No relationship between mean plasma glucose and glycated haemoglobin in patients with cystic fibrosis-related diabetes

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Abstract

Aim. – Cystic fibrosis-related diabetes (CFRD) prevalence has increased dramatically with the improved life expectancy of patients with cystic fibrosis (CF). Glycated haemoglobin (HbA1c) is an important tool for monitoring blood glucose control but, unlike in type 1 and type 2 diabetes, a correlation between HbA1c, fructosamine and mean plasma glucose has not been clearly established in CF. This study aimed to examine the relationship between mean plasma glucose and HbA1c in stable patients with CFRD.

Methods. – Fifteen type 1 diabetes and 13 CFRD patients (HbA1c < 9.0%; no anaemia), matched for age and body mass index (BMI), provided 72 capillary blood glucose profiles taken 3 days/month for three months. At the end of this time, HbA1c and fructosamine were measured. Mean plasma glucose was estimated using the Diabetes Control and Complications Trial (DCCT) conversion formula, and linear regressions carried out to establish its relationship with HbA1c and fructosamine.

Results. – In type 1 diabetes patients, mean plasma glucose correlated significantly with HbA1c (r = 0.68; P = 0.005). In CFRD patients, no correlation was found between mean plasma glucose and HbA1c (r = 0.24; P = 0.460). Also, no association was found between mean plasma glucose, representing the month before blood sampling, and fructosamine in either group.

Conclusion. – Unlike in type 1 diabetes, HbA1c did not correlate with mean plasma glucose in CFRD subjects. Thus, having a normal HbA1c may not be sufficient to indicate a low risk of diabetes complications in CFRD. Further studies are required to explain such a discrepancy.

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Résumé

Absence de corrélation entre la valeur de la glycémie moyenne et l’hémoglobine glyquée chez les patients atteints de diabète secondaire à la mucoviscidose.

But. – La prévalence du diabète associé à la mucoviscidose (DbMV) a augmenté avec l’amélioration de la survie des patients atteints de mucoviscidose. Contrairement aux patients atteints de diabète type 1 ou 2, les corrélations entre l’hémoglobine glyquée (HbA1c), la fructosamine et la glycémie moyenne ne sont pas bien caractérisées chez les sujets avec DbMV. Cette étude décrit la relation entre la glycémie moyenne et l’HbA1c ou fructosamine dans un groupe de DbMV stable sur le plan médical.

Méthode. – Quinze diabétiques type 1 (DT1) et 13 sujets DbMV ont été recrutés. Chaque patient a fourni 72 glycémies capillaires recueillies sur 3 jours/mois durant trois mois. À la fin du trimestre, des prélèvements pour HbA1c et fructosamine ont été faits. La glycémie moyenne fut estimée à partir de la formule de conversion du Diabetes Complication and Control Trial (DCCT). Les relations entre la glycémie moyenne et HbA1c ou fructosamine ont été établies par régression lineaire.

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**1. Introduction**

Progress in nutritional and medical care over the past few decades has largely improved life expectancy in cystic fibrosis (CF) patients [1]. However, along with the increased survival, cystic fibrosis-related diabetes (CFRD) has become the major comorbidity in this population [2–4], occurring in around 13% of all patients with CF and in more than 30% of patients aged over 30 years [1,5]. CFRD patients are also at risk of developing diabetes-specific complications, making the early recognition and treatment of this condition of crucial importance [5–7].

For both type 1 and type 2 diabetes, large studies such as the Diabetes Control and Complications Trial (DCCT) and the UK Prospective Diabetes Study (UKPDS) have clearly established that lowering plasma glucose is a major therapeutic goal to prevent diabetes-specific complications such as retinopathy, neuropathy and nephropathy [8,9]. The DCCT data have also established the relationship between glycated haemoglobin (HbA1c) and mean plasma glucose and, thus, identified HbA1c as the best tool for monitoring average blood glucose control [10]. HbA1c values less than 7% are the widely accepted goal to ensure good control and to guide treatment choices to reduce the risk of diabetes-specific complications [11].

In CF patients, the relationship between HbA1c and mean plasma glucose has not been clearly established and may be modified by numerous factors, including altered red cell turnover and/or different glycation processing, reflected by the specific glucose-excision pattern seen in this population. Specifically, glycaemic variations in CF patients are characterized by an abrupt postprandial increase followed by rapid normalization of plasma glucose [12].

