TITLE: CONTINUOUS GLUCOSE MONITORING GUIDED INSULIN THERAPY IS ASSOCIATED WITH IMPROVED CLINICAL OUTCOMES IN CYSTIC FIBROSIS-RELATED DIABETES.

RUNNING TITLE: CGM GUIDED INSULIN THERAPY

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Abstract:

Introduction:

Continuous glucose monitoring (CGM) allows assessment of day to day glycaemic excursions and detects early glucose handling abnormalities that may not be apparent on oral glucose tolerance testing (OGTT). However, there is little published evidence as to whether these early dysglycaemic changes are amenable to treatment. We present outcomes following CGM guided insulin initiation at our centre.

Methods

Adults without a prior diagnosis of cystic fibrosis related diabetes (CFRD) whom underwent >72 hours CGM at our adult CF centre were included in the study. Clinical outcomes including weight and pulmonary function changes over the next 12 months were compared between groups based on CGM results and subsequent management.

Results

CGM profiles for 59 patients were analysed. Insulin was commenced in 37 patients who had evidence of hyperglycaemia on CGM. Significant improvements in mean [95% confidence intervals] forced expiratory volume in 1 second (FEV_1) (+4.3% predicted [1.06-7.48], p=0.01) and weight (+1.2kg [0.32-2.15], p=0.01) were observed at 3 months in the insulin group. Annual rate of pulmonary function decline was also improved following insulin initiation.

Conclusion

Insulin treatment targeted towards glycaemic excursions seen on CGM is associated with improvements in lung function and weight with subsequent reduced pulmonary function decline.

1. Introduction

Increasing survival in cystic fibrosis (CF) has brought increasing co-morbidities, the most common of which is cystic fibrosis related diabetes (CFRD) occurring in up to 50% of adults.[1] The mechanisms underpinning CFRD are incompletely understood, however its pathogenesis appears to be driven by progressive insulin deficiency with insulin resistance, incretin axis abnormalities, and primary cystic fibrosis transmembrane conductance regulator (CFTR) protein dysfunction playing contributory roles.[2-6] CFRD is associated with increased pulmonary exacerbations, increased mortality and accelerated pulmonary function decline often preceding the point at which diagnosis is made.[1, 7, 8]

Traditional guidelines consider that a diagnosis of diabetes mellitus should be based upon the glycaemic response to a 75 g oral glucose load (the oral glucose tolerance test, OGTT), where glucose cut-off thresholds are those associated with an increased incidence of macro-vascular disease in an ageing population.[9] However in CF, dysglycaemia is a dynamic process due to variable insulinopenia, a heightened metabolic rate during inter-current infection, and poorer respiratory outcomes occur at a lower threshold of glucose intolerance. Furthermore, risk of microvascular dysfunction is higher in CF and therefore lower thresholds for diagnosis and treatment may be appropriate. [10] The OGTT is a static test that may not detect these early glucose handling abnormalities and is uncomfortable for patients: it is therefore less appropriate for people with CF, who have a high treatment burden and some form of dynamic glucose measurement is indicated. In keeping with this, the latest CF guidelines indicate that glucose monitoring over a period of time is more appropriate, even when the OGTT is first used. [11]

Continuous glucose monitoring (CGM) is one such strategy and involves the use of a small sensor sited in the subcutaneous interstitial fluid that makes frequent glucose measurements. These devices are worn for three to five days and hence enable an accurate glucose profile to be visualised. CGM has been validated in the CF population and can detect glucose handling abnormalities otherwise missed by an OGTT.[12-14]

Our practice is to use CGM to identify patients who may benefit from intervention and also to optimise management in those with CFRD. In this study we investigate the impact of CGM guided insulin initiation on clinical outcomes.

2. Methods:

2.1 Study population and clinical parameters

Adults with CF but without a previous diagnosis of CFRD (as defined by prior use of hypoglycaemic agents, diabetic OGTT or abnormal CGM) who had undergone CGM at our centre between 2013 and 2016 were included. Transplant recipients were excluded. Baseline clinical parameters are shown in Table 1. For change in lung function, the best % predicted forced expiratory volume in 1 second (FEV_1) calculated using Global Lung Function Initiative (GLI) reference values was compared one year before and after CGM, and for shorter term outcomes at 3 months before and after respectively. [15] For changes in nutritional state, weight was recorded similarly at 3 and 12 months pre and post CGM. Total intravenous antibiotic days were noted during the year before and after CGM.

