tyrosine kinase activity in TNF-α– And obesity-induced insulin resistance. Science. 1996;**271**(5249):665-668

[48] Ofei F, Hurel S, Newkirk J, Sopwith M, Taylor R. Effects of an engineered human anti–TNF-α antibody (CDP571) on insulin sensitivity and glycemic control in patients with NIDDM. Diabetes. 1996;**45**(7):881-885

[49] Amiel SA, Sherwin RS, Simonson DC, Lauritano AA, Tamborlane WV. Impaired insulin action in puberty: A contributing factor to poor glycaemic control in adolescents with diabetes. The New England Journal of Medicine. 1986;**315**(4):215-219

[50] Nezer N, Shoseyov D, Kerem E, Zangen DH. Patients with cystic fibrosis and normoglycemia exhibit diabetic glucose tolerance during pulmonary exacerbation. Journal of Cystic Fibrosis. 2010;**9**(3):199-204

[51] Iwanicki C, Logomarsino JV. Impaired glucose tolerance, body mass index and respiratory function in patients with cystic fibrosis: A systematic review. The Clinical Respiratory Journal. 2019;**13**(6):341-354

[52] Yi Y, Norris AW, Wang K, Sun X, Uc A, Moran A, et al. Abnormal glucose tolerance in infants and young children with cystic fibrosis. American Journal of Respiratory and Critical Care Medicine. 2016;**194**(8):974-980

[53] Sterescu AE, Rhodes B, Jackson R, Dupuis A, Hanna A, Wilson DC, et al. Natural history of glucose intolerance in patients with cystic fibrosis: Ten-year prospective observation program. The Journal of Pediatrics. 2010;**156**(4):613-617

[54] Lanng S, Hansen A, Thorsteinsson B, Nerup J, Koch C. Glucose tolerance in patients with cystic fibrosis: Five year prospective study. BMJ. 1995;**311**(7006):655-659

[55] Scheuing N, Holl RW, Dockter G, Hermann JM, Junge S, Koerner-Rettberg C, et al. High variability in oral glucose tolerance among 1,128 patients with cystic fibrosis: A multicenter screening study. PLoS One. 2014;**9**(11):e112578

[56] Milla CE, Billings J, Moran A. Diabetes is associated with dramatically decreased survival in female but not male subjects with cystic fibrosis. Diabetes Care. 2005;**28**(9):2141-2144

[57] Schwarzenberg SJ, Thomas W, Olsen TW, Grover T, Walk D, Milla C, et al. Microvascular complications in cystic fibrosis-related diabetes. Diabetes Care. 2007;**30**(5):1056-1061

[58] Scheuing N, Holl RW, Dockter G, Fink K, Junge S, Naehrlich L, et al. Diabetes in cystic fibrosis: Mulitcenter screening results based on current guidelines. PLoS One. 2013;**8**(12):e81545

[59] Moran A, Brunzell C, Cohen RC, Katz M, Marshall BC, Onady G, et al.

Clinical care guidelines for cystic fibrosis-related diabetes: A position statement of the American Diabetes Association and a clinical practice guideline of the Cystic Fibrosis Foundation, endorsed by the pediatric Endocrine Society. Diabetes Care. 2010;**33**(12):2697-2708

[60] Waugh N, Royle P, Craigie I, Ho V, Pandit L, Ewings P, et al. Screening for cystic fibrosis-related diabetes: A systematic review. Health Technology Assessment. 2012;**16**(24):24

[61] Hameed S, Jaffé A, Verge CF. Advances in the detection and management of cystic fibrosis related diabetes. Current Opinion in Pediatrics. 2015;**27**(4):525-533

[62] Juvenile Diabetes Research Foundation Continuous Glucose Monitoring Study Group. Continuous glucose monitoring and intensive treatment of type 1 diabetes. The New England Journal of Medicine. 2008;**359**(14):1464-1476

