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Original Article

Abnormal glucose tolerance and lung function in children with cystic fibrosis. Comparing oral glucose tolerance test and continuous glucose monitoring

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ABSTRACT

Background: Cystic fibrosis (CF) related diabetes (CFRD) is a common complication of CF. CFRD is associated with declining lung function even before its onset. Regular screening for CFRD using oral glucose tolerance test (OGTT) is recommended. Additionally, continuous glucose monitoring (CGM) has surfaced as a possible surveillance method, but evidence for its use and concordance with OGTT has not been established.

Methods: Children were prospectively recruited at CF center Lund to undergo both intermittent scan CGM (isCGM) and OGTT. Lung function was evaluated by spirometry and multiple breath washout. Demographic and clinical data were collected from the Swedish national CF registry.

Results: 32 patients participated in the study, yielding 28 pairs of isCGMs and OGTTs. The OGTTs showed that two patients met the criteria of CFRD, seven had impaired glucose tolerance (IGT) and indeterminate glycemia (INDET) was found in eleven cases. The isCGM percent of measurements >8mmol/L and the number of peaks per day >11 mmol/L have correlations with intermediate OGTT glucose time points, but not the 2hour glucose value. Patients with abnormal glucose tolerance (AGT) had lower lung function than those with normal glucose tolerance demonstrated by both FEV1% predicted and lung clearance index (LCI).

Conclusion: Correlations can be found between isCGM and OGTT in regards to the latter's intermediate time points. LCI demonstrates as well as FEV1% of predicted, worse lung function in children and adolescents with abnormal glucose tolerance in CF.

Background

Cystic fibrosis (CF) related diabetes (CFRD) is a very common co-morbidity associated with CF. CFRD can occur at any age and its prevalence increases with increasing age. CFRD affects approximately 1-2% of children under 10 years of age, 10-20% of the age group between 10 and 20 years old and 40-50% of adults with CF [1,2]. Guidelines of the European Cystic Fibrosis Society and the CF Foundation state that all CF patients, not having been diagnosed with diabetes, should be screened for CFRD during a period of clinical stability using the standard WHO protocol for oral glucose tolerance test (OGTT) [2,3]. CFRD screening should be performed annually from the age of 10 years. Although CFRD is rare before 10 years of age, abnormal glucose metabolism is present from a very young age and for this reason, some CF centers begin screening at an earlier age [1,4,5].

CFRD is associated with worse lung function, lower BMI, female gender, previous allergic pulmonary aspergillosis (ABPA) and liver disease and several studies have demonstrated clinical decline in the years before the diagnosis of CFRD, both regarding growth and lung function [6–8]. Even in very young children there is evidence

Abbreviations: CFRD, CF related diabetes; OGTT, oral glucose tolerance test; isCGM, intermittent scan, continuous glucose monitoring; AGT, abnormal glucose tolerance; IGT, impaired glucose tolerance; INDET, indeterminate glycemia; NGT, normal glucose tolerance; LCI, lung clearance index.

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that abnormal glucose metabolism is associated with pulmonary inflammation [9].

Elevated results of mid-OGTT glucose levels (blood glucose levels during OGTT at 30, 60 and 90 minutes) are generally referred to as INDET. There is emerging evidence that mid-OGTT glucose levels may be even more predictive of clinical decline than the 2-h level in regard to lung function decline and INDET has been shown to be a predictive indicator of evolving CFRD [10,11].

