

Cystic Fibrosis and Associated Diabetes



STUDY PROTOCOL
Dr Stephen O'Riordan and
Professor Hilary Hoey
April 2005

Study protocol:

1. PRINCIPAL INVESTIGATOR: Dr. Stephen O’Riordan,

Prof. Hilary Hoey, Prof. Andrew Green, Dr Colm Costigan, Dr Nuala Murphy, Peter Greally, Dr. Dubheasa Slattery, Dr Gerry Canny and Dr Edna Roche.

CURRENT POST, AND PERIOD HELD:

Dr. Stephen O’Riordan, Paediatric Specialist Registrar in Endocrinology and Diabetes year 5.

INSTITUTION:

The National Childrens Hospital, Tallaght. Trinity College Dublin and The Childrens University Hospital, Temple Street, Department of Paediatric Endocrinology and Respiratory Medicine at: Our Ladys Hospital for Sick Children, Crumlin. University College Dublin and The National Centre for medical Genetics, Crumlin.

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2. PROJECT TITLE:

The prevalence of Cystic Fibrosis-Related Diabetes and non-diabetes in the three major paediatric respiratory units in Dublin. Continuous glucose monitoring, quality of life and genetic analysis will be assessed in a prospective 12month multi-centre trial.

BRIEF CURRICULUM VITAE OF APPLICANT

Dr Stephen O’Riordan

Summary of Qualifications

- Education: Terenure College 1981-1990.
- Royal College of Surgeons in Ireland, Dublin, and Graduation 31ST May 1996.
- Awards: Temple Street Gold Medal for Paediatrics, 1996.
- MRCPi in Paediatrics- awarded in February 2000.
- Gold medal and first prize at National Cystic Fibrosis meeting in Killarney February 2005.

Professional Experience:

Specialist Paediatric Registrar (SPR):

- SPR in TSCUH, Temple St. Prof Gill, PaedsTutor/Lecturer-1 year July04-June 05.
- SPR in OLHSCrumlin, Dublin, Dr. D. Duff, Cardiology, 6months ending July 2004.
- SPR in OLHSCrumlin, Dublin, Dr. M Waldron, Nephrology, 6months.
- SPR in National Maternity Hospital, Holles street, Dublin: 12 month period.
- SPR in Temple Street Hospital, A+ Emergency, 6 months.
- SPR in Cork University Hospital, Cork: Endocrinology, 6months.
- SPR in AMNCH Tallaght Hospital, Dublin. Prof.H.Hoey: Endocrinology, 6months.
- SPR in OLHSCrumlin, Dublin, Dr. M Waldron, Nephrology, 6months.
- SPR in OLHSCrumlin, Dublin, Dr. D. Duff, Cardiology, 6months ending July 2004.
- SPR in TSCUH, Temple St. Prof Gill, PaedsTutor/Lecturer-1 year July04-June 05.
- Paediatric registrar: 12 months in Limerick Regional & Maternity Hospitals, Dr. S.M. Basheer, Dr. M. Mahony, Dr. T. Stack and Dr. L. Carroll.
- SHO Paediatric, 2 year crumlin scheme as follows: 6 month period.
- January – Dec 99: paediatric SHO in Limerick Maternity Hospital, also covering three months in the Limerick Regional Hospital, General and Neonatology – six month period.
- July – Dec 98: Our Lady’s Hospital for Sick Children, Crumlin under Dr. Costigan, General and Endocrinology – six month period.
- January 98 – July 98, Our Lady’s Hospital for Sick Children, Crumlin – six months under Professor McMenamin and Dr. Webb, Neurology – six month period.
- July 1997 – Dec 1997, Coombe Womens Hospital – under Dr. Griffin, Dr. Deasy, Dr. Sheridan and Dr. White, Neonatologist – 6 month period.
- Internship: Beaumont Hospital, 1996-97-Mr.Broe, Mr. Hickey, Prof Walsh & Dr O’Connell.

Presentations:

- 2005 IPA spring meeting, O’Riordan S, Hoey H. Cystic Fibrosis Related Diabetes (CFRD)-The Bitter sweet facts! Reaudit of 2003 study, The National Children’s Hospital, Tallaght 2005
- 2003-IPA, O’Riordan S, Hoey H. Cystic Fibrosis Related Diabetes (CFRD) and impaired Glucose Tolerance (IGT) in the National Children’s Hospital, Tallaght 2003.
- 2001-Diabetes UK, Annual professional Meeting- IDDM pregnancies+Neonatal
- 2001- IPA, IDDM 20years of Pregnancy in Holles Street.
- 2001- ‘Pete the Pancreas’-Published booklet for newly diagnosed children with Diabetes