The relationship between mean plasma glucose and HbA1c in CF patients has been recently explored in a pilot study [14]. This study suggested that the relationship between mean plasma glucose and HbA1c in CF patients was similar to that previously described for type 1 diabetics in the DCCT [10]. However, that study included a high proportion of normal glucose-tolerant CF patients and did not include a control group.

In addition, the relationship between fructosamine and mean plasma glucose has not been well-explored in CFRD patients. It is generally accepted that fructosamine is a protein reflecting a three-week period of glycaemic control compared with approximately eight weeks for HbA1c. Thus, it is postulated that fructosamine may be another tool to assess glycaemic control in a CFRD population that often experiences changing medical conditions and different glycation processing.

The aim of our study was to describe the relationship between mean plasma glucose and HbA1c in patients with CFRD compared with type 1 diabetic patients matched for body mass index (BMI) and age, but without CF. We also assessed the relationship of fructosamine in these two patient groups.

**2. Research design and methods**

**2.1. Subjects**

Fifteen type 1 diabetic patients and 13 matched patients with CFRD were recruited from the endocrinology and cystic fibrosis clinics, respectively, of the Hôtel-Dieu de Montreal Hospital, part of the centre hospitalier de l’université de Montréal (CHUM). CFRD diagnosis was based on either ongoing pharmacological treatment or two consecutive abnormal values during an oral glucose tolerance test (OGTT) undertaken during a stable period, as previously described [12]. To be included, all participants had to be medically stable. Exclusion criteria included hospitalization, additional or changed corticosteroid therapy, anaemia, pregnancy or an unstable pulmonary condition diagnosed by a trained CF pneumologist in the six weeks prior to as well as during the study. The study was approved by the CHUM research ethics committee. All patients gave their written informed consent to participate.

**2.2. Measurements of anthropometric values**

At both the beginning and end of the study, anthropometric measures plus a review of the overall health condition and medication were taken for each participant. Each CF patient also underwent a complete pulmonary-function test.

**2.3. Measurements of capillary blood glucose and mean plasma glucose determination**

For each subject, capillary blood glucose was determined and self-monitored using a OneTouch Ultra® Blood Glucose Meter, specifically provided for the study by LifeScan. Each patient kept a glycaemic journal, including readings of pre-meal, post-meal (1–2 hours), bedtime and overnight glucose values—taken three days each month (including two weekdays and one weekend day and, if possible, during the last week of
the month)—over a period of three months following entry into the study. Mean daily capillary blood glucose was obtained for each participant calculated from the area under the curve (AUC) using Tai’s model [13]. Mean plasma glucose was determined by multiplying the mean AUC over 24 hours by a factor of 1.1, according to the DCCT formula [10,15]. This transformation takes into account differences between capillary and venous blood glucose values.

2.4. Measurements of HbA1c and fructosamine values

At the end of the three-month period, venous samples were drawn from each patient, and measurements of HbA1c and fructosamine levels were performed using immunochemistry (immunoturbidimetric) assays (ADVIA1650, Bayer HealthCare Diagnostics Division, Toronto, Ontario, Canada). The HbA1c dosage was a DCCT-aligned method using a normal range of 4.8–6.0%, and HbA1c values were compared with mean plasma glucose data collected over the three months (72 capillary readings). Only the last month’s mean plasma glucose values (24 capillary readings) were used for fructosamine (normal values: 200–270 μmol/L).

2.5. Statistical analysis

Data are presented as proportions and means ± S.D. Unpaired Student’s t test was used for comparison of the baseline continuous characteristics between the two groups (CFRD and type 1 diabetes). Given the small sample size, Spearman correlation coefficients were used to look for an association between mean plasma glucose and HbA1c or fructosamine in each group. Regression equations were obtained by simple linear regression. Statistical significance was defined as P values < 0.05. Statistical analyses were performed using SAS software (version 9.1).

3. Results

3.1. Subjects

Fifteen patients with type 1 diabetes (5 women, 10 men) and 13 with CFRD (7 women, 6 men) were recruited. These two groups were similar in terms of demographic and biochemical parameters, such as a complete blood-count profile with no anaemia or low mean corpuscle volume values suggestive of iron deficiency (Table 1). However, patients with type 1 diabetes presented with significantly higher values of HbA1c and fructosamine than CFRD patients. All patients were established on intensive insulin therapy before entering the study except for two CFRD patients, who were controlled by an oral hypoglycaemic agent and by diet alone, respectively. CF patients had a mean forced expiratory volume (FEV1) of 2.20 ± 0.61 L, corresponding to an average of 69% of the predicted values, which remained constant throughout the study (P = 0.336).