2.2 **CGM profiling and treatment.**

CGM was performed as per local protocol at our centre. Briefly, CGM devices (Freestyle Navigator, Abbott UK) were worn for up to 5 days and calibrated with self-measurement blood glucose (SMBG) five times across the first 72 hours of monitoring. Results were accepted where there was at least 72 hours monitoring and appropriate calibration. Subjects completed a food and exercise diary for the entire CGM period which was reviewed in conjunction with the downloaded glucose profile. Glucose levels >7.8mmol/L for >4.5% of the whole CGM period were considered significantly hyperglycaemic as previously described [16], the remainder were classed as “normal”. In those with hyperglycaemia, if there were clear triggers in the food diary amenable to dietary modification, e.g. sugary soft-drinks or sub-optimal pancreatic enzyme supplementation, a period of dietary modification was advised (dietary modification group). If there were no triggers amenable to dietary modification insulin therapy was considered (insulin group). Local protocol for insulin initiation consists of insulin detemir once daily but alternative regimes are considered after taking the CGM glycaemic profile, patient choice and lifestyle into account.

2.3 Statistical analysis:

Statistical analysis was performed using R (R Foundation for Statistical Computing, Vienna, Austria). Baseline clinical characteristics are presented as mean and standard deviation for continuous variables and count and percentage for categorical variables. 95% confidence intervals are given for the outcome variables. Elsewhere, differences between independent groups were calculated by Mann-Whitney or unpaired t-test for non-parametric and parametric results respectively. Differences in clinical parameters before and after treatment were calculated using a paired t-test.

3. Results

The CGM profiles of 59 adults with CF (mean age [SD] 28 [9] years, mean FEV_1 64.9 [22.0] %predicted, 58% male) formed the dataset (Table 1). Average CGM period was 4899 minutes (3.4 days). The most frequent indication for CGM (27/59 episodes, 46%) was an elevated capillary blood glucose during an inpatient stay or at annual screen. An unexplained drop in FEV_1, unexplained weight loss or osmotic symptoms accounted for 21/59 (36%), 7/59 (12%) and 3/59 (5%) respectively.

3.1 Clinical Parameters at CGM

At CGM 52/59 (88%) had evidence of dysglycaemia: 15/52 (29%) had clear nutritional triggers and dietary modification was advised whilst the remaining 37 (71%) were treated with insulin. 35/37 (94.6%) were commenced on insulin detemir once daily (average [range] initial dose 4.9 units [2-10]) and 2/37 (5.4%) insulin lispro 2 units. Time spent above 7.8mmol/L was inversely associated with baseline FEV_1 (r= -0.38, p<0.01) and also FEV_1 decline in the preceding year (r=-0.31, p=0.01). At baseline there were no differences in age, sex, *P. aeruginosa* colonisation or genotype, but the insulin group had poorer mean lung function than the dietary modification and normoglycaemic groups (% predicted FEV_1 56.7% vs. 79.7% and 76.6% respectively, p<0.001), had more IV days in the preceding year (37 days vs. 6 days and 13.1 days respectively, p<0.01) and a lower weight (61.2 kg vs. 74.1 kg and 69.0 kg respectively, p<0.01).

A moderate positive correlation was observed between time spent with blood glucose >7.8mmol/l and HbA1c (r=0.376, p<0.01). Of those with evidence of abnormal glucose handling, 37/52 (71%) had at least one excursion >11.2mmol/L, and 28/52 (59%) spent >1% of time above 12mmol/L. Hypoglycaemic episodes (<4.0mmol/L)

were equally prevalent between the hyperglycaemic and normal groups (29% and 36% respectively, p=0.12). Mean annual decline (SD) in % predicted FEV_1 was -0.4%/yr (2.1), -1.3%/yr (3.7) and -1.74%/yr (2.9) for the normal, dietary modification and insulin initiation groups respectively.

3.2 Outcomes

Clinical outcomes are presented in table 2. In the insulin group improvements were observed in % predicted FEV_1 (+4.27% [1.1-7.48] p=0.01, see Figure 1A) and weight (+1.2kg [0.3-2.1], p=0.01, see Figure 1B) in the first 3 months of treatment and although at 12 months treatment lung function was no longer significantly greater than pre-treatment, the rate of pulmonary function decline had significantly improved (+1.92%/yr, p=0.02). No differences in annual intravenous antibiotic days were observed following insulin initiation.