[63] Moran A, Becker D, Casella SJ, Gottlieb PA, Kirkman MS, Marshall BC, et al. Epidemiology, pathophysiology, and prognostic implications of cystic fibrosis-related diabetes: A technical review. Diabetes Care. 2010;**33**(12):2677-2683

[64] American Diabetes Association. Classification and diagnosis of diabetes: Standards of medical care in diabetes. Diabetes Care. 2020;**43**:S14-S31

[65] Juvenile Diabetes Research Foundation Continuous Glucose Monitoring Study Group. Variation of interstitial glucose measurements assessed by continuous glucose monitors in healthy, nondiabetic individuals. Diabetes Care. 2010;**33**(6):1297-1299

[66] Noronha RM, Damaceno N, Muramatu LH, Monte O, Calliari LEP. Importance of screening with oral glucose tolerance test for early diagnosis of cystic fibrosis-related diabetes mellitus. Pediatric Diabetes. 2014;**15**(4):309-312

[67] Middleton PG, Wagenaar M, Matson AG, Craig ME, Holmes-Walker DJ, Katz T, et al. Australian standards of care for cystic fibrosis-related diabetes. Respirology. 2014;**19**(2):185-192

[68] Yung B, Kemp M, Hooper J, Hodson ME. Diagnosis of cystic fibrosis related diabetes: A selective approach in performing the oral glucose tolerance test based on a combination of clinical and biochemical criteria. Thorax. 1999;**54**(1):40-43

[69] Widger J, Hameed S, Ooi CY, Verge C. Using HbA1c as a screening tool for cystic fibrosis related diabetes. Journal of Cystic Fibrosis. 2016;**15**(2):263-264

[70] Garagorri JM, Rodriguez G, Ros L, Sanchez A. Early detection of impaired glucose tolerance in patients with cystic fibrosis and predisposition factors. Journal of Pediatric Endocrinology & Metabolism. 2001;**14**(1):53-60

[71] Coriati A, Ziai S, Azar M, Berthiaume Y, Rabasa-Lhoret R. Characterization of patients with cystic fibrosis presenting an indeterminate glucose tolerance (INDET). Journal of Cystic Fibrosis. 2016;**15**(1):127-132

[72] Lavie M, Fisher D, Vilozni D, Forschmidt R, Sarouk I, Kanety H, et al. Glucose intolerance in cystic fibrosis as a determinant of pulmonary function and clinical status. Diabetes Research and Clinical Practice. 2015;**110**(3):276-284

[73] Franzese A, Valerio G, Buono P, Spagnuolo MI, Sepe A, Mozzillo E, et al. Continuous glucose monitoring system in the screening of early glucose derangements in children and adolescents with cystic fibrosis.

Journal of Pediatric Endocrinology & Metabolism. 2008;**21**(2):109-116

[74] Tommerdahl KL, Brinton JT, Vigers T, Nadeau KJ, Zeitler PS, Chan CL. Screening for cystic fibrosis-related diabetes and prediabetes: Evaluating 1,5-anhydroglucitol, fructosamine, glycated albumin, and hemoglobin A1c. Pediatric Diabetes. 2019;**20**(8):1080-1086

[75] Chan CL, Hope E, Thurston J, Vigers T, Pyle L, Zeitler PS, et al. Hemoglobin A1c accurately predicts continuous glucose monitoring–derived average glucose in youth and young adults with cystic fibrosis. Diabetes Care. 2018;**41**(7):1406-1413

[76] Godbout A, Hammana I, Potvin S, Mainville D, Rakel A, Berthiaume Y, et al. No relationship between mean plasma glucose and glycated haemoglobin in patients with cystic fibrosis-related diabetes. Diabetes & Metabolism. 2008;**34**(6):568-573

[77] Rana M, Munns CF, Selvadurai H, Donaghue KC, Craig ME. Cystic fibrosis-related diabetes in children—Gaps in the evidence? Nature Reviews. Endocrinology. 2010;**6**(7):371-378