- 2001- IPA- Murphys Law-Gallstones are more common, J O'Mahony LRH
- 2000- Irish Perinatal Society, IDDM 20years of Pregnancy in Holles Street.
- 1999 – Irish Paediatric Association – Saturday 8th May 1999: "FHH – Benign or not"?
- 1998 – Irish Endocrine Citywide Meeting – The College of Physicians – Nov 98, "An unusual case of Hypercalcaemia" supervised by Dr. Colm Costigan.
- 1997 – Irish Perinatal Meeting, National Maternity Hospital, Holles Street., "Neonatal transfers to the Coombe Womens Hospital".
- 1997 – Masters Medal Prize in The Coombe Womens Hospital. Two presentations - "Neonatal Transfers" and Morbidity of pulmonary disease in HIV children in Dublin.
- 1996 – Parathyroid Explorations – Clinical presentation and outcome in 60 consecutive cases presented as a poster at The Irish Nephrology Association, Dec. 1996, O'Riordan S, Abrham K., Walshe J., Osborne H.
- 1996 – Biological Society Research Day, paediatric study, Morbidity of pulmonary disease in HIV infected children in Dublin, supervised by Dr. Karina Butler.

(Publications page 4.)

10. Duration in months, of Implementation Period for the Proposed Research

24 months

Commencement Date Envisaged

1st July 2005

11. Other Departments/Institutions/Laboratories Associated with the Implementation of the Proposal:

Department of Paediatric Endocrinology and Respiratory Medicine at:
Our Ladys Hospital for Sick Children, Crumlin. University College Dublin;
The National Childrens Hospital, Tallaght. Trinity College Dublin and The Childrens University Hospital, Temple Street.

12. PUBLICATIONS:

1. O’Riordan S, Cystic Fibrosis related diabetes-**The Bitter Sweet Facts Part 1 & 2, Diabeteswise**-Journal of Diabetes for health Professional, spring and summer issues 2005.
2. O’Riordan S, Hoey H. Cystic Fibrosis Related Diabetes (CFRD) and impaired Glucose Tolerance (IGT) in the National Childrens Hospital, Tallaght 2004, **Irish Journal of Medical Science**, Nov 2003.
3. O’Riordan S. Murphy JFA. ‘IDDM pregnancies and Neonatal outcome-20year review’, **Irish Journal of Medical Science**, Nov 2003.
4. O’Riordan S. Murphy JFA. **Diabetes Medicine 2002**-‘IDDM pregnancies and Neonatal outcome-20year review’, Diabetes Medicine 2000.
5. O’Riordan S, Gill D. ‘**PETE the PANCREAS**- a booklet for newly diagnosed children with Diabetes.’ Author and all art work, 2000, Sponsored by NovoNordisk and IDF.
6. O’Riordan S. O’Mahony,’ Murphys Law-Gallstones are more common in paediatrics than we think,’ Irish Journal of Medical Science 2000.
7. O’Riordan S. Costigan C, "FHH – Benign or not, an unusual case of Hypercalcaemia," Irish Journal of Medical Science 1999.

PROJECT SUMMARY

Cystic Fibrosis Related Diabetes (CFRD) is an ever-increasing diagnosis with improved survival in children with Cystic Fibrosis (CF).^{1,2,3,4,5} The prevalence of CFRD has been reported to be the second most prevalent form of diabetes in children and Danish studies report an incidence of 50% by 30years of age.¹ It is a clinically unique illness requiring a different approach from Type1 and Type 2 Diabetes.^{1,2} Ireland has no definitive management protocols for CFRD and little is known about the prediabetic or Impaired Glucose Tolerance (IGT) group in Ireland at all. The morbidity and mortality increases by six fold once diagnosed with CFRD, however early intervention with Insulin in the adolescent and adult population has been shown to reduce the number of lower respiratory tract infections; reverse the deterioration in PFTS and weight loss.^{1,2,3,4,5} Prospective data, demographics and prevalence of CF children, with prediabetes and CFRD are warranted in an Irish cohort. To date the screening tools we have for making the diagnosis of CF diabetes is the standard Oral Glucose Tolerance Testing (OGTT), however Danish studies show 33% of cases are missed with OGTT testing alone. The Continuous glucose monitoring system is a new accurate and valid tool which may aid our early diagnosis of CF diabetes.

Aims:

1. To identify the **prevalence** of
 - i. **CF non-diabetes**
 - ii. **CF prediabetes and**
 - iii. **CF related diabetes**

In the three Specialist Respiratory Paediatric Units in Dublin.
(Table 1:page 18 WHO Diagnostic Criteria for CFRD 1998)

Then correlate glucose status with clinical features in the 3 groups identified.

2. The Continuous blood glucose monitoring system (**CGMS**) will be used to assess all the CF children possible as an adjunct to the OGTT testing. We hope this will provide a valid, more accurate diagnostic tool for CF related diabetes and non-diabetes.
3. **Genetics:** association studies with specific genes known to predispose to Type 2 Diabetes, comparing IGT/CFRD and non-CFRD patients in an Irish CF paediatric population.
4. **Quality of life and diet** will be assessed prior to commencing the study and after a 12month period.
5. Provide **best practice guidelines** for the management of children with CFRD and Prediabetes in the Dublin and Ireland.