For those individuals who did not require insulin or dietary modification, no significant differences were seen in weight (-0.66kg, [95% CI -1.91-0.6], p=0.22), lung function (+1.1% [-4.9-2.7], p=0.49) lung function change (+0.01% [-1.82-1.84], p=0.99) or IV antibiotic usage (-1.4 days [-12.7- 9.8], p=0.06) for the period before and after CGM. In the dietary modification group, there were no significant differences at 3 months, however at 12 months FEV_1 was worse (-2.7% [-4.82-0.64], p=0.01) and average IV antibiotic days had increased (+4.6 days [0.6-8.68], p=0.02).

In those receiving insulin there was no correlation between changes lung function or weight and the degree of hyperglycaemia (FEV_1 change r=0.05, [-0.21-0.30], p=0.70; weight change r=0.17, [-0.08 -0.41], p=0.19).

3.3 Repeat Studies

Repeat CGM results were available in 30/37 (81%) individuals commenced on insulin, see Table S1. Average absolute reduction [95% CI] in time spent >7.8mmol/L was 8% [1-14.5]. Changes in average time spent in each glycaemic zone are presented in Figure 2. Again we tested whether improvements seen on repeat CGM correlated with improvements with clinical parameters but no correlations were observed for v, weight, IV days, or episodes of hypoglycaemia.

3.4 Insulin responders

32/37 (86.5%) of those commenced on insulin had improvement in weight and/or lung function at 3 months. Of these, 31/32 (97%) had HbA1c <48mmol/mol and

20/32 (62.5 %) <40mmol/mol, see Figure 3. Only 7/32 insulin responders (21.9%) had more than one excursion >11.1mmol/l across their initial CGM monitoring period.

4. Discussion

The aims of this study were to investigate the impact of CGM guided insulin initiation on clinical outcomes. Although CGM is well validated in CF as a tool to detect early clinically significant glucose handling abnormalities that may not be observed on an OGTT, [12-14] whether these early abnormalities are amenable to treatment is not well established. For the first time, we have shown that CGM-guided insulin therapy can be associated with significant improvements in pulmonary function and weight.

We found that increasing time spent with interstitial glucose levels >7.8mmol/L was associated with poorer baseline lung function and steeper pulmonary function decline in the year preceding CGM. Insulin initiation based on this threshold was associated with improvements in lung function and weight and furthermore the subsequent rate of decline in lung function had been slowed. These findings are consistent with our previous work demonstrating that insulin improves nutritional state and temporarily improves pulmonary function in people with CFRD.[17]

CGM use in CF was first validated over 13 years ago but until recently it was not incorporated into formal CFRD guidelines and its use in the CF community remains heterogeneous. CGM is an accurate screening tool for CFRD that has significant advantages over an OGTT. Firstly, the longer and more frequent monitoring period allows a more sensitive assessment of lower degrees of dysglycaemia which are clinically significant in people with CF but may be missed by an OGTT. Secondly, it provides a “real world” assessment of glucose handling and hence can identify the response to mixed meals, drinks and exercise that an artificial single fasting glucose load cannot. These and the logistically intense nature of an OGTT make it a less appealing diagnostic strategy and previous reports have suggested less than half of centres use OGTT routinely. [18]

The threshold of 4.5% of time spent above 7.8mmol/L was first identified as predicting clinical decline in children with CF and to our knowledge this is the first study to demonstrate its validity in the adult settling. [16] A number of other CGM parameters have been suggested including the presence of any reading >11mmol/L [19, 20], mean glucose [13], and more recently the usefulness of interquartile range and glycaemic variability have been introduced. [21, 22] A threshold based on a continuous outcome (e.g. % time spent >7.8mmol/L) rather than binary outcome (e.g.

presence of any value >11mmol/L) allows quantification of the level of dysglycaemia which can be useful for monitoring treatment response. Furthermore, the cut-off of 7.8mmol/L has biologic plausibility in that airway glucose concentration begins to increase once blood glucose rises above 8mmol/L.[23] Increased airway glucose concentration has been associated with acquisition of respiratory pathogens and hence may play a role in the deleterious clinical outcomes associated with CFRD.[23, 24] Further work is required to establish whether 4.5% is the optimal quantum upon which treatment should be initiated.