Although OGTT is the most widely used method for CFRD screening, continuous glucose monitoring (CGM) has become more frequently used by some CF centers as part of the diagnostic process [3,12]. CGM has been validated for children and adolescents with CF but there are no official clinical guidelines concerning CGM use for the screening of CFRD. CGM has the advantage of examining glycemic control in real life settings and offers data on interstitial glucose levels during the time a sensor is placed on the subject's arm [12,13]. However, its concordance with OGTT is not straight forward and CGM does not reveal the same information as OGTT. Glucose measured in the interstitial fluid may differ substantially from blood glucose values and interstitial values are not used for the diagnosis of diabetes. [14]. Glucose abnormalities demonstrated by CGM have been shown to be associated with impaired lung function in CF patients without CFRD [15,16]. Very few studies regarding CFRD have included lung clearance index (LCI) as a lung function parameter but multiple breath washout has become a more frequently used method for measuring lung function especially in the pediatric population [17,18]. The study presented here was designed to further investigate the relationship between OGTT and CGM in CF patients and to explore the association of an inferior lung function, examined by both spirometry and multiple breath washout, in the presence of blood glucose abnormalities.

Material and methods

All participants had been diagnosed with CF based on typical clinical presentation and identification of disease-causing mutations in the CFTR gene.

Children from the age of 7 and adolescents were prospectively recruited at CF center Lund, Skane University Hospital in the years 2018-2019. Patients previously diagnosed with CFRD were excluded. The study was approved by the local ethical review board (#2018/54) and parents and teenagers aged 15 and older gave their written consent.

The participants were evaluated at their annual assessment where data was collected. They underwent both OGTT and intermittent scan CGM (isCGM) as part of their annual assessment and performed spirometry and multiple breath washout.

OGTT was performed according to WHO guidelines, where 1,75g/kg dextrose (maximum dose 75g) was administered after overnight fasting during clinical stability, and blood glucose levels were measured at 0, 30, 60, 90 and 120 minutes in mmol/L along with baseline HbA1c in mmol/mol. HbA1c was analyzed with Capillarys 3 TERA HbA1c Kit Program.

The isCGM was conducted with the Freestyle libre® equipment. A sensor was applied on the subjects' upper arm and the children and the parents were asked to scan the sensor with their monitor minimally every 8 hours, when possible, for a 14-day period, provided the sensor stayed in place. The isCGM data were downloaded to the Diasend® net application. After completing both OGTT and isCGM, the children were asked to answer a questionnaire regarding the different methods. Additional data were collected from the results of the annual assessments as registered in patients' charts and the Swedish national CF registry, including age, specific CFTR mutation, height (z score), weight (z score), bacterial colonization and lung function including forced expiratory volume in 1 second percent predicted (FEV1% predicted) and lung clearance index (LCI).

Based on the results from the OGTT, CFRD was defined from as fasting blood glucose $\geq$ 7 mmol/L (126 mg/dl) and/or a 120-minute blood glucose value $\geq$ 11.1 mmol/L (200 mg/dl). An impaired glucose tolerance (IGT) was defined as a fasting blood glucose $<$ 7 mmol/L (126 mg/dl) and a 2-hour blood glucose value $\geq$7.8 mmol/L (140 mg/dl), but $<$11.1 mmol/L (200 mg/dl). Indeterminate glycemia (INDET) was defined as a fasting blood glucose $<$ 7 mmol/L (126 mg/dl) and a 120-minute blood glucose value of $<$ 7.8 mmol/L (140 mg/dl), but at least one intermediate blood glucose value $\geq$ 11.1 mmol/L (200 mg/dl). Abnormal glucose tolerance (AGT) is the collective term of all three CFRD, IGT and INDET.

Data collected from isCGMs consisted of the total number of days registered, the total number of measurements, the daily number of measurements, the average interstitial glucose values in mmol/L, the maximal and the minimal values of interstitial glucose in mmol/L and the standard deviation (SD). The number of measurements $\geq$ 11.1 mmol/L (200 mg/dl) were counted from each analysis and the proportion of measurements $>$ 8 mmol/L (144 mg/dl) were calculated.

Multiple breath washout (MBW) was performed on Exhalyzer-D with 3 consecutive measurements per patient resulting in an average LCI value which represents ventilation inhomogenity [19]. FEV1% predicted values were obtained via spirometry using the Global Lung Function Initiative equations [20]. Measurements from the annual review visits were used.