[78] Prentice B, Hameed S, Verge CF, Ooi CY, Jaffe A, Widger J. Diagnosing cystic fibrosis-related diabetes: Current methods and challenges. Expert Review of Respiratory Medicine. 2016;**10**(7):799-811

[79] Brennan AL, Gyi KM, Wood DM, Hodson ME, Geddes DM, Baker EH. Relationship between glycosylated haemoglobin and mean plasma glucose concentration in cystic fibrosis. Journal of Cystic Fibrosis. 2006;**5**(1):27-31

[80] De Luca F, Arrigo T, Nibali SC, Sferlazzas C, Gigante A, Di Cesare E, et al. Insulin secretion, glycosylated haemoglobin and islet cell antibodies in cystic fibrosis children and adolescents with different degrees of glucose tolerance. Hormone and Metabolic Research. 1991;**23**(10):495-498

[81] Rana M, Munns CF, Selvadurai HC, Simonds S, Cooper PJ, Woodhead HJ, et al. Increased detection of cystic-fibrosis-related diabetes in Australia. Archives of Disease in Childhood. 2011;**96**(9):823-826

[82] Burgess JC, Bridges N, Banya W, Gyi KM, Hodson ME, Bilton D, et al. HbA1c as a screening tool for cystic fibrosis related diabetes. Journal of Cystic Fibrosis. 2016;**15**(2):251-257

[83] Coriati A, Elisha B, Virassamynaik S, Phaneuf M, Ziai S, Gauthier M-S, et al. Diagnosis of cystic fibrosis-related glucose abnormalities: Can we shorten the standard oral glucose tolerance test? Applied Physiology, Nutrition, and Metabolism. 2013;**38**(12):1254-1259

[84] Boudreau V, Lehoux Dubois C, Desjardins K, Mailhot M, Tremblay F, Rabasa-Lhoret R. Sensitivity and specificity of cystic fibrosis-related diabetes screening methods: Which test should be the reference method? Journal of Pediatric Endocrinology & Metabolism. 2017;**30**(8):885-887

[85] Clemente León M, Bilbao Gassó L, Moreno-Galdó A, Campos Martorrell A, Gartner Tizzano S, Yeste Fernández D, et al. Oral glucose tolerance test and continuous glucose monitoring to assess diabetes development in cystic fibrosis patients. Endocrinología, Diabetes y Nutrición. 2018;**65**(1):45-51

[86] Lam GY, Sissons S, Smith MP, Brown NE, Leung WM, Estey MP. How reliable is your HbA1c test? Revisiting the use of HbA1c in cystic fibrosis-related diabetes (CFRD) screening. Journal of Cystic Fibrosis. 2019;**18**(2):e14-e15

[87] Peckham D. Routine screening for cystic fibrosis-related diabetes. Journal

of the Royal Society of Medicine. 2009;**102**:36-39

[88] Solomon MP, Wilson DC, Corey M, Kalnins D, Zielenski J, Tsui LC, et al. Glucose intolerance in children with cystic fibrosis. The Journal of Pediatrics. 2003;**142**(2):128-132

[89] Lee KMN, Miller RJH, Rosenberg FM, Kreisman SH. Evaluation of glucose tolerance in cystic fibrosis: Comparison of 50-g and 75-g tests. Journal of Cystic Fibrosis. 2007;**6**(4):274-276

[90] Choudhury M, Taylor P, Morgan PH, Duckers J, Lau D, George L, et al. Association between HbA 1c and the development of cystic fibrosis-related diabetes. Diabetic Medicine. 2019;**36**(10):1251-1255

[91] Moran A, Hardin D, Rodman D, Allen HF, Beall RJ, Borowitz D, et al. Diagnosis, screening and management of cystic fibrosis related diabetes mellitus. Diabetes Research and Clinical Practice. 1999;**45**(1):61-73

[92] Moran A, Pekow P, Grover P, Zorn M, Slovis B, Pilewski J, et al. Insulin therapy to improve BMI in cystic fibrosis-related diabetes without fasting hyperglycemia: Results of the cystic fibrosis related diabetes therapy trial. Diabetes Care. 2009;**32**(10):1783-1788