Interestingly, we did not observe any correlation between degree of hyperglycaemia and clinical improvement following insulin initiation. This may simply be because this study was not powered to detect such a change or that poorer glycaemic control requires a longer time to optimise and was not captured in the follow-up period. Alternatively, it may demonstrate that insulin is uniformly beneficial for those with CFRD and also those in the “pre-diabetic” stage. Pre-diabetes, otherwise termed glucose intolerance or impaired glucose tolerance, represents relative insulin deficiency, which is associated with excess protein catabolism, a pro-inflammatory state and deleterious pulmonary and nutritional outcomes in CF. [25, 26] Hence, one explanation for the apparent lack of relationship between improved clinical outcomes and glycaemic control is that improvements associated with insulin therapy may be mediated by its anabolic and anti-inflammatory properties in addition to its glucose lowering properties.[27]

Where there are clear nutritional triggers for glycaemic excursions our practice has been to advise dietary modification in the first instance. We found this strategy was associated with increased weight loss and intravenous antibiotic use perhaps suggesting this group may also require insulin. However, it must be considered that numbers in this group were small and unfortunately compliance data was not collected hence it is unclear whether the dietary recommendations were adhered to. Larger studies elsewhere have previously shown that increased nutritional intervention can be associated with maintained nutritional status in the “pre-diabetic” phase. [28]

The recent emergence of a primary role for CFTR in beta cell function , together with the understanding that CF may associated with a degree of abnormal glucose metabolism from birth has led to the question of when to commence insulin treatment becoming more pertinent. [6, 29, 30] Whilst the distinction between impaired glucose tolerance and diabetes may be relevant in the management of conventional diabetes, earlier treatment may be of benefit in CF where deleterious clinical outcomes occur

with dysglycaemia and there is excess mortality later in frank CFRD. [31] Equally, as the life-expectancy of people with CF increases the cardiovascular consequences of hyperglycaemia may become more prevalent in the CF population, particularly with the increased vascular dysfunction previously found in relatively healthy people with CF. [32] Thus, further underlining the potential importance of early treatment and optimal control of dysglycaemia. A number of small studies have investigated the use of early insulin in CF and most have demonstrated improvement in clinical outcomes although the overall quality of evidence in this area remains poor and larger prospective studies remain a priority. [26, 33-35]

A limitation of the present study is that it is single-centre and hence its generalisability is uncertain. We have treated adults with CF with insulin based on CGM findings alone and although no changes in clinical outcomes were observed in the group who did not receive insulin, the lack of a true control or comparator group means our findings must be confirmed by prospective trials. Furthermore, our use of CGM was targeted at specific individuals with, for example, unexplained clinical deterioration rather than in a screening program and hence the pre-test probability of a positive result in our cohort will be higher than seen across the whole non-diabetic CF population. Conversely, although we found CGM evidence of dysglycaemia in 52/59 (88%) of CF subjects, higher than that reported by Leclercq *et al* [19], where 26/52 (50%) non-diabetics had evidence of dysglycaemia, our findings were lower than recently reported by Taylor-Cousar *et al* [20], where 10/10 (100%) subjects with a normal OGTT had evidence of impaired glucose handling, but similar to those of Leon *et al* [36] where 13/14 (92.8%) subjects with a normal OGTT had evidence of dysglycaemia on CGM. The variation in study sizes and thresholds utilised for classification of dysglycaemia may partly explain the differing prevalence of CFRD seen across these studies. Although further criticism of our study could be that the dysglycaemia seen on CGM in our cohort might have been detected by OGTT, CGM is well validated in detecting abnormalities not apparent on OGTT, [19, 37, 38] and the mean Hba1c in the insulin treated group was <40mmol/mol, a cut-off below which only 6% have a positive OGTT. [39]

In conclusion, we have demonstrated for the first time that insulin treatment based on CGM abnormalities alone can be associated with improved pulmonary function and weight in the short-term with reduced pulmonary function decline in the longer-term. Prospective clinical trials are needed to define optimal thresholds for early intervention.