Statistical analysis was performed using IBM SPSS Statistics version 26 (IBM Svenska AB, Stockholm, Sweden). Correlations between isCGM and OGTT were calculated using Pearson's correlation test. Continuous data were analyzed for normality of distribution. If normally distributed, the independent samples t-test was used, otherwise a Mann-Whitney U test was performed. Results of these analyses are presented as mean + SD or median (range) respectively. Level of significance was determined at p-value $\leq$0.05.

The children were asked to grade the OGTT and the isCGM experiences, and the ability to remember the isCGM measurements, using the scale: (1)very easy, (2) easy, (3) neither easy, nor difficult, (4) difficult or (5) very difficult. They also had the opportunity to write their own comments.

Results

32 patients provided data on 35 isCGMs and 36 OGTTs. 28 participants provided 33 measurements of both isCGM and OGTT and for each participant one OGTT and one isCGM were used for correlations' calculations. 4 participants had missing data for either isCGM (3) or OGTT(1). Demographic and clinical data of these 32 individuals is shown in Table 1. Data from all 32 patients were used in the comparison of lung function between groups with one measurement per individual respectively. All participants had pancreatic insufficiency and the majority was homozygous for ΔF508 mutation.

Table 1
Demographic and clinical data of the 32 patients.

Age years, median (range)	11.5 (7-16.3)
Female (%)	14 (43.75)
Homozygous ΔF508 n (%)	24 (75)
FEV1% predicted, median (range)	87.35 (57.7-120.9)
LCI, median (range)	8.26(5.78-14)
Height z-score, median (range)	-0.63 (-2.99-1.8)
Weight z-score, median (range)	-0.51 (-2.95-1.19)
Chronic colonization of gram negative bacteria* n (%)	6 (18,75)

* Pseudomonas aeruginosa, Stenotrophomonas maltophilia, Achromobacter xylosoxidans, Burkholderia cepacia complex

Table 2
Results of isCGMs and OGTTs (number).

	Median	Maximum	Minimum
isCGM total number of measurements (29)	1012	2404	488
isCGM number of measurements per day(29)	69.5	114	41
isCGM peak value mmol/L (29)	13.6	17.2	9.4
isCGM percentage of measurements > 8 mmol/L (29)	11.3	31.6	0.6
isCGM average number of peak values above 11 mmol/L (29)	0.5	3.6	0
isCGM standard deviation (29)	1,4	2,3	1,1
isCGM number of days monitored (29)	14	15	6
OGTT fasting blood glucose in mmol/L (31)	5.4	8.5	4.4
OGTT 30 min blood glucose in mmol/L (26)	9.5	12.5	5.9
OGTT 60 min blood glucose in mmol/L (29)	11.1	16.1	5.0
OGTT 90 min blood glucose in mmol/L (24)	9.5	17.0	5.7
OGTT 120 min blood glucose in mmol/L (31)	7.5	14.4	5.0
HbA1c mmol/mol (28)	36	43	32