[93] Ode KL, Frohnert B, Laguna T, Phillips J, Holme B, Regelmann W, et al. Oral glucose tolerance testing in children with cystic fibrosis. Pediatric Diabetes. 2010;**11**(7):487-492

[94] Mueller-Brandes C. New criteria for impaired fasting glucose and screening for diabetes in cystic fibrosis. The European Respiratory Journal. 2005;**25**(4):715-717

[95] Frohnert BI, Ode KL, Moran A, Nathan BM, Laguna T, Holme B, et al. Impaired fasting glucose in cystic fibrosis. Diabetes Care. 2010;**33**(12):2660-2664

[96] Schmid K, Fink K, Holl RW, Hebestreit H, Ballmann M. Predictors for future cystic fibrosis-related diabetes by oral glucose tolerance test. Journal of Cystic Fibrosis. 2014;**13**(1):80-85

[97] Boudreau V, Reynaud Q, Dubois CL, Coriati A, Desjardins K, Durieu I, et al. Screening for cystic fibrosis-related diabetes: Matching pathophysiology and addressing current challenges. Canadian Journal of Diabetes. 2016;**40**(5):466-470

[98] Taylor-Cousar JL, Janssen JS, Wilson A, Clair CG, Pickard KM, Jones MC, et al. Glucose >200 mg/dL during continuous glucose monitoring identifies adult patients at risk for development of cystic fibrosis related diabetes. Journal Diabetes Research. 2016;**2016**:1527932

[99] Gilmour JA, Sykes J, Etchells E, Tullis E. Cystic fibrosis-related diabetes screening in adults: A gap analysis and evaluation of accuracy of glycated hemoglobin levels. Canadian Journal of Diabetes. 2019;**43**(1):13-18

[100] Cystic Fibrosis Foundation Patient Registry. Annual data report. Bethesda MD: Cystic Fibrosis Foundation; 2018

[101] Sheikh S, Localio AR, Kelly A, Rubenstein RC. Abnormal glucose tolerance and the 50-gram glucose challenge test in cystic fibrosis. Journal of Cystic Fibrosis. 2020. (Forthcoming). DOI: 10.1016/j.jcf.2020.01.003

[102] Chase HP, Beck R, Tamborlane W, Buckingham B, Mauras N, Tsalikian E, et al. A randomized multicenter trial comparing the GlucoWatch biographer with standard glucose monitoring in children with type 1 diabetes. Diabetes Care. 2005;**28**(5):1101-1106

[103] Chan CL, Ode KL, Granados A, Moheet A, Moran A, Hameed S.

Continuous glucose monitoring in cystic fibrosis – A practical guide. Journal of Cystic Fibrosis. 2019;**18**:S25-S31

[104] O'Riordan SM, Hindmarsh P, Hill NR, Matthews DR, George S, Greally P, et al. Validation of continuous glucose monitoring in children and adolescents with cystic fibrosis: A prospective cohort study. Diabetes Care. 2009;**32**(6):1020-1022

[105] Dobson L, Sheldon CD, Hattersley AT. Validation of interstitial fluid continuous glucose monitoring in cystic fibrosis. Diabetes Care. 2003;**26**(6):1940-1941

[106] Dobson L, Sheldon CD, Hattersley AT. Conventional measures underestimate glycaemia in cystic fibrosis patients. Diabetic Medicine. 2004;**21**(7):691-696

[107] Schiaffini R, Brufani C, Russo B, Fintini D, Migliaccio A, Pecorelli L, et al. Abnormal glucose tolerance in children with cystic fibrosis: The predictive role of continuous glucose monitoring system. European Journal of Endocrinology. 2010;**162**(4):705-710

[108] Pu MZMH, Gonçalves AC, Minnicucci WJ, Morcillo AM, Ribeiro JD, Ribeiro AF. Continuous glucose monitoring to evaluate glycaemic abnormalities in cystic fibrosis. Archives of Disease in Childhood. 2018;**103**(6):592-596

