

# Investigation of Screening Methods for Impaired Glucose Control in Children with Cystic Fibrosis

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## **ABSTRACT**

The oral glucose tolerance test (OGTT) used for the diagnosis of Cystic Fibrosis Related Diabetes (CFRD) is inconvenient and requires a great deal of patient cooperation. Other investigations such as measuring fasting glucose and glycosylated haemoglobin (HbA1c) concentrations, could offer several practical advantages over the OGTT for diabetic screening. To investigate the ability of these tests to detect impaired glucose control, 111 patients attending the Cystic Fibrosis Clinic at The National Children's Hospital (Dublin, Ireland), were evaluated. All individuals had annual measurements of glucose and HbA1c, and those over 8 years of age underwent a complete OGTT every two years. Compared with the OGTT, HbA1c was highly specific (91%), and an elevated HbA1c usually indicated the presence of impaired glucose tolerance (sensitivity = 80%). A normal HbA1c did not, however, exclude a diagnosis of impaired glucose control. Predictive values (PPV = 47%, NPV = 98%) are in accordance with a useful diagnostic test, however they are affected by the low prevalence of impaired glucose control within this population. In short, it appears that HbA1c as measured in this study would properly identify the vast majority of subjects with impaired glucose control. *TSMJ May 2000, vol 1, 7-11.*

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## **INTRODUCTION**

Cystic Fibrosis (CF) is the most common life-threatening autosomal recessive disease within the Caucasian population, having a carrier rate of 1:25 and occurring at a frequency of approximately 1 in 2000 live births. It is the consequence of abnormal chloride conduction across the apical membranes of epithelial cells, and is due to mutations in the gene encoding the cystic fibrosis transmembrane conductance regulator (CFTR) located on the long arm of chromosome 7.<sup>1</sup> The CFTR protein acts as a cyclic-AMP activated chloride channel, which allows for the transport of chloride ions and the passive movement of water out of the cell. In CF, an abnormality in the CFTR protein blocks the chloride ion transport causing inadequate hydration of the cell's surface, leading to dehydrated secretions and subsequent organ damage.

Pancreatic dysfunction has long been recognised as a hallmark of patients with cystic fibrosis, occurring in approximately 85% of patients. Several studies have shown that the destruction of the exocrine pancreas in CF is an evolutive process characterised by a progressive fibrosis of pancreatic

acinar cells due to inflammatory damage from ductal obstruction.<sup>2</sup> This results in enzyme deficiencies and subsequent malabsorption and malnutrition. In addition to insufficiency of the exocrine pancreas, there is a high incidence of pancreatic endocrine dysfunction. The reported incidence of impaired glucose tolerance in patients with CF ranges from 8-50%, and that of overt insulin dependent Cystic Fibrosis Related Diabetes (CFRD) from 6-10%.<sup>1-4</sup> Impaired glucose tolerance is thought to be related to fibrosis and fatty infiltration of the exocrine pancreas, which disrupts the islet cell's architecture and destroys many of the insulin-secreting beta cells.<sup>5</sup> Clinically, glucose intolerance can present with weight loss and result in an increase in the incidence and severity of respiratory infections. Impaired neutrophil function has been described in the presence of elevated blood glucose levels, and correlations have been made between the incidence of infection and the degree of glucose control.<sup>6</sup>

With the advent of better nutritional maintenance and advancements in the control of infection, the life expectancy of patients with CF has steadily improved over the past three decades. As a

result, many of the sequelae associated with CF are becoming more prevalent. Cystic Fibrosis Related Diabetes is a common complication of CF and a growing problem as survival rates continue to rise. CFRD is distinctly different from the two known types of diabetes mellitus in that it shares features of both. It occurs in slender young adults with an average age of onset usually between 18-21 years. It appears to have a female preponderance<sup>7</sup> and may be more likely to affect individuals who are homozygous for the common  $\Delta F508$  mutation.<sup>2</sup> Patients rarely present with ketoacidosis, but it can occur, especially at the time of initial presentation if there has been a long period of symptomatic hyperglycaemia (e.g. polyuria, polydipsia). As in type 2 diabetes (non-insulin dependent), most patients with CFRD would make enough insulin to suppress ketogenesis. Additionally, glucagon deficiencies have been shown in patients with CF, which may serve to protect against ketone formation.<sup>8</sup> Microvascular complications of CFRD have been recognised<sup>5</sup>, but macrovascular complications have not, presumably because fat malabsorption reduces the likelihood of having elevated serum lipid levels, or simply because patients do not live long enough to develop any related cardiovascular disease. Finally, no immunological serum markers or HLA profiles have been identified that are typical for type 1 (insulin-dependent) diabetes.