Method:

1. **Prevalence:**

A prospective multicenter trial of CF children, aged 8-20years will be undertaken using Oral Glucose Tolerance Testing (OGTT). Three groups will be identified:

- I. **NCF- non-diabetes**
- II. **IGT-CF- prediabetes**
- III. **CFRD- Cystic Fibrosis related diabetes.**

Clinical correlations: Baseline data on the 3 groups will be collected first, as this data is not known in the paediatric CF population in Ireland. This will include age, gender, diet (prior to study dietary advice), birth and infant history (IUGR), family history of insulin dependant and non-insulin dependant diabetes, socio-economic class and time of initial diagnosis of Cystic Fibrosis. Correlation between glucose status and clinical features will be sought. Each group will be followed prospectively for a 12 month period.

2. Quality of life and diet:

Each group will be given identical dietary, healthy living advice and asked to complete an approved QOL Questionnaire at baseline and after the 12month period. All dietary advice is based on dietary guidelines standardized by The Irish Nutrition Institute on Diet and Exercise. The basic dietary advice regards spreading the carbohydrate load equally throughout the day and keeping a high calorie diet (40% fat content) and restricting extra refined sugary foods. We hope to prevent more IGT progressing to CFRD and possibly return more of these CF children to normoglycaemia with diet and exercise alone. This has been shown in a re-audit on the initial pilot study (see pilot study p 9).

3. Genetics:

Genetic studies to date have looked at CF genotype, which is not significantly associated with CFRD. We will have already genotyped patients and can repeat the same studies in this Irish CF paediatric population. We aim to study genes associated with Normal CF, IGT and CFRD, comparing the CFRD to the non-diabetes CF controls. Our principal interest lies in the Insulin VNTR gene, as well as a series of other gene associations for Type 1 and Type 2 Diabetes.

Background: In the mid-eighties it had been suggested that DNA close to the Insulin gene influenced the risk of getting type1 diabetes. It would take another 10years and the development of a comprehensive set of genetic markers before The University of Cambridge confirmed the type1diabetes-associated polymorphism to be a region of DNA close to the insulin gene, called a VNTR(variable number of tandem repeats). In Europeans there are 2 main categories of VNTR alleles: less than 50 repeats and greater than 200 repeats. Studies have shown that people with only a low number of repeats are more likely to have type 1 diabetes than those with at least one higher number allele. Carrying at least one protective allele gives you at least a 50% protection from type 1 diabetes, a very dramatic effect. The Insulin VNTR gene plays a role in regulating the the expression of the insulin gene in the thymus. Thus the insulin VNTR gene may offer protection against autoimmunity by stimulating insulin expression in the thymus and thus increase the body's awareness that insulin is one of its own proteins. Insulin VNTR (class 111 allele) has been shown to be associated with IUGR, diabetic hypertriglycerideamia, atherosclerosis, cardiovascular disease, polycystic ovarian disease, central obesity, insulin resistance and type 2 diabetes. We hypothesise that the Insulin VNTR gene may be associated with CFRD and the progression we see in some CF children and not in others. Insulin VNTR (class 111) gene assays will be done on the DNA of all CF children in the Dublin Paediatric population (once consent have been approved) to determine the possible link between this gene and future development of IGT, CFRD or both. We will also look for Type 2 Diabetes Family History, IUGR, C and

association with the Insulin VNTRgene. These gene assays will be laboratory based, in the National Centre for Medical Genetics and the Dept of Medical Genetics, UCD and Our Lady's Hospital for Sick Children, Crumlin. This will be under the supervision of Prof Andrew Green and Dr. Sean Ennis. Dr Ennis has a PhD in genetics and is experienced in lab based genetic investigations and techniques. I plan to do all these gene assays individually and learn the assay techniques as soon as the study commences.

4. **Best Practice Guidelines:**

Those children diagnosed with CFRD (according to WHO1998/ISPAD 2000 guidelines, page 16) may be treated with insulin at the discretion of the Paediatric Consultant Endocrinologist in each centre. This will not be the focus of this study but we will assess the progress of those children on and not on insulin. The CGMS monitor hopefully will be the new diagnostic tool with OGTT screening and will help us achieve best practice guidelines based on an Irish cohort. This group will be followed with 3-4 times daily home blood glucose monitoring when using the continuous blood glucose monitoring system (CBGM). Pulmonary function tests and regular anthropometry measurements will also be taken

The principle outcomes variables in this study will be:

1. To establish baseline **prevalence and demographics on all CF** children including: weight and height, BMI percentile, Pulmonary function tests and glucose intolerance status.
2. **Intensive monitoring with OGTT and CGMS testing**, (rather than HbA1c and Blood glucose control).
3. **Genetic predisposition** found in some children and not in others.
4. **Quality of life and dietary assessment.**

