The association between HbA_{1c} and the development of cystic fibrosis-related diabetes

Running title

The association between HbA_{1c} and the development of CFRD

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What is already known about this subject?

- HbA_{1c} has a low sensitivity in the diagnosis of cystic fibrosis-related diabetes (CFRD) and the oral glucose tolerance test (OGTT) is the current preferred method of diagnosis.
- There is an association between HbA_{1c} and microvascular damage in CFRD but the extent of this is not fully established.

What are the new findings?

- HbA_{1c} level above 37 mmol/mol (5.5%) is associated with the development of a positive OGTT.
- Higher HbA_{1c} levels are associated with severe forms of retinopathy

How might this impact on clinical practice in the foreseeable future?

- HbA_{1c} level greater than 37mmol/mol (5.5%), in an individual who does not have the formal diagnosis of CFRD, would be an indication for closer scrutiny of their glycaemic control.

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Abstract

Aims/hypothesis

To examine glycated haemoglobin (HbA_{1c}) as a predictor of risk for future development of Cystic Fibrosis-Related Diabetes (CFRD) and assess the association with the development of retinopathy in CFRD

Research and Methods

A 7-year retrospective longitudinal study was conducted in 50 adults with CF comparing oral glucose tolerance test results with HbA_{1c} values in predicting the development of CFRD. Retinal screening data were also compared to HbA_{1c} measurements to assess microvascular outcome.

Results

An HbA_{1c} value greater than or equal to 37mmol/mol (5.5%) (hazard ratio 3.49,CI 1.5-8.1) was significantly associated with the development of dysglycaemia as defined by the OGTT over a 7-year period. Severity of diabetic retinopathy was associated with a higher HbA_{1c} and longer duration of CFRD.

Conclusion

There is a link between HbA_{1c} level and the future development of dysglycaemia in CF based on OGTT, as well as microvascular outcomes. Although current guidance does not advocate the use of HbA_{1c} as a

diagnostic tool in CFRD, it may be of clinical use in determining individuals at risk of future development of CFRD.

Research in context

Keywords

HbA_{1c}, Cystic fibrosis related diabetes, OGTT

Introduction

Cystic Fibrosis Related Diabetes (CFRD) is a condition that is distinct from Type 1 and Type 2 diabetes mellitus. Dysglycaemia in Cystic Fibrosis (CF) is associated with a decline in pulmonary function and body mass index (BMI) [1,2]. This is particularly important as decline in forced expiratory volume in 1 s (FEV1) and BMI are associated with increased mortality in CF [3]. Thus, early detection of dysglycaemia may help to reduce the rate of decline in pulmonary function and microvascular disease. However, controversy remains over the methods used to screen for CFRD [4].

Currently, annual oral glucose tolerance testing (OGTT) is undertaken in many adult CF centres as part of the screening process of CFRD [5]. The OGTT is classified as normal for an individual with CF when the fasting and 2-hour values are within reference range, as defined by WHO [6]. The issue regarding the use of the OGTT in the diagnosis of CFRD is widely debated. It examines glucose levels at two time points. This does not necessarily correlate with clinical outcome in CF as there is a deterioration in an individual's clinical status prior to diagnosis [2,7]. The glycaemic state in a CF

individual is highly fluctuant [8]. Thus, any high glucose which is observed but not demonstrable by the two-hour time points on an OGTT could lead to a negative impact on pulmonary function in an individual with CF [7].

Glycated Haemoglobin (HbA_{1c}) reflects glycaemic control over a period of time. This may have some advantages over the OGTT. The use of HbA_{1c} as a screening tool in CFRD is controversial. Current UK guidance does not recommend using HbA_{1c} as part of the screening process for CFRD as the value is often within the normal range despite an OGTT diagnostic of CFRD [9]. Individuals with CF can have increased red cell breakdown and iron deficiency anaemia, which can affect interpretation of HbA_{1c} [10]. However there is limited evidence on whether HbA_{1c} can provide guidance in determining whether a person with CF may develop dysglycaemia and require further investigation [11]. It is a test that can be taken on a random basis, and thus can potentially reduce the burden of annual OGTT, a cumbersome test that requires individuals to travel from long distances in a fasting state, to a CF centre. In light of the debate surrounding the OGTT, we explored the possibility of whether the HbA_{1c} can be an adjunctive tool in the prediction of individuals who may later develop CFRD.

Objective

To compare OGTT test results and HbA_{1c} measurements in people with adult CF attending the All Wales Adult Cystic Fibrosis Centre and correlate this with retinal screening data in CFRD.

Research Design and Methods

A retrospective longitudinal study was performed from the beginning of 2006–end of 2012, a period of 7 years. In total, 50 people were followed between this period. Fasting plasma glucose and 2-hour post-prandial glucose levels were analysed in individuals who underwent an OGTT as part of their routine annual review. The diagnosis of CFRD using OGTT was based on WHO criteria [6].

A corresponding HbA_{1c} level was measured using high performance liquid chromatography (Tosoh G8 Automated Glycohaemoglobin Analyser), Tosoh Bioscience (Tokyo, Japan).

