The use of fructosamine in cystic fibrosis-related diabetes (CFRD) screening

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Abstract

Objective: To determine whether serum fructosamine correlates with glycemic control and clinical outcomes in patients being screened for cystic fibrosis-related diabetes (CFRD).

Methods: Fructosamine and percent predicted forced expiratory volume in 1 s (FEV1) were measured in patients undergoing a 2 h oral glucose tolerance test (OGTT) for CFRD screening. Fractional serum fructosamine (FSF) was calculated as fructosamine/total protein.

Results: FSF exhibited a positive correlation with 2 h OGTT results ($r^2 = 0.3201$, $p = 0.009$), and ROC curve analysis suggested that FSF can identify patients with an abnormal OGTT (AUC = 0.840, $p = 0.0002$). FSF also exhibited a negative correlation with FEV1 ($r^2 = 0.3732$, $p = 0.035$). Patients with FSF $\geq 3.70 \mu mol/g$ had significantly lower FEV1 (median 47%) compared to those with FSF $< 3.70 \mu mol/g$ (median 90%; $p = 0.015$).

Conclusions: FSF correlated with both OGTT results and FEV1, and reliably identified patients with abnormal OGTT results. This simple blood test shows potential as an effective tool in CFRD screening.

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1. Introduction

Cystic fibrosis-related diabetes (CFRD) is a common complication in patients with cystic fibrosis (CF), and is associated with impaired lung function [1] and increased mortality [2]. Conventional diagnostic biomarkers for diabetes mellitus are unreliable in CFRD, as many patients with this disorder have post-prandial hyperglycemia yet normal fasting glucose. HbA1c underestimates true glycemic control in the CF population, possibly due to increased red cell turnover or inefficient hemoglobin glycation in the presence of intermittent hyperglycemia [3]. Consequently, the current gold standard for CFRD diagnosis is the 2 h oral glucose tolerance test (OGTT) [4]. However, this test suffers from poor patient compliance [5], and the diagnostic threshold is not based on common CFRD outcomes [6].

Fructosamine, or glycated serum protein, is an alternate marker that correlates well with glycemic control in Type 1 and Type 2 diabetes mellitus [7,8]. It is currently used in settings where HbA1c is unreliable [9]. Unlike HbA1c, fructosamine is
not affected by red blood cell turnover. In addition, glycation of albumin, which accounts for ~90% of glycated serum protein, is roughly 9 times more efficient than hemoglobin glycation [10]. Consequently, glycation of albumin is a better reflection of post-prandial hyperglycemia and intermittent spikes of hyperglycemia compared to HbA1c [11]. For these reasons, we assessed the utility of fructosamine in CFRD screening.

2. Methods

Clinically stable adult patients undergoing annual screening for CFRD with the 75 g 2 h OGTT were recruited for this study. Patients who were previously diagnosed with CFRD, received lung transplantation, or were pregnant were excluded. All participants provided written informed consent, and the study was approved by the research ethics board at the University of Alberta.

A serum specimen was collected before commencing the OGTT. Serum fructosamine was measured using the Siemens fructosaminase-based method on the Advia 1800, as described previously [12]. Total protein was measured using the Siemens Biuret method on the Advia 2400. Fractional serum fructosamine (FSF) was calculated as fructosamine/total protein.

Percent predicted forced expiratory volume in 1 s (FEV1) was assessed by spirometry [13]. Only FEV1 values obtained within 3 weeks of the fructosamine measurement were included for analysis, as the half-life of albumin is 3 weeks.

Simple linear regression was performed in Microsoft Excel to assess the correlation between fructosamine and 2 h OGTT results, FSF and 2 h OGTT results, and FSF and FEV1. Coefficients of determination were derived from Pearson correlation coefficients. ROC curve analysis was performed in MedCalc, and the Mann-Whitney U test was used to assess statistically significant differences between groups.

3. Results

3.1. Subjects

Twenty patients participated in the study (eight females and twelve males). The mean age was 34.8 years (range 20–72), and fifteen patients (75%) were on pancreatic supplements. Based on the OGTT results, two patients (10%) had newly diagnosed CFRD, and three (15%) had impaired glucose tolerance (IGT).