[109] Soliman A, DeSanctis V, Yassin M, Elalaily R, Eldarsy N. Continuous glucose monitoring system and new era of early diagnosis of diabetes in high risk groups. Indian Journal of Endocrinology and Metabolism. 2014;**18**(3):274-282

[110] Ahmed MI, Fox R, Shinkins B, Sutton S, Tziaferi V, Gaillard EA. Continuous glucose monitoring systems for the diagnosis of cystic fibrosis-related diabetes (protocol). Cochrane Database of Systematic Reviews. 2018;**2018**(2):CD012953

[111] Brugha R, Wright M, Nolan S, Bridges N, Carr SB. Quantifying fluctuation in glucose levels to identify early changes in glucose homeostasis in cystic fibrosis. Journal of Cystic Fibrosis. 2018;**17**(6):791-797

[112] Frost F, Dyce P, Nazareth D, Malone V, Walshaw MJ. Continuous glucose monitoring guided insulin therapy is associated with improved clinical outcomes in cystic fibrosis-related diabetes. Journal of Cystic Fibrosis. 2018;**17**(6):798-803

[113] Granados A, Chan CL, Ode KL, Moheet A, Moran A, Holl R. Cystic fibrosis related diabetes: Pathophysiology, screening and diagnosis. Journal of Cystic Fibrosis. 2019;**18**:S3-S9

[114] Andersen HU, Lanng S, Pressler T, Laugesen CS, Mathiesen ER. Cystic fibrosis-related diabetes: The presence of microvascular diabetes complications. Diabetes Care. 2006;**29**(12):2660-2663

[115] Van Den Berg JMW, Morton AM, Kok SW, Pijl H, Conway SP, Heijerman HGM. Microvascular complications in patients with cystic fibrosis-related diabetes (CFRD). Journal of Cystic Fibrosis. 2008;**7**(6):515-519

[116] Okoniewski W, Hughan KS, Weiner GA, Weiner DJ, Forno E. Glycemic control and FEV1 recovery during pulmonary exacerbations in pediatric cystic fibrosis-related diabetes. Journal of Cystic Fibrosis. 2020. (Forthcoming). DOI: 10.1016/j.jcf.2019.12.016

[117] Olesen HV, Drevinek P, Gulmans VA, Hatziagorou E, Jung A, Mei-Zahav M, et al. Cystic fibrosis related diabetes in Europe: Prevalence,

risk factors and outcome. Journal of Cystic Fibrosis. 2020;**19**(2):321-327

[118] Miller RJ, Tildesley HD, Wilcox PG, Zhang H, Kreisman SH. Sex disparities in effects of cystic fibrosis-related diabetes on clinical outcomes: A matched study. Canadian Respiratory Journal. 2008;**15**(6):291-294

[119] Sharma R, Florea VG, Bolger AP, Doehner W, Florea ND, Coats AJ, et al. Wasting as an independent predictor of mortality in patients with cystic fibrosis. Thorax. 2001;**56**(10):746-750

[120] Belle-van Meerkerk G, de Valk HW, Stam-Slob MC, Teding van Berkhout F, Zanen P, van de Graaf EA. Cystic fibrosis-related diabetes with strict glycaemic control is not associated with frequent intravenous antibiotics use for pulmonary infections. Diabetes Research and Clinical Practice. 2016;**116**:230-236

[121] Van Sambeek L, Cowley ES, Newman DK, Kato R. Sputum glucose and glycemic control in cystic fibrosis-related diabetes: A cross-sectional study. PLoS One. 2015;**10**(3):e0119938

[122] Mozzillo E, Franzese A, Valerio G, Sepe A, De Simone I, Mazzarella G, et al. One-year glargine treatment can improve the course of lung disease in children and adolescents with cystic fibrosis and early glucose derangements. Pediatric Diabetes. 2009;**10**(3):162-167