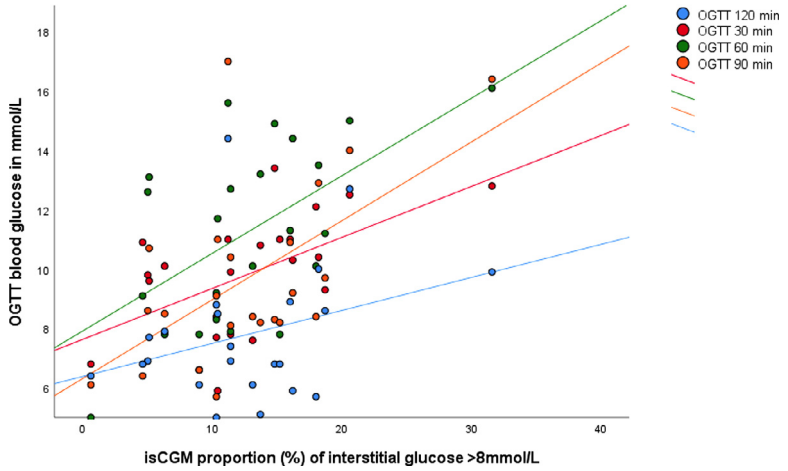

Fig. 1. Correlations between the percentage of measurements above 8 mmol/L during isCGM and OGTT blood glucose values in mmol/L at 30, 60, 90 and 120 minutes. isCGM proportion of interstitial glucose values above 8mmol/L and OGTT blood glucose values at 30 minutes r(25)= 0.546, p= 0.005; 60 minutes, r(26)= 0.515, p= 0.007; 90 minutes r(23)= 0.585, p= 0.003; 120 minutes r(28)=0.311, p=0,1.

IsCGM and OGTT results

Median number of days using isCGM was 14 days and on average 12.67 days. All but two patients had at least one glucose peak above 11 mmol/L, with a median number of 0.5 peaks per day. The median value of measurements >8 mmol/L was 11.3%.

Thirty-two participants provided 31 OGTTs. These showed that 2 patients (6.5%) met the criteria of CFRD, having 2-h blood glucose levels of 14.4 mmol/L and 12.6 mmol/L, respectively. Seven OGTTs (22.5%) showed IGT and INDET was found in another eleven OGTTs (35.5%). Ten participants had NGT (32.2%). Thus AGT was detected in 21 of the OGTTs (67.7%). Table 2 presents the results of the isCGMs and the OGTTs.

Comparing isCGM and OGTT

Comparing the results of the isCGMs and OGTTs, there was a correlation between the percentage of measurements above 8mmol/L in the isCGMs and elevated blood glucose levels found at 30 minutes (p=0.005), 60 minutes (p=0.007) and 90 minutes (p=0.003) in the OGTTs (Fig. 1). Furthermore, a statistically significant correlation between the average number of peak values above 11.0 mmol/L in the isCGMs and elevated blood glucose levels found at 60 minutes (p=0.035) and 90 minutes(p=0.005) in the OGTTs was found .There were no correlations between the isCGM results and 2-h values from the OGTTs.

Specific observations

Two patients receiving gastrointestinal tube feeding once a day had a high proportion of measurements above 8mmol/L and high number of peak values above 11,0 mmol/L, one of which was prescribed insulin therapy after the study despite two OGTTs not revealing CFRD values but IGT.

There was a statistically significant correlation between HbA1c in mmol/mol and the proportion of interstitial glucose measurements > 8mmol/L during isCGM (r(26)= 0.479, p= 0.013). Furthermore, there was a statistically significant correlation between HbA1c in mmol/mol and the average interstitial glucose level (r(26)= 0.517, p= 0.007).

There was no statistically significant difference between patients with normal glucose tolerance (NGT) and AGT according to OGTT in terms of height (z-score), weight (z-score) or HbA1c (mmol/mol). All participants but one with NGT had HbA1c level of < 36.6mmol/mol (5.5%). Six patients had chronic colonization of *Pseudomonas aeruginosa*, two of which had NGT and four patients had AGT according to OGTT. Hence there was no difference in bacterial colonization of gram negative bacteria between these groups.

Questionnaire

The isCGM was well tolerated by all patients. The majority of patients was more positive towards isCGM than OGTT and all but two felt that isCGM was very easy or easy to both carry and to remember to scan, whereas the opinions on OGTT were more evenly