3.2. Relationship between mean plasma glucose and HbA1c

The mean number of capillary blood glucose values available to calculate mean plasma glucose was similar for both groups, with 68.7 capillary blood glucose values/type 1 diabetic versus 68.6 capillary blood glucose values/CFRD patient. Averages of mean plasma glucose were also similar between the two groups, although the mean plasma glucose tended to be lower in the CFRD group.

The relationships between HbA1c and mean plasma glucose in each patient group are shown in Fig. 1. For patients with type 1 diabetes, mean plasma glucose correlated significantly with HbA1c (r = 0.68, P = 0.005) and had the following derived regression equation: mean plasma glucose\(^{\text{Type 1 diabetes}} \approx (1.42 \times \text{HbA1c}) + 1.39.

In the CFRD patients, no significant correlation was found between HbA1c and mean plasma glucose (r = 0.24; P = 0.460).

As the range of values was wider for type 1 than for CFRD patients, we re-analyzed the data using only HbA1c values less than 8%. The relationship remained significant for type 1 diabetes and non-significant for CFRD patients (data not shown).

3.3. Relationship between mean plasma glucose and fructosamine

As shown in Fig. 2, no significant correlation was found in either group between mean plasma glucose values from the last month of observation and fructosamine. The correlation coefficients between mean plasma glucose and fructosamine

Table 1

| Demographic and clinical characteristics of patients with type 1 and cystic fibrosis-related diabetes (CFRD) |
|---------------------------------|-----------------|-----------------|-----------------|-----------------|
| Type 1 diabetes (n = 15) | CFRD (n = 13) | |
| Mean ± S.D. | Mean ± S.D. | |
| Age (years) | 36.5 ± 7.8 | 35.3 ± 8.3 |
| Gender (F/M) | 5 F/10 M | 7 F/M |
| BMI (kg/m²) | 23.7 ± 1.9 | 24.0 ± 2.4 |
| Hb (g/L) (n = 120–160) | 146.5 ± 10.2 | 143.6 ± 10.9 |
| MCV (FL) (n = 80–100) | 90.4 ± 3.9 | 88.1 ± 4.8 |
| Reticulocytes (%) (n = 0.005–0.020) | 0.009 ± 0.003 | 0.009 ± 0.004 |
| MPG (mmol/L) | 9.02 ± 1.55 | 7.95 ± 1.26 |
| HbA1c (%) (n = 4.8–6.0) | 7.4 ± 0.8 | 6.4 ± 0.6 |
| Fructosamine (μmol/L) (n = 200–270) | 328.2 ± 45.6 | 271.2 ± 35.3 |

BMI: body mass index; Hb: haemoglobin; N: normal values; MCV: mean corpuscle volume; MPG: mean plasma glucose; HbA1c: glycated haemoglobin; Fructo: fructosamine.
Fig. 1. Relationship between mean plasma glucose assessed by multiple capillary blood glucose over three months and HbA1c in type 1 and cystic fibrosis related diabetic patients (CFRD) in correlation with the relationship described by the DCCT.

Fig. 2. Relationship between mean plasma glucose assessed by multiple capillary blood glucose over one month and fructosamine in type 1 and cystic fibrosis-related diabetic patients (CFRD).

were \( r = 0.43 \) \( (P = 0.108) \) in type 1 diabetes patients and \( r = 0.50 \) \( (P = 0.095) \) in CFRD patients.

4. Discussion

Our results suggest that, unlike type 1 diabetes, there is no relationship between mean plasma glucose and HbA1c in stable CFRD patients. Also, no correlation was found in either group between mean plasma glucose and fructosamine.

The difficulties in assessing glucose control in a CF population have already been reported. In fact, patients with established CFRD and high glucose readings can present with normal HbA1c values \([12,16,17]\), thereby explaining the poor sensitivity of HbA1c in the detection of CFRD \([12,18]\). When CF patients with or without normal glucose tolerance are compared with healthy control groups, significant differences are noted in the glycaemic kinetics of CF patients such as abrupt postprandial peaks followed by rapid normalization of these glucose excursions \([12,16]\). Overall, these results suggest that conventional measures of glucose control (capillary blood glucose and HbA1c) do not properly estimate—and may even underestimate—mean glucose values in CF patients. This situation is similar to that seen in some type 1 diabetics who present with HbA1c values within the treatment targets in spite of wide glucose variability \([19]\).

