

Cystic Fibrosis Related Diabetes: Too Sweet for Too Long?

Dr Salma Ali (1), Dr Renu Khetan (1), Dr Pooja Sachdev (2) and Dr Jayesh Bhatt (3)

1 Specialist Trainee in Paediatrics 2 Consultant in Paediatric Diabetes and Endocrinology 3 Consultant in Paediatric Respiratory Medicine
Nottingham Children's Hospital, Queens Medical Centre, Derby Road, Nottingham NG7 2UH (United Kingdom)

Background

Cystic Fibrosis Related Diabetes (CFRD), a complication of cystic fibrosis (CF), has become increasingly prevalent as survival in patients with CF has improved. CFRD is more common with increasing age but affects the paediatric population as well, usually in the teenage years although has been known to occur in younger patients. Data from several centres including the US, Denmark and Ireland suggests that the prevalence of CFRD in the adolescent age group is 15-20% and <5% in those younger than 10 years¹. By the third and fourth decades the prevalence is estimated at 40%. CFRD has worsening impact on lung function and nutritional status, independent of pre-existing disease^{2,4}.

The need to identify onset of CFRD is complicated by its complex pathophysiology. Pancreatic islet cells suffer damage as exocrine tissue is destroyed. Whilst insulin insufficiency is present in all patients, glycaemic status and development of CFRD is influenced by multiple factors including genetic predisposition and degree of infection and inflammation. Hyperglycaemia also occurs across a spectrum in CFRD and glycaemic status fluctuates rather than worsening in a linear fashion³. The Oral Glucose Tolerance Test (OGTT) is used as standard for diagnostic purposes in CFRD, however interpretation of the results is less straightforward. Given the known delay in first phase insulin secretion and diminished peak, even in those with normal glucose tolerance, the rationale for an extended OGTT to detect early changes is apparent. Our centre used such an approach and whilst measurement of blood glucose (BG) at 0, 30, 60, 90 and 120 minutes enabled definition of each patient's glycaemic status in terms of Cystic Fibrosis Insulin Deficiency (GFID) grade, these absolute values have little effect on management as shown by our audit of OGTT results obtained during screening in 2013.

Aims

To evaluate:

- adherence to local CFRD screening guidelines;
- whether identifying stages of progressive Cystic Fibrosis Insulin Deficiency (CFID) using the extended OGTT altered management;
- trends in weight, BMI, and FEV1 in CFRD as compared to CF controls.

Methods

Retrospective analysis using patient records from 2013. We quantified measurement of random glucose and HbA1c in those aged 5-10 years and use of OGTT in those ≥ 10 years. Seven patients with CFRD were compared to age and sex matched CF controls using mean z-scores for weight, BMI and FEV1.

Results

The results of the audit examining adherence to CFRD screening guidelines are outlined in Table 1. The extended OGTT approach with criteria used for CFID stages⁴ and number of children in each category is depicted in Table 2. The mean weight and BMI z scores for those with CFRD compared to controls were -0.64 vs -0.02 ($p=0.005$) and -1.26 vs -0.03 ($p=0.0001$). Mean FEV1 was lower in CFRD 1.87l (73.06%) compared to controls 2.35l (89.03%).

Table 1

Modality	Age (in years)	N	% adherence to guideline
HbA1c & random glucose	5-10	21	17 (80%)
OGTT	≥ 10 years	38	30 (70%)

Table 2

N (%)	Result (CFID Grade ⁴)	Peak Glucose (mmol) (on OGTT)	2 hour Glucose (mmol) (on OGTT)
6 (20)	Normal	-	-
11 (37)	CFID1	≥ 8.2	<11.1
6 (20)	CFID2	≥ 11.1	<11.1
7 (23)	CFID3	<7 (BG at 0 min)	≥ 11.1
0 (0)	CFID4	≥ 7 (BG at 0 min)	Not required in presence of fasting hyperglycaemia.

Discussion

Adherence to screening guidelines was <100% but further analysis showed acceptable reasons for lack of screening such as needle phobia or aligning screening bloods with those of annual assessment rather than with specific time-points. 80% of our adolescent patients have some degree of insulin deficiency. 7 patients had CFID3 (blood glucose ≥ 11.1) but less than half were commenced on insulin. In some patients subsequent repeat OGTT had shown lesser degrees of insulin deficiency than CFID3. This may partly be explained by fluctuation of insulin secretion based on pulmonary exacerbations and associated inflammation. Recent international guidance suggests CFRD diagnosis should be assumed from initial detection even if later OGTT demonstrates reversal to normal.¹ Some patients with CFID were commenced insulin on clinical grounds rather than solely the results of the extended OGTT because of unexplained weight loss or decline in lung function with associated insulin deficiency. This included one patient with CFID1 on OGTT but suspicion of clinically significant insulin deficiency which was later confirmed on continuous glucose monitoring.

In our patients with established CFRD there was a significant declining trend in weight, BMI and FEV1 compared to age and sex matched controls without CFRD. This trend did not reverse one year post insulin therapy highlighting the importance of early diagnosis, optimal insulin therapy, and rigorous long term follow up. It is not possible to extrapolate from these results given the small sample size. The results do suggest a need to explore whether insulin therapy at earlier stages of insulin deficiency than CFID3/4 will slow down the rate of decline in nutritional status and lung function. At present, our centre has reverted back to the standard OGTT to diagnose CFRD, with early involvement of the diabetes team and establishment of regular multidisciplinary follow-up clinics.

References

1. Moran et al (2014) ISPAD Clinical Practice Consensus Guidelines 2014 Compendium: Management of cystic fibrosis-related diabetes in children and adolescents; *Pediatric Diabetes* 2014; 15 (Suppl.20): 65-76
2. Marshall et al (2004) Epidemiology of Cystic Fibrosis-Related Diabetes; *J Pediatr* 2005;146:681-7
3. Sterescu et al (2009) Natural History of Glucose Intolerance in Patients with Cystic Fibrosis: Ten-Year Prospective Observation Program; *J Pediatr* 2009; 156 (4):613-7
4. Hameed et al (2011) Cystic Fibrosis Related Diabetes (CFRD) – The End Stage of Progressive Insulin Deficiency; *Pediatric Pulmonology* 2011 46:747–760