Other Paediatric centres have been approached for participation, if the current study population cannot be met, as results will not reach statistical significance.
Conclusion:

This study hopes to provide the prevalence of CFRD and prediabetic-CF children in Dublin. It is hypothesized that early screening with CGMS will identify more CF children in the prediabetic group. Early identification and simple dietary and healthy living guidelines may allow the majority of these children to return to normoglycaemia (see pilot study: O'Riordan & Hoey enclosed with study outline p 9). These results were presented at Irish Paediatric Association spring meeting 2005. We will establish correlation between glucose status and clinical features. Genetically, in the 3 CF paediatric groups, we aim to assess the Insulin VNTRgene:glucose intolerance association. We hope to provide optimum monitoring guidelines with CGMS monitors and OGTT testing at a local and national level. The main focus of this study is to assess children more accurately with the CGMS monitoring system, look at new genetics in CF diabetes and non-diabetes and assess the CF children's diet and quality of life. Finally we will advance the knowledge of CF related diabetes and non-diabetes for the future management of all CF children in Ireland.

(See coloured schematic page)

Description plan of research with 6months run in & recruitment:

**Recruitment 1st Jan - June 2005.
Start date 1st July 2005**

OLHSC n=155 total

NCH n=125 total

TSH n=80 total

Screen ALL CF 8-20yrs with OGTT

Collect baseline demographics on all CFRD children, including: QOL evaluation, Wt, Ht, BMI centiles, PFTs, bloods for genetic assays, and baseline bloods

1. N CF Children NO DM

2. CFRD Children

3. IGT CF/ Prediabetes

Safety and consent

Prospective observation of all
Total CF group aged 8-20 years
n=~160

Identical Dietary and healthy living advice given to all 3 groups in 3 centres.

- Genetic analysis of blood samples only.
- CGMS monitoring at baseline and after 12months will be minimum requirements for study.
- Assessment of OGTT results at 30, 60 and 90mins along with the traditional 0 and 2hour readings.
- 4 monthly examinations and measurements.
- Complete a Quality of life and dietary questionnaire.

After a 12month period of intensive monitoring, assess the CF children with Diabetes and without and compare the 2 groups.

Completion 30th June 2006

Pilot study in The National Children's Hospital in 2003: O'Riordan S. Hoey H. Cystic Fibrosis Related Diabetes(CFRD) and impaired Glucose Tolerance (IGT) in the National Childrens Hospital, Tallaght 2003.

Introduction: CFRD is an ever-increasing diagnosis with improved survival in children with CF, the average life expectancy is now greater than 30years^{a, b, c, d, e, f}. The prevalence of CFRD increases with age and is 50% by 30years of age^{a, b}. It is a clinically unique illness requiring a different approach from Type1 and Type 2 Diabetes^{a, b, c}. Steroids remain an important therapy in CF especially in treating Allergic Bronchopulmonary Aspergillosis (ABPA), however they may push these children into the Diabetic range.

Aim:

- 1 To define the prevalance of CFRD and IGT in our Cystic Fibrosis population
2. To explore the screening methods for those attending the National Children's Hospital
3. To identify precipitating factors inducing CFRD

Method: A retrospective audit of all children with Cystic Fibrosis related Diabetes and those with impaired glucose tolerance. Assessment was undertaken using Oral Glucose Tolerance Testing (OGTT) defined by the WHO and HbA1c, (DCCT compliant).