Conflict of Interest: None declared

Acknowledgements: None declared

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Figure 1: Changes in lung function (A) and weight (B) over the study period. Insulin was commenced at time 0 for the insulin group. Data are presented as mean+/- SEM

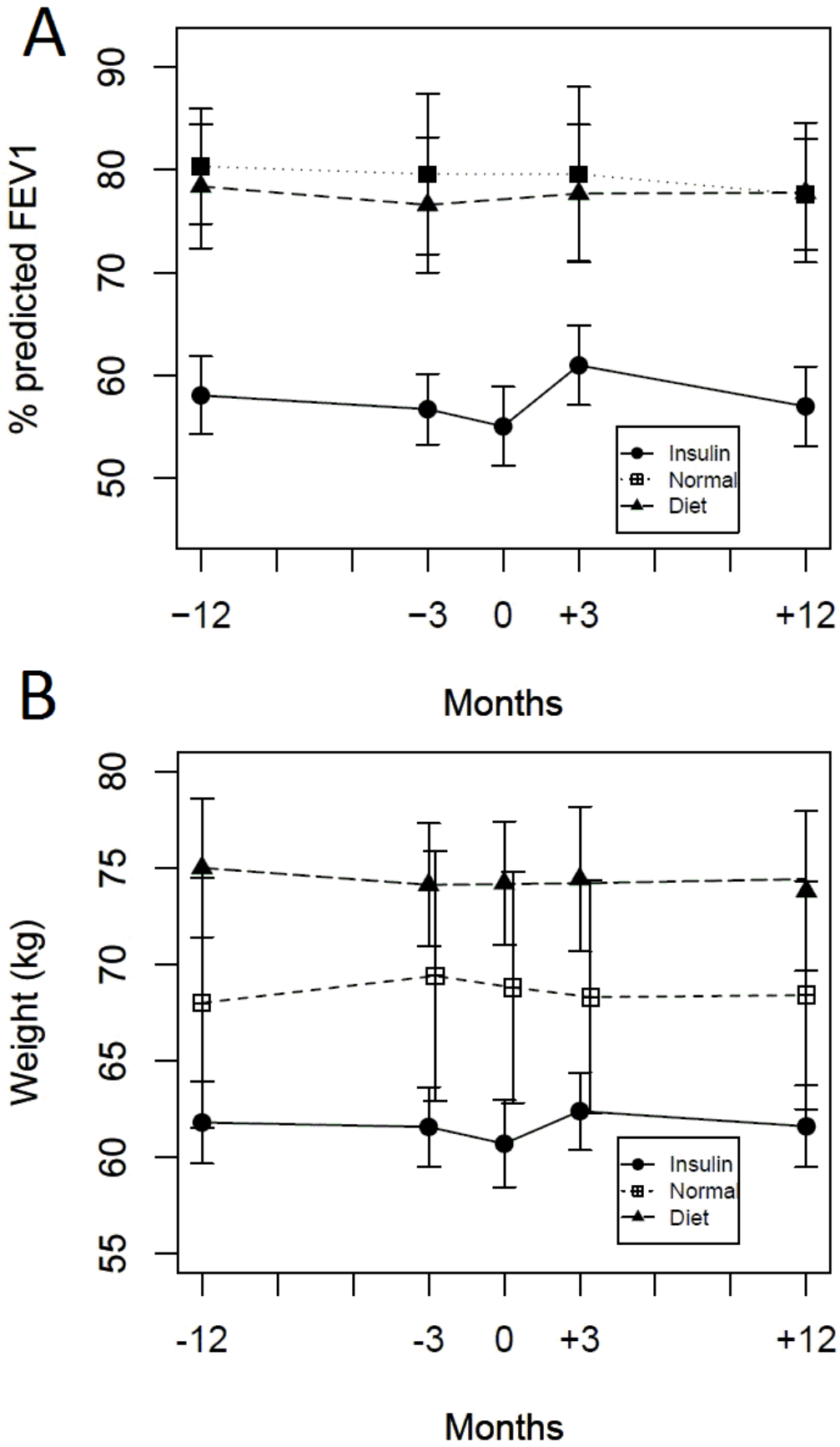


Figure 2: Mean % CGM period spent in each glycaemic range pre and post insulin initiation. **p<0.01 ***p<0.001