There may be different explanations for the discrepancy between mean plasma glucose and HbA1c in the CF population. It may be speculated that the specific pattern of postprandial glucose excursions seen in CF subjects \([12,16]\) has an effect on the glycation process of HbA1c, which may require longer glycaemic excursions than the typically present in CF patients to correctly represent mean plasma glucose \([20]\). A shortened red blood cell lifespan may also be involved, although direct evidence of such a process in CF is scarce \([21]\). Anaemia and iron deficiency are frequently seen in CF \([22,23]\) and may also affect the validity of HbA1c dosage by increasing HbA1c values \([20]\), as demonstrated in type 1 diabetic patients \([24]\). Having only included patients with normal haemoglobin and mean corpuscle volume values, we did not measure markers of iron stores. However, the two groups had comparable and within-normal-range values of reticulocytes, a marker of haemoglobin regeneration, suggesting an absence of major red cell turnover in the group of CF patients (Table 1). Thus, further investigations are required to establish whether or not treatment of iron deficiency modifies HbA1c values, as it has been previously suggested for type 1 diabetic patients \([24]\).

In addition, high doses of vitamins C and E may well have inhibited haemoglobin glycation, leading to falsely lowered HbA1c values \([25–27]\). All the CFRD patients took supplements of vitamins C and E compared with only three of the type 1 diabetics. However, the findings of a randomized controlled trial do not support a significant impact of vitamin supplementation on HbA1c validity \([28]\).

Other established causes of inappropriately low HbA1c values are related to rapid red cell turnover, as seen in cases of haemolysis and patients treated for folate or vitamin B12 deficiency \([29,30]\). It should be noted that two different groups have reported unreliably low values of HbA1c in large cohorts of HIV patients and suggested that subclinical haemolysis related to antiretroviral treatment could be an explanation \([31]\). If confirmed in a larger cohort, the absence and/or diminished validity of HbA1c to estimate glucose control in CFRD patients will have major implications. Further studies would then be necessary to appropriately establish the tools and targets to monitor and achieve the necessary blood glucose control for preventing diabetes complications in CF patients.

The fact that fructosamine also appears to be an inappropriate marker of glucose control in both type 1 diabetics and CFRD patients is intriguing, and suggests that fructosamine is not as reliable as HbA1c for estimating glucose control in diabetic patients, as previously reported \([20,32]\).

Our observations differ from previously published data suggesting that the relationship between mean plasma glucose and HbA1c in CF patients is comparable to the correlation reported in
the DCCT [14]. However, this earlier study included CF patients with a high proportion of normal glucose-tolerant patients, no control group and mean plasma glucose was assessed by a continuous glucose monitoring system (CGMS) over a period of 48 hours. Even though CGMS has been validated in CF patients [33] and provides a much more detailed glucose profile during the observational period than does capillary blood glucose, two days may be too short to allow correlation with HbA1c—which reflects mean glucose values over the preceding two to three months—especially in CF patients, who often present wide day-to-day variability. Nevertheless, it is possible that a single capillary blood glucose taken within one or two hours after a meal, as in the present study, will also not reflect the true glucose profile of these patients, thereby explaining our negative results. This means that, as previously suggested, earlier and more frequent postprandial blood glucose readings, or longer CGMS monitoring, may be more appropriate for the evaluation of glucose control in CF patients [16].

There are a number of available methods for measuring HbA1c that assess different glycated components of haemoglobin [20]. Although we used a method aligned with the DCCT gold-standard reference, it is nevertheless possible that it introduced a bias, considering the small number of patients in each of our study groups. This means that a larger study, using various methods to evaluate mean plasma glucose such as multiple capillary blood glucose readings, CGMS for a longer period and HbA1c assessed by various methods, could be more sensitive to elucidate the relationship between HbA1c and mean plasma glucose in CFRD.

In contrast to a recent study [14], we could find no significant relationship between mean plasma glucose and HbA1c in CF patients. Thus, further investigations into the validity of HbA1c as a tool for monitoring average glucose control in a larger population is an essential step for establishing treatment targets to prevent diabetes-specific complications in CF patients.

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