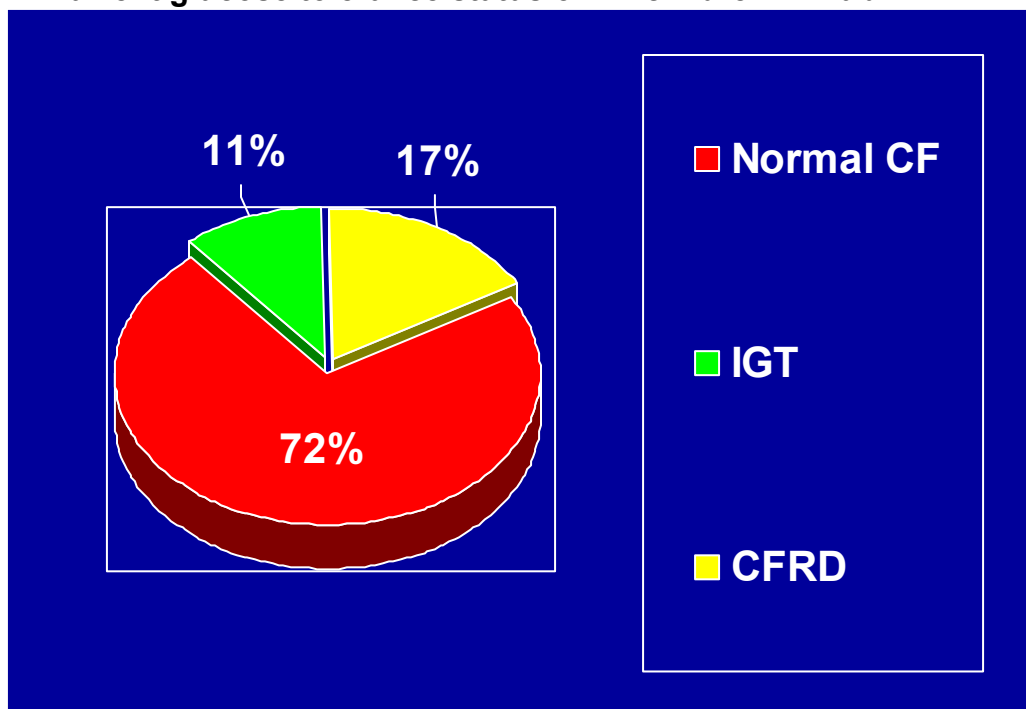
Results: n=125 children with cystic fibrosis (CF) attending AMNCH. Only 80 were aged 10-19years at time of screening. We identified 9 with Diabetes, one was excluded with co-existing CF and Type 1 Diabetes from the study. 8 (10%) children had CFRD, ranging in age from 3-20years. The mean age of diagnosis of Diabetes was 14.7years (range 12-19years). 27(34%) had IGT, 12 males and 15 females, ranging in age from 7-19years(mean 14.2years). The total number of CFRD and IGT is 35/(44%), 16 males and 19 females with a mean age of 15.6years. The mean HbA1c is 6.1%. The majority (66%) of CF genotypes were homozygous for DF508. Insulin antibodies were identified in 25% of the CFRD group. 50% of the CFRD group required steroid therapy, which precipitated decompensation to frank Diabetes. 26% of the IGT children were on steroid therapy. All the CF children developing Diabetes showed a slowly progressive onset and started using small amounts of intermediate acting insulin. Insulin requirements ranged from 0.2-1.0iu/kg/day, with a mean of 0.41iu/kg/day.

Discussion: This study shows that the incidence of CFRD 10% is high. The IGT group account for 34% of the CF population, this group are expected to develop CF related Diabetes and need close follow-up. The mean insulin requirement is 0.41iu/kg/day, these are small doses considering the majority of these children were post-pubertal. The mean HbA1c is 6.1% in the 2 groups. The HbA1c was insufficient for diagnosis as there is often a marked discrepancy between the HbA1c and OGTT levels at 2hours. However HbA1c remains a useful management tool to monitor metabolic control. 25% of the CFRD were insulin antibody positive. We identified 4/8(50%) in the CFRD group and 7/27(26%) of the IGT group on steroid therapy. Steroids pulse therapy is an important precipitant of Diabetes in these children with CF, triggering 50% of CF related Diabetes in this population

Conclusions:

1. The incidence of CFRD in this population is high at 10%.
2. The total incidence of IGT and CFRD is 44% (35/125) in this CF paediatric population.
3. HbA1c is not diagnostic in CF children with IGT and should not be relied on, for follow-up.
4. Repeated yearly OGTTs are essential for diagnosing CF related Diabetes.
5. Annual assessment with a structured protocol is essential to pick up CF related Diabetes.
6. As with all diabetes the insulin regimens must be individualised and there was no significant difference in metabolic control with different regimens.
7. Steroid therapy may be vital for patient management in CF, therefore these children should be monitored closely for evolution of Diabetes, especially if impaired glucose intolerant.

Re-audit 2004, 1 year after initial pilot:
Current glucose tolerance status of CF children in Dublin



The IGT-CF group showed some unique changes in follow-up data to the initial pilot study:

- One year ago, there were 27 IGT-CF children at the NCH,
- 18 returned to normoglycaemia with dietary advice alone ie a reduction of 43%. Only 9 IGT-CF children remain in the NCH cohort.
- One CFRD child has died, CFRD was newly diagnosed in 2 children and 4 CFRD children were transferred on to Adult Care.

Summary of re-audit 1 year after pilot study:

- This study provides the prevalence:
 1. **Non-Diabetes CF 72%,**
 2. **Prediabetic-CF 11% and**
 3. **CFRD 17% of all CF children in Dublin, January 2005.**
- We provide basic demographics on an ever changing group of CF children according to their glucose status.
- **Dietary and exercise** advise alone have reverted **43%** of the Prediabetic CF children to normoglycaemia.
- Steroids remain important therapy in CF children but may also trigger **impaired glucose tolerance and Cystic Fibrosis Related Diabetes.**

PROJECT OUTLINE:

Entry into trial: Diagnosis of CF, age 8-20 years and attending one of the 3 Dublin Paediatric Respiratory units.

