Glucose monitoring devices for diagnosis of cystic fibrosis related diabetes in c...

Use of Continuous Glucose Monitoring devices enhance diagnosis of Cystic Fibrosis Related Diabetes in Children in a District General Hospital.

Background

Cystic fibrosis related diabetes(CFRD) is quoted to affect about 2% of children with Cystic Fibrosis and about 35% of patients will develop it by adulthood(1). The condition was hardly known when life expectancy in the disease was quite poor but there is evidence that this is now beginning to change as CFRD is becoming a common complication in adolescents and its association with more severe disease(2). Because the condition can be clinically silent, several guidelines including the European Cystic Fibrosis Society advocate routine screening from a certain age usually about age 10(3). The usual routine test is the Oral Glucose Tolerance Test in which a 75g Glucose load is given and blood glucose levels measured in intervals at 0 and 120 minutes. Despite these, there is still no uniformity as to the exact screening methods in the United Kingdom. A 2014 survey found widespread variation in screening processes for CFRD, these varied from age of screening to methods of screening(4, 5)The WHO still recommends the OGTT as a diagnostic tool for diabetes which is based on Blood Glucose at 0 and at 120 minutes(6)

Current guidelines for the OGTT take the 120minute reading as gold standard in diagnosis but there is still no consensus as to the exact way of interpreting the test. The fact that glucose levels chosen to represent the diagnosis in CF patients equates to levels at which retinopathy occurs rather than lung function deterioration is almost self-defeating (7). If the whole

point is to detect early to be able to prevent complications, then waiting for two hours may not be very helpful. Many of these patients start with post-prandial raised blood glucose before full blown diabetes and as such may have a normal 2-hour mark blood glucose(8). Relying on this measure(minute-120) may thus miss those who have had a transiently large rise in glucose levels. This is much so a review by the NIHR in 2012 advocated the use of IGT(Impaired Glucose Tolerance) as opposed to the abnormal 2-hour OGTT result in diagnosing and managing CFRD (9) In our centre we have combined the first hour OGTT level with Continuous glucose monitoring and this has enabled prompt diagnosis. This resulted in quicker institution of treatment and has in turn enhanced the pulmonary function and improved the spirometry reports for these patient’s bar one. We present below results from our current crop of five patients with CFRD and data is still being collected for future reports.

Patient characteristics and results.

The patients in this series were all female. Although figures have been quoted in literature about CFRD being more common in older females (10), some authors have found no differences in distribution by sex(11). We included five patients with Cystic fibrosis who were all previously diagnosed and four of them met the criteria for annual OGTT in our unit i. e. 10 years and older, stable respiratory status and involvement in annual reviews. The 6 year old patient was picked up initially on random testing and then, OGTT followed by CGM monitoring. All were under follow up of the specialist cystic fibrosis multidisciplinary team and had regular spirometry and weight assessments according to the Cystic fibrosis follow up protocols.

Age from diagnosis of cystic fibrosis till CRFD ranged from 5 to 16 years(? include median age: too few patients). All of them had been on routine steroids but were off steroids as at diagnosis. All our patients bar one had insulin prescribed and were started on MDIs (Multiple Daily Injections) and two of them ended up on basal insulin alongside MDIs with meals. They all continued with their routine care with the MDT and involved the endocrine consultant for frequent reviews of their insulin regime. One patient was not commenced on insulin as the postprandial blood glucose excursions resolved during monitoring.

We usually start on MDI’s with continuous CGM monitoring over the following weeks and if fasting hyperglycaemia persists, we start a small dose of Basal Insulin-Lantus® at a smaller dose than we would normally start for our Type 1 diabetics. Three patients who received insulin showed a significant improvement in FEV1 (7-12%) except a very young child who hadn’t yet mastered the technique for reliable spirometry. Our patients showed significant weight gain between 0. 8% and 6. 0% with the oldest patient having the smallest weight gain (this perhaps reflects normal paediatric growth curves).

All patients are still being followed up and more data is being collected for future analysis. These are shown in the table below.

Sex	Age(yrs.)	OGTT (mins)			CGM?	Insulin rx?	Insulin Regime	Duration of CF diagnosis	Improvem treatment
		0	60	120					Wt (%) FE

1	F	6	4.4	10.9	7.0	Yes	Yes	MDI	5	+2.6	-1
2	F	12	4.9	13.0	9.0	Yes	Yes	MDI then Basal	12	+6.0	+
3	F	15	4.9	10.8	7.3	Yes	Yes	MDI then Basal	15	+7.1	+
4	F	17	4.9	N/A	13.4	Yes	Yes	MDI	16	+0.8	+
5	F	13	5.4	N/A	10.8	Yes	No	N/A	12	N/A	N/

RESULTS.