Statistical analysis

The TRIPOD guidelines, were followed in the design and analysis of the study [12]. R statistical environment and SPSS 18 were used in statistical analysis. Pearson's chi-squared was used to assess categorical data. The Mann-Whitney U test was used for non-parametric data. Receiver operating characteristics (ROC) curves were generated as part of sensitivity and specificity assessment. The log rank test was used to estimate the predictive value of HbA_{1c} in the development of CFRD and CF with impaired glucose tolerance (CF dysglycaemia), which was the primary outcome of the study.

Results

Of the 71 individuals with CF who had a recorded OGTT, 50 individuals were identified who initially had CF with normal glucose tolerance based on OGTT in 2006. These were followed up from over the 7 years from the beginning of

2006. In the remaining 21 individuals, five had CFRD and sixteen had CF with impaired glucose tolerance. The mean age of the 50 individuals with CF with normal glucose tolerance was 26 years (± 6.5 SD); FEV1 percentage predicted mean was 68 (± 25 SD) and mean BMI was 22.6 kg m^2. The mean HbA_{1c} was 38mmol/mol (5.6%) (Table 1). Of these 50 individuals, 18 had a HbA_{1c} less than 37mmol/mol (5.5%) and 32 individuals had a HbA_{1c} greater than or equal to 37mmol/mol (5.5%). In the follow up period, 4 individuals with a HbA_{1c} <37mmol/mol (5.5%) developed dysglycaemia in the form of impaired glucose tolerance or CFRD. In the group with a HbA_{1c} ≥37mmolmol (5.5%), 18 individuals developed dysglyceamia.

A ROC curve was generated to determine the strength of the association between the value of HbA_{1c} compared to 2-hour plasma glucose in the OGTT in the development of diabetes over the 7-year period. The median time to diagnosis was 4 years. The area under the fitted ROC curve was 0.76 for HbA_{1c} in 2006 (p=0.012). To have a test of higher sensitivity and moderate specificity, an HbA_{1c} level ≥ 37mmol/mol (5.5%) would have 100% sensitivity but 45% specificity, in terms of prediction of development of CFRD, based on CF Trust diagnostic criteria, with OGTT data as the outcome. The area under the curve was greater when using HbA_{1c} as the baseline variable compared to fasting plasma glucose (area under the curve value of 0.645). This suggests that HbA_{1c} level is closely associated with the development of CFRD, using OGTT as the outcome diagnostic test.

The predictive value of HbA_{1c} level ≥37mmol/mol (5.5%) for the future development of CFRD and impaired glucose tolerance in the 50 individuals, who were initially CF with normal glucose tolerance in 2006, was examined

using a Log rank test (Figure 1). The time to development of the first abnormal OGTT between 2006 and 2012 was investigated. The analysis revealed that individuals with HbA_{1c} ≥37mmol/mol (5.5%) were significantly more likely to develop an abnormal OGTT (p=0.009) over a 7-year period (Hazard ratio 3.49; 95%CI 1.5 to 8.1).

A separate review of diabetic retinopathy was undertaken. This was based on reports from the diabetes retinal screening service in Wales. Of 43 individuals with CFRD who underwent retinal screening between 2010 and 2012,19 individuals (44%) had evidence of diabetic retinopathy, based on their most recent retinal screen (mean HbA_{1c} 68 mmol/mol (8.4% ± 1.4%)). This ranged from mild non-proliferative diabetic retinopathy to clinically significant macular oedema. Of the 24 individuals with no diabetic retinopathy, the mean HbA_{1c} was 54mmol/mol (7.1%±1%SD). This difference was significant ($p<0.05$). Individuals with more severe forms of diabetic retinopathy were older, compared to those individuals who had no diabetic retinopathy or non-proliferative retinopathy. They also had greater HbA_{1c} levels (P=0.038) and a larger percentage had a trend to a longer duration of CFRD (over 5 years), although this was not statistically significant.

Discussion

Our longitudinal retrospective study identifies a link between glycated haemoglobin and future glycaemic status in CF and microvascular outcome. Although current guidance does not recommend the use of HbA_{1c} as a screening tool in CFRD and our study also does not advocate this, there is relatively little information concerning the use of HbA_{1c} in prediction of the

development of CFRD. Glycated haemoglobin is currently recommended for monitoring purposes in individuals who already have CFRD, as an overall assessment of glycaemic control [5]. However, our findings suggest that HbA_{1c} could also be used in assessing individuals at risk of developing CFRD, in addition to the OGTT, rather than solely in monitoring once a diagnosis has been made. An HbA_{1c} level of 37mmol/mol (5.5%) and above, would aid in determining who is at risk of developing CFRD and thus identify a proportion of individuals who would benefit from additional testing to identify dysglycaemia. This could be advocated at times of infective exacerbations or if weight loss is noted.