Screening:

Oral Glucose Tolerance Testing (OGTT- WHO compliant) will provide the study with 3 main groups:

- i. **CF non-diabetes**
- ii. **CF prediabetes and**
- iii. **CF related diabetes**

Once identified we will retrospectively review the notes for 1-2 years and establish: age, sex, pubertal staging, CF clinical status, blood picture, pulmonary function testing profiles and full anthropometry. Each group will then be monitored 4monthly if possible, depending on compliance with CGMS monitoring system for a 12month period.

Specific objectives:

In a prospective study of all CF children with 3 different degrees of glucose intolerance we aim to prevent further progression in all groups. Return a percentage of the IGT group to normoglycaemia. Accurately assess this CF cohort with the CGMS monitoring system, look at new genetics in CF diabetes and non-diabetes and assess the CF children's diet and quality of life. Finally we will advance the knowledge of CF related diabetes and non-diabetes for the future management of all CF children in Ireland.

Statistics: Power calculations estimate we have adequate power in this study group to show a standard deviation: 0.7 for BMI, 0.4 for FEV1 and 0.6 for FVC. (See attached: Statistics sheet, Tables 1, 2a& 2b)

Visits:

- **ONE:** Zero time, baseline evaluation and data collection at visit one includes:
 - Wt, Ht and BMI and ideal weight for height percentage.
 - Bloods (outlined in description)
 - Pulmonary function testing profiles-FEV1 and FVC.
- **TWO:** 4 months,
- **THREE:** 8 months,
- **FOUR:** conclusion at 12 months

Compare and contrast those CF children with and without diabetes:

- i. Quality of life,
- ii. Genetic predisposition,
- iii. Diet,
- iv. OGTT results and
- v. CGMS trends.

Primary outcomes:

Compare and contrast those CF children with and without diabetes:

- i. Prevalence of CF diabetes and non-diabetes,
- ii. CGMS trends and OGTT results,
- iii. Genetic predisposition,
- iv. Diet,
- v. Quality of life.
- vi. Provide best practice guidelines for CF diabetes and non-diabetes in Ireland.

PROJECT DESCRIPTION:

➤ Aims of project:

1. To identify all CF diabetes and non-diabetes in children aged 8-20years of age and define their prevalence in three National Specialist Dublin Paediatric Respiratory Units. Then correlate glucose status with clinical features in the 3 groups identified.
2. The Continuous blood glucose monitoring system (**CGMS**) will be used to assess all the CF children possible as an adjunct to the OGTT testing. We hope this will provide a valid, more accurate diagnostic tool for CF related diabetes and non-diabetes. OGTT intermediate values will also be assessed.
3. **Genetics:** association studies with specific genes known to predispose to Type 2 Diabetes, comparing IGT/CFRD and non-CFRD patients in an Irish CF paediatric population.
4. **Quality of life and diet** will be assessed prior to commencing the study and after a 12month period.
5. Provide **best practice guidelines** for the management of children with CFRD and Prediabetes in the Dublin and Ireland.

➤ **Work leading up to this project:** Pilot study (enclosed) O’Riordan S, Hoey H. Cystic Fibrosis Related Diabetes CFRD) and impaired Glucose Tolerance (IGT) in the National Childrens Hospital, Tallaght 2003, Published in Irish Journal of Medical Science, Nov, vol 172, 2003 (page 9).

➤ Follow on from Pilot Study:

Anecdotal findings in a recent update of the data in the three Dublin Paediatric Hospitals has led us to believe that over 50% of the IGT group previously 28 in number is now reduced to 9 in the AMNCH group. This is primarily from introducing a standardised dietary advice sheet and advising regular exercise (page 10 re-audit)

➤ **Underlying objectives:**

Monitor:

- a. Growth-height velocity
- b. BMI, weight and height
- c. Pubertal staging
- d. Pulmonary function tests-FEV1 and FVC
- e. HbA1c levels
- f. Number of admissions and recurrent Lower respiratory tract infections.

Specific objectives

- Compare and contrast those CF children with and without diabetes: quality of life, GENETIC predisposition, diet, OGTT results and CGMS trends.
- We also hope to follow the natural progression of the IGT-CF children with standard dietary and exercise advice.

Study design: this is a prospective observational multi-centre trial to assess

Statistics: Power calculations

Table 1a

Parameter	Starting mean	SEM	SD	Finishing mean	Diff	Delta
BMI	16.9	0.7	2.96984848	19.1	2.2	0.74
FEV1	37.9	4	16.9705627	44.4	6.5	0.38
FVC	60.6	4.8	20.3646753	73.2	12.6	0.62

Showing a standard deviation (Delta): 0.7 for BMI, 0.4 for FEV1 and 0.6 for FVC.