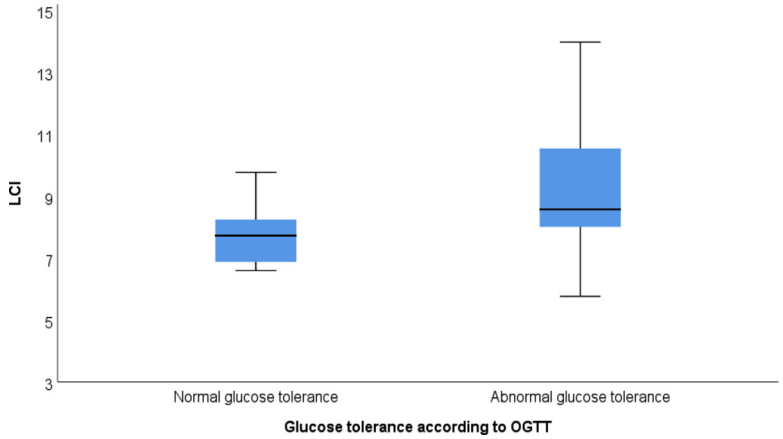

Fig. 2. The difference in lung function measured by LCI. LCI in NGT: (N=10), mean 7.88, SD 1.09. LCI in AGT: (N=19), mean 9.46, SD 2.3995%CI -2.91 - -0.25, p= 0.022.

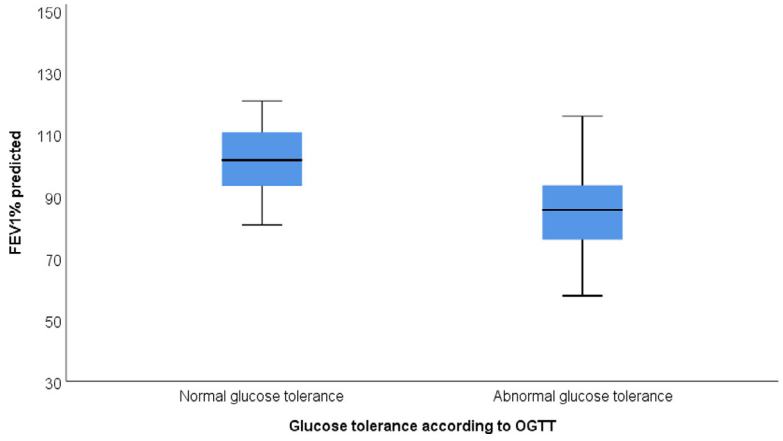

Fig. 3. The difference in lung function measured by FEV1% predicted. FEV1% predicted in NGT: (N=10), mean 100.95, SD 12.52. FEV1% predicted in AGT: (N=21), mean 85.56, SD 14.79 95%CI 4.30-26.49, p=0.008LCI in NGT: (N=10), mean 7.88, SD 1.09LCI in AGT: (N=19), mean 9.46, SD 2.3995%CI -2.91 - -0.25, p= 0.022.

spread with both positive and negative experiences. Most comments were regarding the OGTT, including comments on the taste of the glucose liquid and problems with iv access.

Abnormal glucose tolerance and lung function

There was a significant difference in lung function between patients with NGT and AGT, both measured by LCI (p= 0,022) and FEV1% predicted (p=0.008) (Figs. 2 and 3). When analyzing the different types of AGT, the participants having INDET had a significantly lower FEV1% of predicted (p=0.01) and a higher LCI (p=0.043) compared to their counterparts with NGT. For FEV1% predicted the median (range) for the NGT group was 102(81-121) and for the INDET group 84(58-111). In regard to LCI the median (range) for the NGT group was 7.7(6.6-9.8) and for the INDET group it was 8.8(5.8-13.0).

The analysis of the isCGM results in relation to lung function showed that there was a significant difference in lung function, measured as FEV1% predicted, between those with equal or more than 0.5 peaks > 11mmol/L per day in interstitial glucose and those with fewer than 0,5 peaks per day (p=0.018; . The same trend was seen for LCI and peaks per day but it did not reach statistical significance (p=0.052). No difference was found in lung function in regard to the proportion of measurements with interstitial glucose above 8 mmol/L or the average interstitial glucose values on isCGM.