Glycated haemoglobin as a screening tool has been examined in a number of studies. A $HbA_{1c} \geq 5.8\%$(40mmol/mol) was advocated as a cut off level which was predictive of a positive OGTT by Burgess *et al* [11]. In contrast Boudreau *et al*, demonstrated a HbA_{1c} level ≥5.8%(40mmol/mol) was limited by low sensitivity and specificity (68.2 and 60.5% respectively) when compared to OGTT results [13]. Small-scale studies examining the use of HbA_{1c} also do not support HbA_{1c} as a sole screening tool in CFRD, although they have used different levels of HbA_{1c} in their research [14].

Based on our investigation, we do not support the use of HbA_{1c} to screen for CFRD, but rather suggest that a HbA1c above 37mmol/mol (5.5%) is associated with a high risk of development of CFRD and warrants closer scrutiny. We would recommend further studies in continuous glucose monitoring (CGM) to document the presence of dysglycaemia for those individuals with a raised HbA_{1c}. Although our study did not compare CGM with HbA_{1c}, there is evidence of a correlation between the two measurements [15].

This may reveal a population, not diagnosed by the conventional OGTT, who could benefit from receiving insulin treatment. The fluctuating glycaemic profile in CF, suggests that a normal OGTT does not necessarily exclude CFRD and dysglycaemia. Additionally, there may be evidence of a deterioration in clinical status prior to a formal diagnosis of CFRD. Thus, HbA_{1c} may be a useful adjunctive tool, to highlight those with underlying dysglycaemia, who would benefit from treatment. Currently, CGM is undertaken in many CF centres in the UK and can aid clinicians in determining underlying dysglycaemia, although not validated for diagnostic purposes.

This study was based on an adult population; thus we cannot translate our results to the paediatric CF population. However, it may highlight a population who may benefit from treatment. Administration of insulin is the mainstay of therapy in CFRD, which reverses weight loss in CFRD and potentially improves survival [16]. Insulin in the pre-diabetes stage may also improve clinical outcome in CF although studies examining this have been small scale [17].

In our study, we are limited by the small population size as OGTT was introduced in 2005 in our CF centre. Thus, we cannot apply our findings strictly to current clinical practice and large, longitudinal population studies are required to validate our findings. We have assessed glycaemic control over a 7-year time frame, which has advantages over recent studies that have observed larger populations of individuals with CF but over a shorter time duration [12,13]. A further limitation is that we did not measure haematological

parameters in our population, which could affect interpretation of our findings in HbA_{1c}.

We have previously shown microvascular damage in the form of retinopathy is evident in CFRD and associated with increasing HbA_{1c} although this does not reflect the true extent of the condition due to poor uptake of retinal screening in CFRD [18]. The presence of more severe retinopathy in some individuals with a relatively short duration of CFRD attests to the possibility that dysglycaemia has been present for a longer duration. Schwarzenberg *et al* identified the presence of any form of diabetic retinopathy in 16% of CFRD individuals with fasting hyperglycaemia [19]. The difference in prevalence compared to our population may be related to the screening process. The findings from our study highlight the impact of CFRD on microvascular outcome, which is more prevalent compared to previous study findings [19]. There have been reports of diabetic retinopathy in individuals who have not been diagnosed with CFRD [20]. In our findings, one female had moderate diabetic retinopathy but who had CFRD for only 2 years. This conveys the importance of the early diagnosis of dysglycaemia in CF. The use of HbA_{1c} may allow clinicians to predict the development of CFRD at an early stage and allow early screening of microvascular changes.

Early diagnosis and treatment is important to prevent the decline in health of the CF population. We demonstrate that HbA_{1c} is associated with a future risk of developing CFRD in individuals with CF within a 7-year time frame, and who may thus require increased vigilance in monitoring glycaemic control. More longitudinal studies are needed to establish what are the most

appropriate diagnostic tests for dysglycaemia in a CF population.

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Table 1 Clinical characteristics of the 50 individuals based on glycaemic status in 2006.

Number of individuals within each group	CF-normal glucose tolerance N=50
Gender male and female	29 Male 21 Female
Mean age in years (±SD)	26 (±6.5)
FEV_1 % predicted (±SD)	68 (±25)
BMI kg/m^2 (±SD)	22.6 (±3.9)
HbA1c(mmol/mol)	38mmol/mol (±4.4)
HbA1c %	5.6 (±0.4)

FEV1 % predicted, BMI (kg/m^2) and age in years are represented as mean values and ±SD.

Figure legend

Figure 1 – Survival curve displaying the time to development of CFRD/CF with impaired glucose tolerance based on HbA1c. The graph illustrates the time to development of dysglycaemia (CFRD/CF-impaired glucose tolerance) in individuals with HbA1c ≥37 mmol/mol (5.5%, dotted line) compared to individuals with HbA1c < 37 mmol/mol (5.5%, solid line). The number remaining at risk at 2, 4 and 6 years is shown below the graph. At the end point of the observation, at 7 years, 14/18 individuals with HbA1c < 37 mmol/mol (5.5%) remained at risk, compared with 14/32 individuals with HbA1c ≥ 37 mmol/mol (5.5%). Analysis by log rank test, p=0.009.