➤ **Scientific methodology and approach**

Definitions:

1. CFRD-(see table 1)
2. IGT or Prediabetes-(see table 1)

➤ **Oral Glucose Tolerance Testing (OGTT):**

1. Ensure child to be fasting from 12midnight.
2. Baseline blood samples at t=0 minutes include: Glucose, Insulin, C-peptide, HbA1c, Biochemistry U+E, Ca, Mg, PO4, LFTs, GGT, IgG, IgA, IgE, RAST and Vitamin A, D & E.
3. A glucose load is given orally; dose 1.75g/kg up to a max of 75g, the drink must be consumed in 5-10minutes.
4. Collect further blood samples for glucose and Insulin at t= 30, 60, 90,120mins.
5. Not all children will have insulin and C-peptides, these will be done on a selective basis(particularly the glucose intolerant and diabetes children) and selection will be made after all the standard OGTT have been completed.

Diagnosis of diabetes in Cystic Fibrosis:

When one does a literature review on CFRD, one would think it a simple task to find a consensus on the diagnostic criteria. However this is not the case. Despite the lack of equivalent studies in CF the same glycaemic thresholds have been adopted as the standard for diagnosis of CFRD. Dobson et al and others have established that CF patients with normal fasting and 2hour values have higher 30, 60 and 90min values than

non-CF patients with similar fasting and 2hour values. Despite this the OGTT remains the most frequently used diagnostic criteria for CFRD.

Different diagnostic criteria are used in different countries:

The United States: The North American CF Foundation, following the 1998 consensus conference guidelines recommends annual fasting glucose levels. It also recommends fasting and post-prandial levels during hospitalization for an acute illness.

- USA (Moran et al 1998^{1,2}) has different guidelines to the WHO and includes CFRD without fasting hyperglycaemia.
- Classification in the US describes four major categories:
 1. Normal or non-diabetic CFchildren-NGT
 2. Impaired glucose tolerance: 7.8-11.1mmol/L-IGT
 3. CFRD with fasting hyperglycaemia
 4. CFRD without fasting hyperglycaemia

Thus many of the US studies have larger populations due to the inclusion of these CFRD patients without fasting hyperglycaemia.

Europe: In Europe the OGTT remains the gold standard. This discrepancy between the US and Europe is primarily due to the lack of agreement on whether it is important to diagnose and treat CFRD without fasting hyperglycaemia. The question is unanswered to date but if one is to consider treating a CF child with impaired glucose tolerance then one must surely treat the CFRD children with or without fasting hyperglycaemia.

- Denmark (Koch et al 2001a^{3,12}) The European Epidemiology Registry of Cystic Fibrosis reported diabetes in 5% of 10-14year olds and 12.6% of 15-19year olds. However ascertainment of diagnosis was variable.
- UK (CF Trust document, June 2004) OGTT and serial blood glucose monitoring are the most specific and sensitive tools presently available to screen for CFRD.
- Ireland currently has no consensus guidelines to date.

Screening-are these different strategies accurate and reliable?

1. **HbA1c-** poor sensitivity for diagnosis but may be used in monitoring. The red blood cell bone marrow turnover is much less than 3months in CF patients. This results in lower HbA1c levels with the same degree of glycaemia versus non-CF patients.
2. **Random blood glucose**-not sensitive enough.
3. **Glycosuria-** a poor test in an already catabolic state.
4. **Fasting blood glucose**-not reliable and lots of false positives.
5. **Oral Glucose Tolerance Testing (OGTT)** This is the gold standard. However Danish research has shown because CFRD is usually asymptomatic, 33% of CFRD can be missed if one relies on OGTTs alone. Dobson et al. report high levels at 30, 60 and 90minutes in CF diabetes but also in the prediabetes stages. These intermediate values have not been assessed in a prospective trial and no standard values exist. We hope to assess these 30, 60 and 90minute OGTT results prospectively and improve our knowledge of OGTT testing in CF diabetes and non-diabetes.
6. **Continuous glucose monitoring system (CGMS)**-This has been shown to be reliable and accurate. However to date this is not a diagnostic tool but an important adjunct to the OGTT and an important monitor of glucose profiles as patients progress from non-diabetes to IGT to CFRD. Important studies are

awaited to assess the OGTT limitations and the CGMS improving reliability in assessment and diagnosis.

- **Home Blood Glucose Monitoring (HBGM):** Three to four times daily finger prick monitoring ie paired Fasting Blood Glucose (FBG) and 2hour post-prandial (2HPP) finger prick test daily will be necessary for the CF children when they are on the CGMS monitoring system.
- **Continuous Blood Glucose Monitoring (CBGM):** subcutaneous catheter inserted for 72-96hours. This new mini-computer provides >300 readings in 24hours will be done 4 Monthly if possible and if the CF children are willing to comply. This provides accurate, valid assessment of all glucose readings in the home environment for both, diabetic and non-diabetic, CF children.
- **Insulin:** If a CF child is already on insulin this management will be the responsibility of the Paediatric Endocrinologist at that centre and not within the remit of this study.

➤ **Genotype analysis:**

There is debate about whether there is predisposing genetic factor in certain CF children to develop CFRD. This study hopes to elucidate this by looking at the Normal CF children, the prediabetic-CF and CFRD children. The main genetic focus in this study will be Insulin VNTR gene correlation with glucose intolerance (page 6) but other gene analysis will also be conducted.