[123] Wooldridge JL, Szczesniak RD, Fenchel MC, Elder DA. Insulin secretion abnormalities in exocrine pancreatic sufficient cystic fibrosis patients. Journal of Cystic Fibrosis. 2015;**14**(6):792-797

[124] Alicandro G, Battezzati PM, Battezzati A, Speziali C, Claut L, Motta V, et al. Insulin secretion, nutritional status and respiratory function in cystic fibrosis patients with normal glucose tolerance. Clinical Nutrition. 2012;**31**(1):118-123

[125] Brennan AL, Gyi KM, Wood DM, Johnson J, Holliman R, Baines DL, et al. Airway glucose concentrations and effect on growth of respiratory pathogens in cystic fibrosis. Journal of Cystic Fibrosis. 2007;**6**(2):101-109

[126] Gill SK, Hui K, Farne H, Garnett JP, Baines DL, Moore LSP, et al. Increased airway glucose increases airway bacterial load in hyperglycaemia. Scientific Reports. 2016;**6**(1):27636

[127] Garnett JP, Kalsi KK, Sobotta M, Bearham J, Carr G, Powell J, et al. Hyperglycaemia and Pseudomonas aeruginosa acidify cystic fibrosis airway surface liquid by elevating epithelial monocarboxylate transporter 2 dependent lactate-H+ secretion. Scientific Reports. 2016;**6**:37955

[128] Baker EH, Clark N, Brennan AL, Fisher DA, Gyi KM, Hodson ME, et al. Hyperglycemia and cystic fibrosis alter respiratory fluid glucose concentrations estimated by breath condensate analysis. Journal of Applied Physiology. 2007;**102**(5):1969-1975

[129] Garnett JP, Gray MA, Tarran R, Brodlie M, Ward C, Baker EH, et al. Elevated paracellular glucose flux across cystic fibrosis airway epithelial monolayers is an important factor for Pseudomonas aeruginosa growth. PLoS One. 2013;**8**(10):e76283

[130] Philips BJ, Redman J, Brennan A, Wood D, Holliman R, Baines D, et al. Glucose in bronchial aspirates increases the risk of respiratory MRSA in intubated patients. Thorax. 2005;**60**(9):761-764

[131] Merlo CA, Boyle MP, Diener-West M, Marshall BC, Goss CH, Lechtzin N. Incidence and risk factors for multiple antibiotic-resistant Pseudomonas aeruginosa in cystic fibrosis. Chest. 2007;**132**(2):562-568

[132] Frost F, Nazareth D, Shaw M, Walshaw MJ. Cystic fibrosis related

diabetes is not independently associated with increased Stenotrophomonas maltophilia infection: Longitudinal data from the UK CF registry. Journal of Cystic Fibrosis. 2019;**18**(2):294-298

[133] Ziegler B, Oliveira CL, Rovedder PM, Schuh SJ. Abreu e Silva FA, de Tarso Roth Dalcin P. glucose intolerance in patients with cystic fibrosis: Sex-based differences in clinical score, pulmonary function, radiograph score, and 6-minute walk test. Respiratory Care. 2011;**56**(3):290-297

[134] van den Borst B, Gosker HR, Zeegers MP, Schols AM. Pulmonary function in diabetes: A metaanalysis. Chest. 2010;**138**(2):393-406

[135] Konstan MW, Hilliard KA, Norvell TM, Berger M. Bronchoalveolar lavage findings in cystic fibrosis patients with stable, clinically mild lung disease suggest ongoing infection and inflammation. American Journal of Respiratory and Critical Care Medicine. 1994;**150**(2):448-454

[136] Bruce MC, Poncz L, Klinger JD, Stern RC, Tomashefski JF Jr, Dearborn DG. Biochemical and pathologic evidence for proteolytic destruction of lung connective tissue in cystic fibrosis. The American Review of Respiratory Disease. 1985;**132**(3):529-535