Prior to 1990, no published guidelines were available for the identification CFRD. In an effort to standardise the diagnosis of CFRD, the American Cystic Fibrosis Foundation, as well as the International Expert Committee on the Diagnosis and Classification of Diabetes Mellitus, developed the criteria used for identifying early signs of impaired glucose control.<sup>9</sup> This involved screening patients for glucose intolerance in the following manner:

- Urinalysis 2-3 times per year
- Fasting and 2-hour postprandial blood glucose every 2-4 years during late childhood
- Fasting and 2-hour postprandial blood glucose every 2 years, starting in the mid-teenage years

Since CFRD is such a late complication of CF, modifications to these guidelines are fairly common. In a survey of medical practices in the U.S. done by Allen et al., it was found that there was a substantial variability in physician practices in screening for abnormalities in glucose homeostasis in patients with CF.<sup>10</sup> Similarly, The National Children's Hospital (NCH) in Dublin, Ireland, has adopted a variation of this protocol whereby all CF patients 8 years or older undergo a "complete" Oral Glucose Tolerance Test (OGTT) every two years, and all CF patients, regardless of age, have fasting serum glucose and glycosylated haemoglobin concentrations determined every year.

The purpose of this study was to examine the present screening guidelines used at NCH for identifying impaired glucose control in CF patients, and to compare the results with other published works, in an effort to propose a simple and efficient screening tool.

## METHODS

One hundred eleven patients (54 male:57 female) with an age range of 1-19 years, who attended the cystic fibrosis clinic at The National Children's Hospital Dublin, Ireland, from 1982-1999 were considered in the investigation. Glycosylated haemoglobin (HbA1c) concentrations were estimated on all patients on an annual basis in the out patient clinic and at times of hospital admission. HbA1c was determined by ion exchange chromatography and expressed as a percentage of the total haemoglobin. HbA1c measurements were classified as either normal or elevated, based on whether it was below or above the upper limit of the reference ranges. The normal ranges for a fasting glucose concentration and HbA1c were defined as 2.8-7.0 mmol/L and 2.6-5.8% respectively.

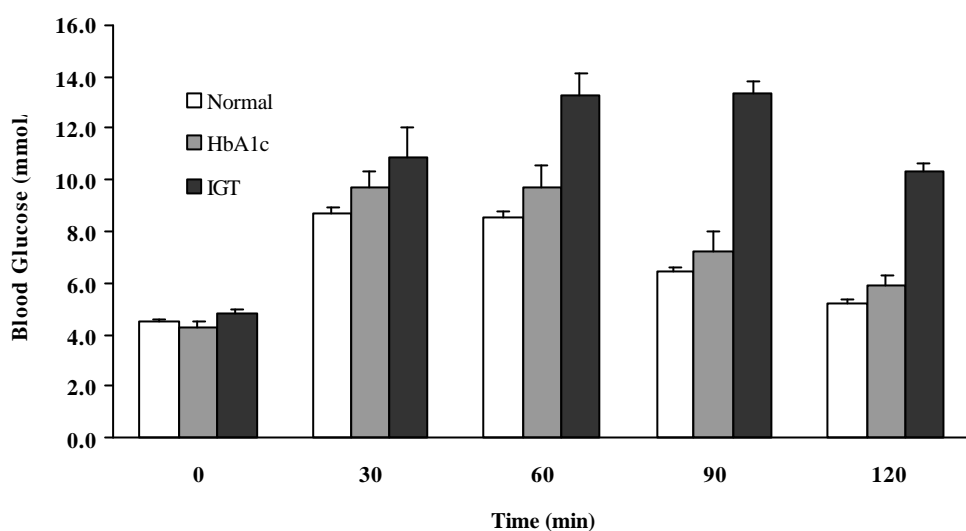
In addition to measuring glucose and HbA1c, subjects over the age of 8 years underwent an Oral Glucose Tolerance Test (OGTT) every 2 years. The OGTT protocol was in accordance with the WHO recommendations in which 1.75 g of carbohydrate/kg was given orally, in the form of Polycal (113 ml in 200 ml of water), followed by estimation of intravenous blood glucose concentrations at 30 min intervals from 0-120 min. Each subject was classified according to the WHO criteria as having normal glucose tolerance, impaired glucose tolerance, or overt diabetes mellitus. Subjects with a plasma glucose concentration of 8.8 mmol/L or less at 120 min post-prandial were considered to have normal glucose tolerance, those with a value of 8.9-11.1 mmol/L were considered to have impaired glucose tolerance, and those with a value of 11.2 mmol/L or more were diagnostic for diabetes mellitus.

