The relationship between fasting plasma glucose and HbA1c during intensive periods of glucose control in antidiabetic therapy

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HIGHLIGHTS

- We examine FPG and HbA1c of type 2 diabetic patients 4 and 8 weeks after starting treatment.
- We determine linear and nonlinear regression between FPG and HbA1c.
- HbA1c reaches quasi-equilibrium after about 8 weeks of glucose control.
- Four-week HbA1c measurements are in excess by about 0.7 mmol/mol.
- Regression curves can be used to estimate glycemic status even during intensive glucose control.

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ABSTRACT

Objective: HbA1c measurements are typically less variable than fasting plasma glucose (FPG) for diagnosing diabetes, and for assessment of progress on glucose control therapy. However HbA1c reaches steady-state relative to average plasma glucose over about 120 days. HbA1c thus overestimates average FPG during first three months of starting therapy in newly diagnosed diabetic patients, and care needs to be exercised in interpreting HbA1c measurements during this period. At steady-state excellent regression exists between HbA1c and FPG. We hypothesize that this regression can also be used to obtain reliable estimates of HbA1c relative to FPG at 4 and 8 weeks following the onset of therapy.

Materials and methods: We collected FPG and HbA1c data of type 2 diabetic patients over the first 8 weeks of starting antidiabetic treatment. We fit linear and nonlinear regression models to steady-state data, and estimated how much measured HbA1c deviates at 4 and 8 weeks from these theoretical relations.

Results: If measured HbA1c is decremented by 0.7% (8 mmol/mol) at 4 weeks and 0.3% (3 mmol/mol) at 8 weeks, this corrected HbA1c is a better predictor of the corresponding FPG. Using hyperbolic regression, corrections to HbA1c are 0.5 and 0.1% (5 and 1 mmol/mol), respectively.

Conclusion: With the corrections proposed here, HbA1c measurements can be better interpreted in the early weeks of antidiabetic treatment.

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1. Clinical significance

In current clinical thinking HbA1c is thought to be useful as a stable measure of average FPG only over 3–6 months. Our data analysis shows that HbA1c can be an excellent predictor of FPG in a much shorter period, in particular, in spite of any glucose changes that may be taking place due to antidiabetic treatment. Mathematical modeling shows that a hyperbolic relation provides an excellent correspondence (to within 0.5 mmol/mol) between HbA1c and FPG within 4 weeks of standard therapy. These results thus have implications for the personalization of first-line antidiabetic therapy.

2. Introduction

Type 2 diabetes mellitus (T2DM) is a rapidly growing epidemic in large parts of the world, especially in India and southeast Asia,
but, despite the urgency, there is no single consensus regarding its diagnosis or treatment. The most widely adopted tests for both diagnosis and treatment are those recommended by the American Diabetes Association (ADA), published and updated annually as the Standards of Medical Care in Diabetes (American Diabetes Association, 2014). The oldest, traditional test for diabetes is based on measuring fasting plasma glucose (FPG). In recent years, however, the ADA has included the measurement of glycated hemoglobin (HbA1c) as one of its accepted tests; in contrast, The World Health Organization (WHO) does not acknowledge HbA1c among its recommendations. Specifically, the ADA lists the following four criteria to diagnose diabetes: (i) HbA1c ≥ 6.5%, (ii) FPG ≥ 126 mg/dL (7.0 mmol/L), (iii) 2-h plasma glucose (PG) ≥ 200 mg/dL (11.1 mmol/L) in an oral glucose tolerance test (OGTT), or (iv) a random plasma glucose ≥ 200 mg/dL. In addition to their use in diagnosis, glucometric measurements are also dependent upon for antidiabetic therapy. The objective of treatment in diabetic patients is to ensure a glycemic reduction as close to healthy levels as possible. Glucose control targets are determined by the physician keeping in mind factors such as the duration of the disease, life expectancy, risk of hypoglycemia and other complications (American Diabetes Association, 2014).

The HbA1c test has now become a preferred method in many circumstances (Bonora and Tuomilehto, 2011; Davidson, 2004; Bennett et al., 2007; Nomura et al., 2012). In India, for example, the test is relatively easily administered, especially in urban centers. HbA1c has the advantage of a much lower variability, while FPG measurements need to be repeated, typically three times, to reduce variance and establish confidence (Ollerton et al., 1999). It is therefore not surprising that FPG tests tend to be impractical. On the other hand, the drawback of the HbA1c test is that HbA1c is assumed to reach steady-state relative to average plasma glucose only over a timescale associated with the lifespan of a red blood cell, about 120 days, hence HbA1c measurements are typically thought to reflect an average glucose over the previous 40–60 days. In particular, when newly diagnosed diabetic patients undergo glucose control therapy HbA1c is not considered useful for the initial couple of months. Similarly, clinical studies that alter glucose cannot expect to interpret HbA1c values in the usual manner while the control is active (and for some time after). However, to the best of our knowledge, these estimates have not been directly verified quantitatively. It is therefore imperative to reexamine the question: How soon after beginning therapy in newly diagnosed diabetics can HbA1c be used to obtain meaningful estimates of the corresponding FPG? In other words, the lower variability of HbA1c makes it attractive to ask if it can be directly useful even during glucose control by antidiabetic treatment.