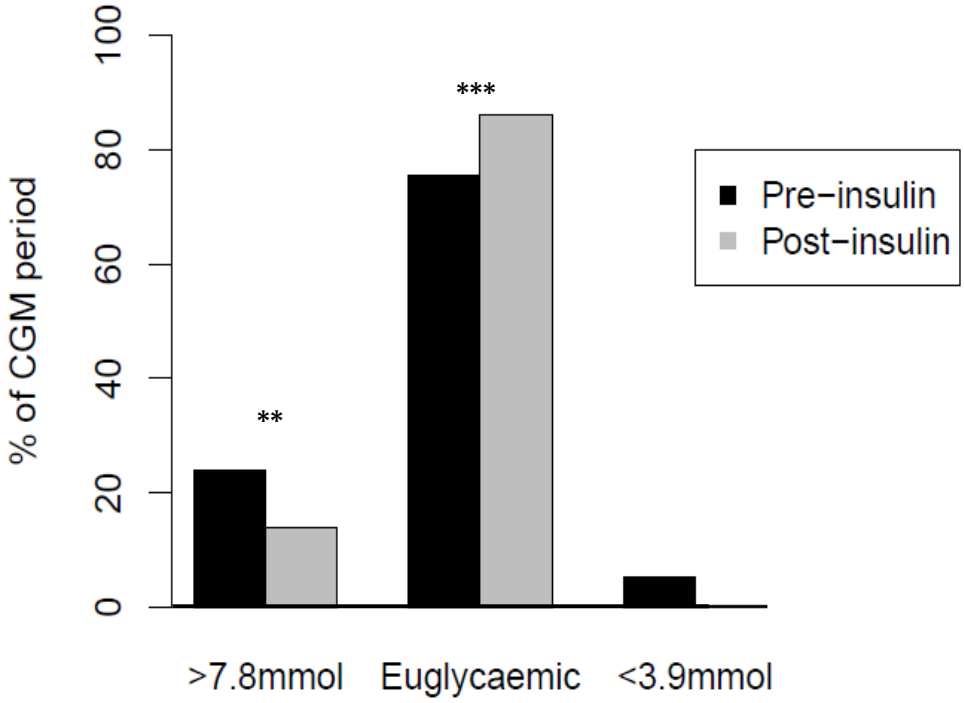
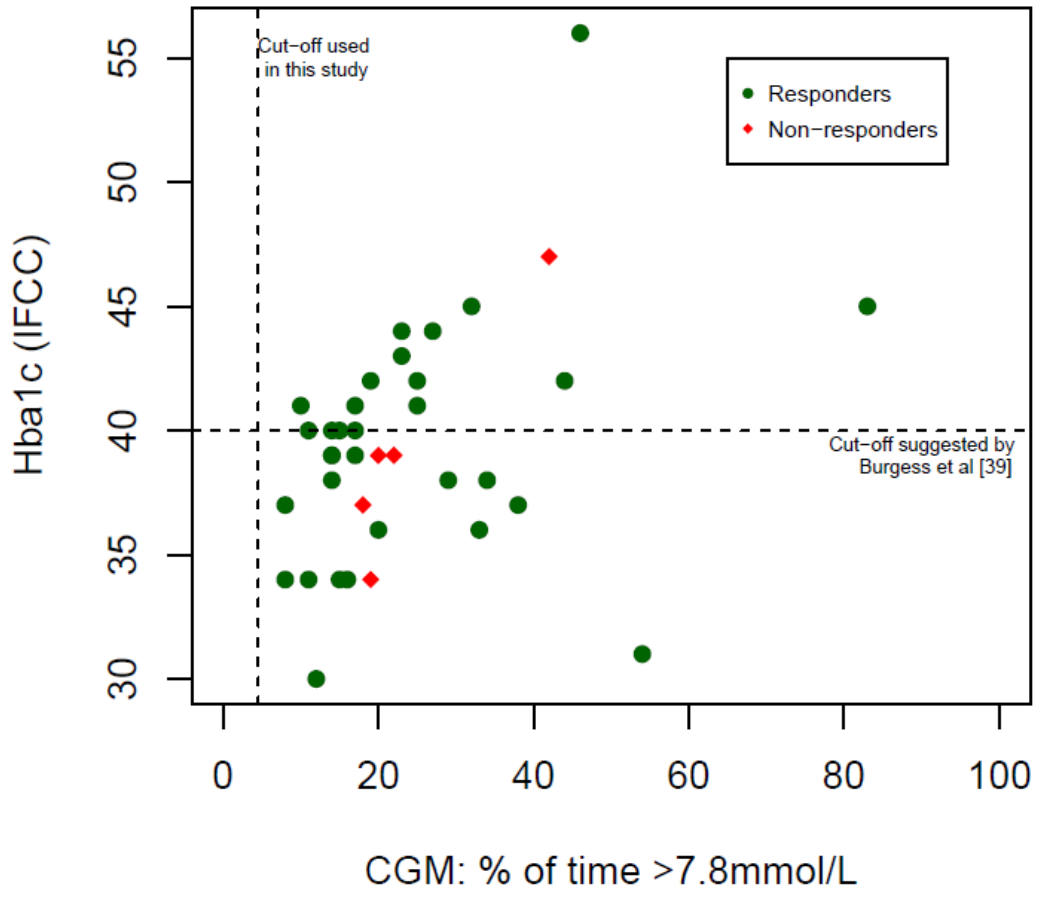