Discussion

Abnormal glucose metabolism is an important aspect of CF with the spectra ranging from glucose abnormalities in the early years of life evolving into CFRD with increasing age. The importance of detecting glucose abnormalities is gaining more attention because of the association with clinical deterioration [21]. In this treatise we have compared two methods for detecting an affected glucose metabolism, OGTT and isCGM. In our study population, a high proportion of the subjects investigated with OGTT show abnormal glucose tolerance (67.7%). Likewise, the results of the isCGM show a high proportion of measurements with interstitial glucose values above 8 mmol/L and a high number of peak values per day above 11.0 mmol/L which is more than Clemente Léon *et al* found in their cohort [22]. This could partially be explained by the fact that all participants in our study population have class one or class two CFTR mutations in each allele and are therefore more likely to have AGT and develop CFRD. This further strengthens the notion that CFRD screening is important especially for patients with the more serious mutations. In order to minimize the participants' effort they were not asked to record dietary intake during their isCGM registration period. This could be a disadvantage in the interpretation of the isCGM results since it is not possible to determine if a high proportion of carbohydrates in their diet could be an important factor.

There are certain important limitations to OGTT in CFRD screening. One is the fact that this method of screening is taken from type 2 diabetes, which has a different pathophysiology from CFRD

and there is evidence that the 2-h blood glucose level and fasting glucose level are not as important values in CF as they are in type 2 diabetes [23]. Only one participant in our study had an elevated fasting blood glucose level and two had a 2-h blood glucose level consistent with CFRD. It is important to seek better methods to evaluate glucose metabolism abnormalities in CF and both IGT and INDET have shown to be of clinical significance, especially when it comes to lung function, also illustrated in this study. Not all papers have included INDET as an important measurement and therefore the OGTT results in these cases may underestimate the glucose abnormalities.

Previous studies have not all been able to show a clear correlation between OGTT and isCGM results in CFRD screening [22,24]. Our results reveal that there is a significant correlation between the proportions of interstitial glucose levels above 8mmol/L during isCGM and the INDET values. Furthermore, there is a correlation between the number of peaks per day above 11 mmol/L and the INDET values. This indicates that these variables from the isCGM could be the most important ones in the surveillance of glucose abnormalities in CF. However, the lack of correlation between isCGM and the 2h value from the OGTTs is of great consideration since the CFRD diagnosis could be missed if only CGMs were to be used in CFRD screening. Furthermore, even though some correlations were found between isCGM and OGTT these were not of great power in this modest sample and therefore caution is advisable in this regard.

Lung function is one of the most important outcome measures in CF and the relationship between glucose abnormalities and a decline in lung function has been previously demonstrated [7,15,25]. Multiple breath washout, however, has not been frequently used to examine lung function in relation to glucose abnormalities, and our goal was to contribute to this knowledge by including LCI as a lung function variable. The difference in lung function between patients with AGT and NGT is demonstrated by both methods in this study. Interestingly, the difference in lung function between the NGT group and the INDET group is demonstrated by both LCI and FEV1% predicted even in a small cohort like this one, which emphasizes the important connection between the mid glucose values in the OGTT and lung function. The same difference was not seen in regards to IGT and CFRD and the smaller numbers may involve some explanation for that.

There are still gaps in our knowledge when it comes to understanding the link between AGT and lung function. Certainly, bacterial colonization and inflammation are important factors as demonstrated in several papers [9,26,27]. We found a relatively low number of patients in our cohort with chronic colonization of *P. aeruginosa* and other gram negative bacteria. There was no difference in chronic bacterial colonization of these bacteria between the groups of NGT and AGT as in the former there were 2 cases out of 10 and 4 cases out of 21 in the latter. Interestingly all four patients with chronic colonization and AGT belonged to the group of INDET cases which could further implicate the clinical significance of INDET. Our intention is to explore further this observation in future research.