[137] Ntimbane T, Krishnamoorthy P, Huot C, Legault L, Jacob SV, Brunet S, et al. Oxidative stress and cystic fibrosis-related diabetes: A pilot study in children. Journal of Cystic Fibrosis. 2008;**7**(5):373-384

[138] Arora NS, Rochester DF. Respiratory muscle strength and maximal voluntary ventilation in undernourished patients. The American Review of Respiratory Disease. 1982;**126**(1):5-8

[139] Arora NS, Rochester DF. Effect of body weight and muscularity on human diaphragm muscle mass, thickness, and area. Journal of Applied Physiology. 1982;**52**(1):64-70

[140] Konstan MW, Morgan WJ, Butler SM, Pasta DJ, Craib ML, Silva SJ, et al. Risk factors for rate of decline in forced expiratory volume in one second in children and adolescents with cystic fibrosis. The Journal of Pediatrics. 2007;**151**(2):134-139

[141] Sanders DB, Emerson J, Ren CL, Schechter MS, Gibson RL, Morgan W, et al. Early childhood risk factors for decreased FEV1 at age six to seven years in young children with cystic fibrosis. Annals of the American Thoracic Society. 2015;**12**(8):1170-1176

[142] Coderre L, Fadainia C, Belson L, Belisle V, Ziai S, Maillhot G, et al. LDL-cholesterol and insulin are independently associated with body mass index in adult cystic fibrosis patients. Journal of Cystic Fibrosis. 2012;**11**(5):393-397

[143] Bizzarri C, Lucidi V, Ciampalini P, Bella S, Russo B, Cappa M. Clinical effects of early treatment with insulin glargine in patients with cystic fibrosis and impaired glucose tolerance. Journal of Endocrinological Investigation. 2006;**29**(3):RC1-RC4

[144] Bizzarri C, Montemitro E, Pedicelli S, Ciccone S, Majo F, Cappa M, et al. Glucose tolerance affects pubertal growth and final height of children with cystic fibrosis. Pediatric Pulmonology. 2015;**50**(2):144-149

[145] Cheung MS, Bridges NA, Prasad SA, Francis J, Carr SB, Suri R, et al. Growth in children with cystic fibrosis-related diabetes. Pediatric Pulmonology. 2009;**44**(12):1223-1225

[146] Terliesner N, Vogel M, Steighardt A, Gausche R, Henn C, Hentschel J, et al. Cystic-fibrosis related-diabetes (CFRD) is preceded by

and associated with growth failure and deteriorating lung function. Journal of Pediatric Endocrinology & Metabolism. 2017;**30**(8):815-821

[147] White H, Pollard K, Etherington C, Clifton I, Morton AM, Owen D, et al. Nutritional decline in cystic fibrosis related diabetes: The effect of intensive nutritional intervention. Journal of Cystic Fibrosis. 2009;**8**(3):179-185

[148] Bennett P, Burch T, Miller M. Diabetes mellitus in American (Pima) Indians. The Lancet. 1971;**298**(7716):125-128

[149] Olszowiec-Chlebna M, Koniarek-Maniecka A, Stelmach W, Smejda K, Jerzyńska J, Majak P, et al. Predictors of deterioration of lung function in polish children with cystic fibrosis. Archives of Medical Science. 2016;**2**:402-407

[150] Coriati A, Ziai S, Lavoie A, Berthiaume Y, Rabasa-Lhoret R. The 1-h oral glucose tolerance test glucose and insulin values are associated with markers of clinical deterioration in cystic fibrosis. Acta Diabetologica. 2016;**53**(3):359-366

[151] Bourdy S, Rabilloud M, Touzet S, Roche S, Drai J, Martin C, et al. 178 glucose tolerance in cystic fibrosis patients over a 3-year period (DIAMUCO study). Journal of Cystic Fibrosis. 2015;**14**:S103

[152] Chan CL, Vigers T, Pyle L, Zeitler PS, Sagel SD, Nadeau KJ. Continuous glucose monitoring abnormalities in cystic fibrosis youth correlate with pulmonary function decline. Journal of Cystic Fibrosis. 2018;**17**(6):783-790