Statistical evaluations of the data were performed using Microsoft Excel 97™. A correlation test was used to assess the strength of association between fasting glucose and HbA1c concentrations. A two by two table was constructed and sensitivity, specificity, a positive predictive value (PPV), and a negative predictive value (NPV) were calculated to determine how well elevated HbA1c levels are at predicting impaired glucose tolerance.

## RESULTS

A total of 286 glycosylated Hb concentrations, and 93 oral glucose tolerance tests were analysed in the study.

To investigate the importance of a raised HbA1c in relation to glucose tolerance, all subjects who had an OGTT were divided into three groups according to the result of the test: the first group had normal HbA1c levels and normal OGTT results,



**Figure 1.** Mean glucose concentrations (+S.E.M.) during oral glucose tolerance tests in 93 patients with cystic fibrosis. Normal group (n=76), raised HbA1c (n=9), impaired glucose tolerance (n=8).

the second group had raised HbA1c and normal OGTT results, and the third group had raised HbA1c and abnormal OGTT results. The average age ± standard deviation of the subjects in first group was 11.9 ± 3.1 years (range = 8-18), in the second group was 12.2 ± 3.1 years (range = 9-18), and for the third group it was 13.4 ± 3.7 years (range = 8-17). Figure 1 shows the mean glucose concentrations during the course of the test for each of the three groups. Subjects in groups 1 & 2 produced similar glucose profiles; with a peak mean glucose concentration occurring at 30min and mean glucose concentrations of 5.2 and 5.9 mmol/L respectively at 120 min. In group 3, the peak mean glucose concentration was reached at 60 min, with a mean glucose concentration of 10.3 mmol/L at 120 min. (see Figure 1)

Based on all of the results, a flow chart was constructed to illustrate the progression of impaired glucose control (Figure 2). Out of the 111 subjects, 16 (14%) have had at least one elevated fasting glucose concentration, 17 (15%) had elevated HbA1c concentrations, and 8 (7%) were classified as having impaired glucose tolerance. Of the 8 subjects with impaired glucose tolerance, 2 had been previously diagnosed with insulin dependent diabetes mellitus. Table 1 shows the results of the glycosylated Hb tests in all of the subjects and evaluates its ability to

predict impaired glucose tolerance. The sensitivity (the true positive rate) was 80%, the specificity (the true negative rate) was 91%, the positive predictive value (PPV) was 47%, and the negative predictive value (NPV) was 98%.

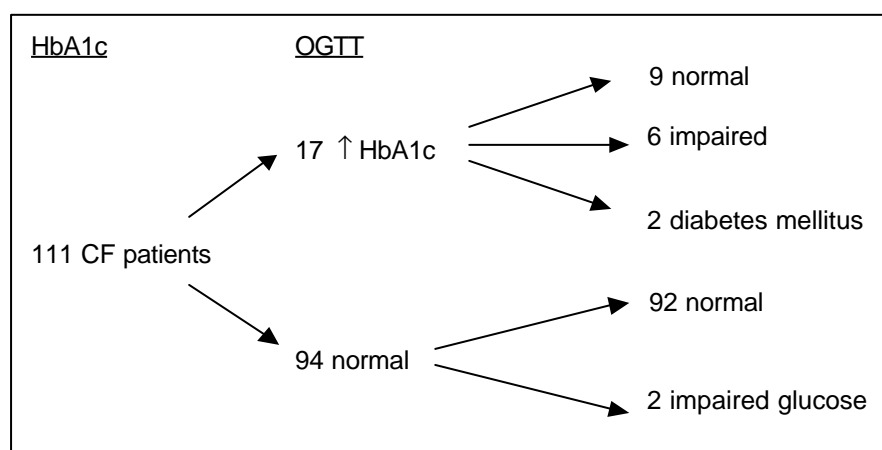
### DISCUSSION

The oral glucose tolerance test is assumed as

	Oral Glucose Tolerance Test		Totals	
	Impaired	Normal		
HbA1c	Elevated	8	9	17
	Normal	2	92	94
Totals	10	101	111	

Sensitivity = 8/10 ≈ 80%  
Specificity = 92/101 ≈ 91%  
PPV = 8/17 ≈ 47%  
NPV = 92/94 ≈ 98%

**Table 1.** A two by two table showing the results of glycosylated Hb test, and assessing its ability to predict impaired glucose tolerance. PPV = Positive Predictive Value, NPV = Negative Predictive Value.