DISCUSSION:

One of the categories in the classification of the OGTT result is the Indeterminate Hyperglycaemia(12). Quite a few children with CF will start off in this range and In fact, the figure for children in this category can be as high as 20%(13) and they are known to be at high risk of developing full blown CFRD

The prevalence of CFRD increases with age(14) but the actual prevalence will be hard to determine as it is an insidious condition and without universal

screening we may only be seeing the tip of the iceberg currently. This may account for only one of five patients in our cohort being very young while the rest are clustered in their adolescence. The quoted article(14) reports its presence in about 26% of 10-20year olds.

Female preponderance is known in CFRD. A large UK study found higher female incidence and in patients with CTFR class I and II gene mutations. In that study, females were also 60% more likely to develop CFRD(15). With incidence known to increase with age and sex, the question is should there be different screening criteria based on sex? This is a subject for future research. Some authors have wondered whether this female dominance is due to earlier puberty and its challenge to glucose homeostasis(16).

Several articles have confirmed the utility of CGMs in assessing patients for CFRD(17-19). CGMs give much better insights into temporary swings of hyperglycaemia and will help target insulin therapy. Compared to the OGTT alone, CGM increased pick-up from 11. 9% to about 50% in a paediatric population(19) . The CGM was also able to detect hyperglycaemia missed by OGTT in a small study(18). In our cohort, CGM played a role not only in the diagnosis but in the decision to commence basal insulin due to overnight hyperglycaemias (20). While we currently use the OGTT as a first step, there is scope to extend CGMs to all well CF patients from the age of 10years with their consent. CGMs have some downside though, it can be expensive, they are unattractive to some children and the discomforts of wearable technology limits the use by some children. HbA1C is not a recommended screening tool for CFRD(12), it is quite unreliable in CFRD and a study found it to have underestimated the presence of the disease in about 70% of

patients diagnosed by the OGTT(21). Random blood glucose checks are useful during times of illness but as a screening tool is of limited utility. It is likely to miss transient rises and is a no-brainer as an inferior tool compared to the use of the CGM.

Insulin is the recommended treatment for CFRD. Both the American guidelines and the European CF society guidelines advocate the same approach (3, 12). This may be so as it known that pulmonary function tests, weight and other clinical parameters may already be worsening before detection of hyperglycaemia(22, 23). This may mean that decline in nutritional state and lung function may be results of a relative hypoinsulinemic state. Insulin improves function even in the absence of fasting hyperglycaemia as demonstrated in the CFRDT trial(24). The bigger question with insulin treatment is the ‘’when’’? question. Do you commence immediately the diagnosis is made or do you wait to see self-resolution after excluding any contributory factor? The answer must be a carefully considered clinical decision based on not just the blood glucose numbers but the overall clinical picture. Considerations include age, BG excursions, weight loss, deteriorating lung function and the ability of the family to cope with yet another treatment in an already burdensome condition (CF). Hypoglycaemia remains a significant risk for insulin therapy in CFRD patients(24) and families must be taught about the dangers of hypoglycaemia and how to manage it before discharge from a health facility. There isn’t enough evidence to choose one regimen of treatment over the other and this is a clinical decision. All five patients were reviewed by the Diabetologist and decisions were individualised. The starting dose is also relatively small as

these patients still have some native insulin production. This phase is sometimes described as being akin to the ‘’honeymoon period’’ of Type 1 Diabetes Mellitus.

We commenced our patients on rapid acting insulin Novorapid® with meals at first to deal with postprandial BG rises and eventually added basal (Lantus®) for two of them with fasting hyperglycaemia.

All the patients started on insulin showed improvement in weight and FEV1. This tallied with known report from literature including one which found that even chronic weight loss in fasting-hyperglycaemia negative CFRD was reversed by insulin therapy(24). Bizzari in a small study (25) demonstrated improvement in BMI and a significant change in FEV1 of patients with CFRD. It is almost a universal agreement (26-28) and in fact treating with insulin has been shown to improve Nutritional state and FEV1 in the long term not just the short term. It is reported to delay deterioration in lung function by about 34 months.(29)

CONCLUSION:

Our patient cohort have shown some respiratory and metabolic improvement with treatment of CRFD with insulin. This is a known phenomenon as also stated by another previous study (30). This is only possible with earlier detection which in turn leads to earlier intervetion. Monitoring with the CGM after a minute-60 raised BG may help earlier detection of CFRD and initiation of treatment. Our unit shall soon initiate a protocol for routine CGM’s for minute-60 abnormal OGTT. The results of this longitudinal cohort study will hopefully shed more light on onset of CRFD in the paediatric population. Now

the key to arresting and reversing deterioration is early detection and instituting the appropriate treatment. This will if well managed, reduce the burden of the disease on the patients and their families and improve the general quality of life.

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