Figure 3: HbA1c plotted against % of CGM period spent in hyperglycaemic range for those patients treated with insulin. Subjects who showed clinical response are represented in green circles, those who did not are represented in red diamonds.



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416 **Table 1: Baseline characteristics**

	Normal	Dietary modification	Insulin	*p*
Total	7	15	37	
Male (%)	3 (42.9)	3 (20.0)	19 (51.4)	0.12
F508del homozygous (%)	3 (42.9)	9 (60.0)	26 (70.3)	0.35
Age, years (SD)	29.3 (8.6)	30.9 (10.2)	26.6 (8.24)	0.27
***P. aeruginosa* (%)**	5 (71.4)	13 (86.7)	32 (86.5)	0.58
Pancreatic insufficiency (%)	4 (57.1)	12 (80.0)	33 (89.2)	0.11
BMI (SD)	23.5 (4.6)	24.4 (3.9)	22.1 (3.9)	0.16
HbA1c, mmol/mol (SD)	36.57 (4.5)	37.9 (3.7)	39.4 (4.8)	0.26
Annual IV days (SD)	13.1 (14.5)	6.2 (6.4)	37.2 (39.9)	0.006
FEV_1, %predicted (SD)	76.6 (17.5)	79.7 (23.3)	56.7 (18.1)	<0.001
Weight, kg (SD)	69.04 (17.14)	74.13 (12.45)	61.2 (13.27)	0.009
Annual FEV_1 decline, % predicted (SD)	-0.41 (2.10)	-1.30 (3.67)	-1.74 (2.89)	0.56

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418 **Table 2: Paired analysis of clinical outcomes following CGM grouped by**
419 **intervention.**

		Mean change (95% CI)	p	Mean Change (95% CI)	p	Mean change (95% CI)	p
Predicted FEV_1 (%)	*3 month*	1.1% (-4.97,2.68)	0.49	0.0% (-3.92,3.92)	0.9	+4.27% (1.06,7.48)	0.01
	12 months	-0.54% (-4.8,5.86)	0.81	-2.7% (-4.82,-0.64)	0.01	+1.07% (-0.88,3.01)	0.27
Weight (kg)	*3 months*	-0.66 (-1.91,0.6)	0.25	+0.3 (-2.49 ,1.89)	0.77	+1.23 (0.32,2.15)	0.01
	12 months	0.41 (-1.47,2.29)	0.61	-1.21 (-2.47, 0.06)	0.06	+0.75 (-0.32,1.81)	0.17
Annual change in predicted FEV_1	*12 months*	+0.01 (-1.82,1.84)	0.99	-2.57 (-6.2,1.1)	0.14	+1.92 (0.21,3.63)	0.02
IV antibiotic days	*12 months*	-1.4 (-12.7,9.8)	0.79	+4.6 (0.6,8.68)	0.02	-1.5 (-9.8,12.7)	0.79

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Table S1: Changes in time spent in each glycaemic zone during CGM period for each group pre and post intervention. (Diet group n = 7, Insulin group n= 17)

	Diet group		Insulin group	
	Pre	*Post*	*Pre*	*Post*
>7.8mmol/L	11%	8%	24%	16%
Euglycaemia	88%	91%	75%	84%
<3.8mmol/L	1%	1%	1%	0%