➤ **Inclusion and exclusion criteria:**

Inclusion criteria for study:

1. All CF children older than 8years and <20ars^{a, b, d, f}
2. CF children younger than 8ears with deteriorating PFTS, weight loss and increasing acute lower respiratory tract infections requiring intravenous antibiotic therapy

Exclusion criteria for study:

1. All CF children older than 20ars.^{a, b, d, f}
2. CF children younger than 8ears

Inclusion criteria for OGTTs:

As for study inclusion criteria.

Exclusion criteria for OGTTs:

1. Acute Lower respiratory tract infection, requiring intravenous antibiotic therapy
2. Temporarily on steroid therapy

➤ **Nutrition:**

Identical nutritional support will be provided to both treatment and non-treatment groups during this study. This will be based on the Irish Nutrition and Dietetic Institute guidelines for CFRD. This will be in standard one page format and provided to all CF children at each baseline visit. This information will then be compounded at each further 3monthly visit during the course of the trial.

➤ **Implications of research findings:**

There is an increased morbidity and mortality in CF related diabetes, therefore we must screen earlier and treat more aggressively. The theory behind starting insulin or oral hypoglycaemic agents is to overcome the Insulin deficient state firstly and secondly to provide the anabolic effect of Insulin in already catabolic CF children. Many studies have shown that HbA1c is not a good diagnostic tool but it may still be helpful in monitoring the CFRD and impaired glucose tolerance in CF children. The current screening and diagnostic tools for CF diabetes are inadequate; we hope to prove the CGMS system is both valid and accurate in monitoring CF children.

The main focus of this study is to assess children more accurately with the CGMS monitoring system, look at new genetics in CF diabetes and non-diabetes and assess the CF children's diet and quality of life.

Finally we hope to provide new best practice guidelines based on an Irish cohort for screening and management of CF diabetes and non-diabetes.

Statistics: Power calculations: Power was calculated based on data from study reference:

1. Lanng S. **Diabetes Mellitus in cystic fibrosis: effect of insulin therapy on lung function and infections.** Acta Paediatr 1994,83:849-853. (Enclosed page 851)

I understand the referenced study is based on known CFRD patients and treatment with insulin for a 2year period, however we hope to show a similar effect in the our CFRD children. Furthermore we plan to retrospectively review all the study group charts prior to commencing the study in order to obtain our own baseline parameters of CF clinical status namely BMI, FEV1, FVC and Shwachman score

Table 1b

Parameter	Starting mean	SEM	SD	Finishing mean	Diff	Delta
BMI	16.9	0.7	2.96984848	19.1	2.2	0.74
FEV1	37.9	4	16.9705627	44.4	6.5	0.38
FVC	60.6	4.8	20.3646753	73.2	12.6	0.62

This study has not been done before in children however, we estimate from our calculations that we have adequate power in this study group to show a standard deviation: 0.7 - BMI, 0.4 - FEV1 and 0.6- FVC.

Table 2a

Alpha	Power 0.05	Power	
		80.00%	90.00%
Delta	N	Sample size in each group	
		0.5	63
0.6	44	59	
0.7	33	43	
0.8	25	33	
0.9	20	26	
1	16	22	

Our sample size in both treatment and control group is estimated at n=35 CF-IGT children, (p-value 0.05) represents the probability of detecting effect if there is one, for a power of 80% and 90%

Table 2b

N	35Sample size in each group	
	Alpha (p-value)	Delta Power
0.05	0.5	0.54
	0.6	0.69
	0.7	0.82
	0.8	0.91
	0.9	0.96

When working out the power calculations for 80% & 90% we understand our sample size is sufficient to show a significant statistical result, however we may have drop outs or

parents who are not inclined to consent to this study. Thus we have contacted other Paediatric units in Ireland:Limerick, Cork, Galway, Drogheda and Wexford with a view for inclusion in this study if further CF children are required.

Table 1: WHO Diagnostic Criteria for CFRD (1998):

Table 1

WHO Diagnostic Criteria for CFRD 1998:

- **CFRD:** 2hour plasma glucose \geq 11.1mmol/L during a 75g oral glucose tolerance test,
Fasting plasma glucose \geq 7.0mmol/L on 2 or more occasions, at least on 2 separate abnormal measurements
- **IGT:** 2hour post prandial 75g of anhydrous glucose, blood glucose \geq 7.0 and \leq 11.1mmol/L

Oral Glucose Tolerance Testing:

75g of in 300ml water:

- Venous blood $<$ 7.8mmol/L= **Normal**
- Venous blood $>$ 7.8 & $<$ 11.1mmol/L= **IGT**
- Venous blood $>$ 11.1mmol/L= **Diabetes-Including CFRD**

At least 2 separate abnormal measurements.

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