**Figure 2.** Results of glycosylated haemoglobin and oral glucose tolerance tests in 111 patients with cystic fibrosis.

the “gold standard” for the detection of impaired glucose control and the diagnosis of diabetes. However, performing a complete OGTT is not only time consuming and expensive, but is also physically demanding on the individual being tested. It requires the patient to be fasting, with nothing to eat or drink for at least 8-10 hours prior to the test, taking in a considerable amount of carbohydrate in one sitting, and a great deal of co-operation in the collection of blood samples every 30 min for two hours. Furthermore, there is evidence to suggest that the results of the test vary with age, activity level, metabolic stress, time of day, and several other factors.<sup>11</sup> Therefore, other tests are being investigated for their ability to predict impaired glucose metabolism.

Measurement of glycosylated Hb (HbA1c) has been suggested as an alternative to the OGTT in screening for impaired glucose control.<sup>12</sup> Poor glucose control with a corresponding increase in plasma glucose concentrations results in the glycosylation of Hb. The concentration of glycated haemoglobin is increased within erythrocytes in proportion to the degree of chronic hyperglycaemia, and therefore serves as an indirect measure of the average blood glucose concentration, over the previous 1-2 months. This method is now widely used for monitoring long-term glucose control in known diabetic patients, however its use as a screening tool has yet to be thoroughly evaluated.

Glucose intolerance was found in 8 of the 17 (47%) patients who had one or more raised measurements of HbA1c. In addition, all but 2 patients who had consistently normal HbA1c concentrations also had normal glucose tolerance. Based on the results of the two tests, three groups were identified: (1) normal HbA1c & OGTT (2) raised HbA1c & normal OGTT (3) raised HbA1c & impaired OGTT. The glucose profiles were similar in groups 1 & 2, with comparable glucose concentrations recorded at 120 min. Furthermore, peak glucose concentrations in both groups occurred at 30 min, which is consistent with a normal population.<sup>2</sup> In group 3, however, the mean glucose concentration was elevated at 120 min (10.3 mmol/L) and the peak mean glucose concentration was reached at 60 min. The discrepancy between groups 1 & 2 with group 3 might offer a clue as to the natural history / progression of glucose intolerance. Since more than half (53%) of the subjects with a raised HbA1c also had a similar OGTT profile to those with normal HbA1c, it can be suggested, based on the trend of increasing mean age in the 3 groups that an elevated HbA1c may be an early sign of glucose intolerance. It is however noted that the difference is not statistically significant. In an effort to support this hypothesis, sensitivity & specificity test are required.

When compared with the OGTT, an elevated HbA1c had an 80% sensitivity rate, meaning that 8 out of 10 elevated HbA1c measurements showed either impaired glucose tolerance or overt diabetes. The true negative rate, or specificity was 91%, meaning that 92 out of 101 subjects with a normal HbA1c had a normal OGTT. Since the specificity and sensitivity rates do not account for the prevalence of impaired glucose tolerance within the population, predictive values were calculated (PPV = 47%, NPV = 98%) to assess the ability for the HbA1c test to detect glucose intolerance. Since the prevalence of impaired glucose tolerance in this population was low, the PPV was also low because the number of elevated HbA1c results that predicted normal glucose tolerance was increased in relation to those that predicted impaired glucose tolerance. By the same rationale, the NPV was high, which is the percentage of normal HbA1c measurements that also have normal glucose tolerance.

In short, these values basically suggest that if a CF patient has a normal HbA1c there is a 98% chance that he / she also has normal glucose tolerance, and if HbA1c is elevated, there is a 47% chance that he / she will have impaired glucose tolerance. Therefore, for the purposes of screening for CFRD, measurement of glycosylated Hb appears to be a reasonable test for assessing glucose control.

The central purpose of most screening programs is to identify people who are at risk of developing a serious disease, so that they might have the advantage of early treatment to prevent complications of the disease. With respect to the screening of CFRD, measuring HbA1c should be considered as an alternative to the OGTT, at least in the early years of disease. It is a test that is not influenced by recent activity, food intake, or metabolic stress, and therefore patient co-operation is minimal. Furthermore, only one small blood sample is required to perform the test, which alleviates the added stress on the child due to multiple needle pricks or the insertion of an intravenous cannulae. Certainly, large multi-centre studies should be done to better understand the natural history of CFRD in patients with cystic fibrosis. One internal review of a large CF clinic in the U.S. has already shown that the prevalence of CFRD increases from 9% in five to nine year olds, to 43% in patients 30 and older.<sup>13</sup> This information is useful in that it tells us that we are screening for a disease with a very low prevalence in the younger age groups, with a moderately invasive screening tool. Since there appears to be enough evidence to suggest that alternative screening tools are just as capable at detecting impaired glucose tolerance at an early age, we must further investigate this possibility in an effort to reduce the amount of strain that already debilitates the children suffering from cystic fibrosis.

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