3.2. Relationship between fructosamine and OGTT results

Serum fructosamine exhibited a significant positive correlation with 2 h OGTT results (Fig. 1A, \( r^2 = 0.2389, p = 0.029 \)). While controversial, some have advocated for the need to normalize serum fructosamine results to the total protein concentration [14]. Given that poor nutritional status and malabsorption are common in the CF population, a reduction in the total protein level could affect fructosamine concentration in a manner that is independent of glycemic control. To mitigate this, we calculated fractional serum fructosamine (FSF), and re-examined the relationship. Correction for total protein concentration improved the correlation between FSF and 2 h OGTT results (Fig. 1B, \( r^2 = 0.3201, p = 0.009 \)).

ROC curve analysis (Fig. 2) revealed that FSF can distinguish patients with normal glucose tolerance from those with abnormal glucose tolerance (either IGT or CFRD), with an area under the curve (AUC) of 0.840 (\( p = 0.0002 \)). The optimal FSF cutoff was \( \geq 3.70 \) mol/g, which identified IGT and CFRD with 100% sensitivity and 67% specificity.
3.3. Relationship between FSF and lung function

An ideal screening test for CFRD would not only identify abnormalities in glycemic control, but would also correlate with relevant clinical outcomes [6]. We therefore evaluated the relationship between FSF and lung function in our patient cohort (Fig. 3A). FSF exhibited a significant negative correlation with FEV1 ($r^2 = 0.3732$, $p = 0.035$). In addition, patients with FSF $\geq 3.70$ μmol/g have significantly lower FEV1 (median 47%) compared to those with FSF $<3.70$ μmol/g (median 90%, $p = 0.015$) (Fig. 3B).

4. Conclusions

Given the limitations of the OGTT, there is great interest in identifying an alternate screening test for CFRD. Despite underestimating glycemic control in CF patients, HbA1c was recently proposed as an effective screening tool, reducing the need for an OGTT by 50.7% [15]. However, conflicting results have been reported [16,17], and a large proportion of patients with IGT would be missed [18]. OGTTs with shorter time points have also been examined [6], with 1 h results exhibiting a significant negative correlation with FEV1 in children [19] and adults [20]. However, the strength of these associations is relatively weak ($r^2 = 0.05$ to 0.13) and validation studies are needed. Furthermore, these tests still bear the same inconveniences as the 2 h OGTT.

In the only other study to date examining the utility of fructosamine in CFRD, Godbout and colleagues assessed the relationship between raw fructosamine results and mean plasma glucose concentration over the preceding month in patients diagnosed with CFRD [3]. No significant correlation was identified; however, this study may have been underpowered and fructosamine results were not corrected for total protein concentration.

To our knowledge, the current study is the first to examine the utility of fructosamine in CFRD screening. The finding of a significant positive correlation between FSF and 2 h OGTT results suggests that FSF may be a useful marker in this context. Based on the ROC curve analysis (Fig. 2), an optimal FSF cutoff of $\geq 3.70$ μmol/g identified abnormal glucose tolerance (IGT and CFRD) with 100% sensitivity and 67% specificity. Thus, FSF could be the first step in screening for IGT and CFRD, where only those that test above the cutoff would require a confirmatory OGTT. This would eliminate the need for an OGTT in a large proportion of CF patients. Studies are underway to validate this approach in a larger cohort and identify optimal screening thresholds for IGT and/or CFRD. Since FSF is a simple and convenient blood test that does not require consumption of a glucose drink or an extended stay at the laboratory, this marker may have the potential to improve CFRD screening compliance.

The significant negative correlation between FSF and FEV1 suggests that this marker may be associated with clinically relevant CF outcomes. Indeed, patients with FSF $\geq 3.70$ μmol/g had significantly lower FEV1 compared to those with FSF $<3.70$ μmol/g. Interestingly, two of the patients with FSF $\geq 3.70$ μmol/g had an FEV1 $<50\%$ despite normal OGTT results, suggesting that FSF may be able to identify clinically relevant hyperglycemia that would otherwise be missed by the OGTT. Larger studies are needed to confirm these findings and assess the potential of FSF as a diagnostic test for CFRD.

In summary, FSF exhibited a significant positive correlation with 2 h OGTT results and a significant negative correlation with FEV1 in patients being screened for CFRD. In addition, FSF reliably identified patients with an abnormal OGTT. These results suggest that this simple blood test could be an effective tool in CFRD screening.

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Conflicts of interest

None.

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