[153] Prentice BJ, Chelliah A, Ooi CY, Hameed S, Verge CF, Plush L, et al. Peak OGTT glucose is associated with lower lung function in young children with cystic fibrosis. Journal of Cystic Fibrosis. 2020;**19**(2):305-309

[154] Reynaud Q, Rabilloud M, Roche S, Poupon-Bourdy S, Iwaz J, Nove-Josserand R, et al. Glucose trajectories in cystic fibrosis and their association with pulmonary function. Journal of Cystic Fibrosis. 2018;**17**(3):400-406

[155] Leclercq A, Gauthier B, Rosner V, Weiss L, Moreau F, Constantinescu AA, et al. Early assessment of glucose abnormalities during continuous glucose monitoring associated with lung function impairment in cystic fibrosis patients. Journal of Cystic Fibrosis. 2014;**13**(4):478-484

[156] Prentice BJ, Ooi CY, Strachan RE, Hameed S, Ebrahimkhani S, Waters SA, et al. Early glucose abnormalities are associated with pulmonary inflammation in young children with cystic fibrosis. Journal of Cystic Fibrosis. 2019;**18**(6):869-873

[157] Lam GY, Doll-Shankaruk M, Dayton J, Rodriguez-Capote K, Higgins TN, Thomas D, et al. The use of fructosamine in cystic fibrosis-related diabetes (CFRD) screening. Journal of Cystic Fibrosis. 2018;**17**(1):121-124

[158] Onady GM, Stolfi A. Insulin and oral agents for managing cystic fibrosis-related diabetes. Cochrane Database of Systematic Reviews. 2016;**4**:CD004730

[159] Barrio R. Cystic fibrosis-related diabetes: Novel pathogenic insights opening new therapeutic avenues. European Journal of Endocrinology. 2015;**172**(4):R131-RR41

[160] Bellin MD, Laguna T, Leschyshyn J, Regelmann W, Dunitz J, Billings J, et al. Insulin secretion improves in cystic fibrosis following ivacaftor correction of CFTR: A small pilot study. Pediatric Diabetes. 2013;**14**(6):417-421

[161] Kelly A, De Leon DD, Sheikh S, Camburn D, Kubrak C, Peleckis AJ, et al. Islet hormone and incretin secretion in cystic fibrosis after four

months of ivacaftor therapy. American Journal of Respiratory and Critical Care Medicine. 2019;**199**(3):342-351

[162] Minicucci L, Haupt M, Casciaro R, De Alessandri A, Bagnasco F, Lucidi V, et al. Slow-release insulin in cystic fibrosis patients with glucose intolerance: A randomized clinical trial. Pediatric Diabetes. 2012;**13**(2):197-202

[163] Kolouskova S, Zemkova D, Bartosova J, Skalicka V, Sumnik Z, Vavrova V, et al. Low-dose insulin therapy in patients with cystic fibrosis and early-stage insulinopenia prevents deterioration of lung function: A 3-year prospective study. Journal of Pediatric Endocrinology & Metabolism. 2011;**24**(7-8):449-454

[164] Drummond RS, Ross E, Bicknell S, Small M, Jones GC. Insulin therapy in patients with cystic fibrosis related diabetes mellitus: Benefit, timing of initiation and hypoglycaemia. Practical Diabetes International. 2011;**28**(4):177-182

[165] Hameed S, Morton JR, Field PI, Belessis Y, Yoong T, Katz T, et al. Once daily insulin detemir in cystic fibrosis with insulin deficiency. Archives of Disease in Childhood. 2012;**97**(5):464-467

[166] Pu MZMH, Christensen-Adad FC, Gonçalves AC, Minicucci WJ, Ribeiro JD, Ribeiro AF. Insulin therapy in patients with cystic fibrosis in the pre-diabetes stage: A systematic review. Revista Paulista de Pediatria. 2016;**34**(3):367-373