The question still remains whether in the presence of AGT it is possible to prevent or diminish the decline in lung function with earlier intervention. There are indeed studies showing an association between improved weight and lung function, and earlier treatment of glucose abnormalities [28]. The CGM could help detect patients eligible for insulin treatment earlier than indicated by OGTT results. In order to answer that question large prospective studies must be conducted though. Furthermore, it is essential to establish whether glucose abnormalities in CGM have a clinical relevance. Chan *et al* showed that higher and more variable glucose levels correlate with lung function decline measured by FVC% predicted and FEV1% predicted respectively [16]. Leclercq *et al* demonstrated the importance of peak values above 11 mmol/L (200mg/dl) in relation to lung function measured by FEV1% predicted and FVC% predicted and infection with Pseudomonas aeruginosa [15]. In our study, however, the association between the results of the isCGM and lung function were not as strong as the OGTT counterparts. This is particularly important for those CF centers relying more on CGM results than OGTT in CFRD screening. We found that the average peak glucose values above 11 mmol/L on isCGM and the INDET values on OGTT were the most important markers of lower lung function values, but more research is required to further explore this relationship. Future studies will also have to determine whether CGM can reveal risks of developing CFRD, also in the pediatric population, as suggested by Taylor-Cousar et al [24].

The disadvantage of studies on the use of CGM in screening for CFRD, is lack of standardization to compare the results between studies. There are various equipment for CGM and different centers and research groups have published data for different periods of time and in different settings, unlike OGTT which is performed in a more standardized way. It would be of great benefit to aim for a more standardized approach and one step in that direction is presented in a practical guide by Chan *et* al, which can hopefully spur future efforts in this arena [12].

The recent study of Gilmour *et al* has demonstrated an alternative approach for CFRD screening in order to reduce the need for OGTT. Introducing the cutoff HbA1c value of 5.5% (36.6 mmol/mol) as an indicator for the need for further screening with OGTT could be an attractive method but has not yet been validated for the pediatric population [29]. In our study all but one of the NGT participants had their HbA1c level below this cutoff point which is promising but the cohort is too small to make any concrete assumptions. In the paper of Chan *et al* HbA1c was found to correlate with the average CGM derived glucose level in youth and our study is in line with their findings [30]. HbA1c could indeed have a role in CFRD screening and future studies will hopefully continue to explore this possibility.

From a patient perspective it seems that the isCGM is well tolerated and even for periods up to 14 days, there were very few problems or complaints about this method of screening. Almost all of the participants had the sensor on for the whole 2 weeks, which is longer than previous studies have been able to establish. When using the isCGM more frequently it would become even easier for the patients, as they get more experienced, and CGM does offer a better oversight of the blood glucose levels in everyday life.

One of the limitations of this study is the small number of participants even though a large proportion of eligible patients from the pediatric CF center in Lund participated. The small number risks some bias as for the inclusion of children receiving gastrointestinal tube feeding. However, it is important to take these into account in research on glucose abnormalities as it is highly relevant for children receiving this nutritional treatment. There are certain limitations to the use of the Freestyle libre equipment such as the need for scanning the sensor repeatedly every eight hours which perhaps is not always possible in real life and missing data can therefore be substantial. More recent technology can minimize this problem and can give more accurate evaluations.

The conclusion of this paper is that isCGM can be a valuable addition to OGTT in evaluating glucose abnormalities in CF although its clinical implications are not fully understood and standardization of its use is required. We need to learn more about the effects of AGT on lung function and if these effects are preventable by early intervention. Our recommendation, from a clinical perspective and for the purpose of adding further knowledge on abnormal glucose tolerance in CF, is to use both OGTT and CGM in the evaluation of glucose metabolism in CF. Shifting the focus from CFRD diagnosis to AGT in CF could be an important step in improving the care of CF patients.

Credit author statement

All authors have made substantial work in to this paper

Helga Elidottir: Study design. Ethical application. Study protocoll. Recruiting patients. Writing most of the paper. Statistics with assistance.

Stefanie Diemer: Ethical applications and study protocoll with Helga. Consent forms and participant information. Critical review of the paper.

Erik Eklund: Superior supervisor . Critical review and corrections of the study protocol, ethical application and this paper.

Christine Hansen: Co-supervisor . Study protocoll. Recruiting patients. SPSS statistics work with Helga. Critical review and corrections of the whole process and this paper.

Declaration of Competing Interest

Authors declare no conflict of interest

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