Good physiological models do not currently exist to directly estimate FPG from HbA1c measurements. Several factors interfere with the accuracy of HbA1c measurements including genetic makeup, fetal hemoglobin and chemically modified derivatives of hemoglobin, i.e. carbamylated hemoglobin found in patients with renal problems, and interpretation of HbA1c results may be affected by factors such as acute blood loss or hemolytic anemia, which reduces the life period of RBCs (NGSP, 2010). Various authors have attempted to mathematically model the glycosylation of hemoglobin (Higgins and Bunn, 1981; Beach, 1979; Osterman-Golkar and Vesper, 2006; Hamren et al., 2008; De Winter et al., 2006; Uehlinger et al., 1992; Mortensen and Vølund, 1988; Moller et al., 2013). Higgins and Bunn (1981) were among the earliest to investigate the kinetics of glycosylation of hemoglobin. Based on their work, Beach (1979) studied an age-structured dynamic model of glycosylation, and derived an analytical expression for the variation of total HbA1c with time. Notably, their study assumed a fixed erythrocyte life span. Other biochemical models of glycosylation can be found in Mortensen et al. (1984), Mortensen and Vølund (1988) where various refinements of Beach (1979) were considered. Recently, Osterman-Golkar and Vesper (2006) proposed a discrete time model considering the incremental increase of HbA1c and its loss due to multiple factors like erythrocyte clearance and chemical instability of HbA1c. The authors note, however, that their results are sensitive to the parameters in their model. Other recent models exploring glucose–HbA1c relation take into account various effects of RBC turnover rates: a homogeneous RBC lifespan is considered in Uehlinger et al. (1992), in De Winter et al. (2006) the authors construct a random destruction model, and in Hamren et al. (2008) a transit-compartment model. A very recent study by Möller et al. (2013) suggests that accurate results can still be obtained at the population level even with ignoring differences in RBC lifespan. A natural solution, therefore, to the difficulty in obtaining a physiologically precise relationship between hemoglobin and its glycosylation in vivo, therefore, is epidemiological, that is, to determine the regression relation between the two variables from apopulation study. Such correlation studies between glucose and HbA1c are clearly important because of their clinical relevance.

Considerable work has shown that various measures of blood glucose correlate very well with glyciated hemoglobin when blood glucose is relatively stable over a period of about three months in both type 1 (Svendsen et al., 1982; Røhling et al., 2002; Derr et al., 2003; McCarter et al., 2006; Nathan et al., 1984, 2008) and type 2 diabetes, as well as in control subjects. Svendsen et al. (1982) have shown a curvilinear, power-law relationship exists between a 5-week mean plasma glucose (MPG) and HbA1c, when HbA1c values are relatively unchanged over two years (n=15; type 1 diabetic patients). Røhling et al. (2002) examined type 1 diabetic patients from the Diabetes Control and Complications Trial (DCCT) to show that a linear regression correlates 7-point MPG and HbA1c (n=1439). Nathan et al. (2008) computed an average glucose (AG) based on self-monitored interstitial glucose monitoring in type 1 (n=268) and type 2 (n=159) diabetic patients to show that HbA1c is linearly correlated with AG over the previous three months (n=80 nondiabetic subjects). Derr et al. (2003) investigated the effects of glycemic variation and mean blood glucose (MBG) on HbA1c in type 1 and type 2 diabetic patients to show that HbA1c is a linear predictor of MBG over the previous 90 days. The steady-state relationship between FPG and MBG has been investigated extensively in type 2 diabetic patients (Paisey et al., 1980; Avignon et al., 1997; Bouma et al., 1999). Paisey et al. (1980) have shown that a mean of at least three fasting capillary blood glucose have good correlation with HbA1c (n=106). Avignon et al. (1997) compared plasma glucose collected at different times during the day (prebreakfast, prelunch, postlunch, extended postlunch) with a single measurement of HbA1c (n=66) taken within 10 days of the glucose data collection. Multivariate regression showed that postbreakfast glucose correlated better with HbA1c, than prebreakfast glucose, a result that confirmed previous findings of Conen et al. (1977). On the other hand, Bouma et al. (1999) (n=1020 patients) have argued that FPG values do not reliably predict HbA1c, especially when FPG is continuously changing as a result of antidiabetic therapy. They studied diabetic patients undergoing therapy with either oral hypoglycemic agents or diet control; they concluded that only 66% of patients with good HbA1c values could be identified through their FPG values. In particular, Bouma et al. recommended that both HbA1c and FPG need to be measured every 3 months during glycemic control.

The FPG-HbA1c steady-state curves discussed above are not a priori valid over early periods of antidiabetic treatment. The problem can be restated as the following: While repeated FPG measurements are a true reflection of the actual glucose status during this time, an HbA1c measurement is biased by an earlier
period when glucose was high, and therefore overestimates the "actual" HbA1c. The rationale of our study is: the extent to which measured HbA1c deviates from the steady-state FPG-HbA1c relationship needs to be quantified. We note that such estimates are not readily available in the literature.

Here we examine the relation between FPG and HbA1c, using two regression models: a linear model and a nonlinear, hyperbolic model that is motivated in part by the biochemistry of glycosylation. We compare model predictions of HbA1c against patient data. In particular, we are interested in asking whether it is possible to reconcile measured FPG and HbA1c, during the first several weeks of antidiabetic treatment.

3. Methods

Trial design and patients. We examined newly diagnosed type 2 diabetic patients (n=51) attending the Diabetes Unit, KEM Hospital, Pune, India, with FPG concentration greater than 126 mg/dl (6.9 mM) and healthy non-diabetic subjects (n=50) with FPG concentration of ≤126 mg/dl (6.9 mM), as described previously [Acharaya et al., 2014]. Fasting blood samples were collected at baseline (0-week) and at 4 and 8 weeks from non-diabetic subjects as well as diabetic patients. During the study period diabetic patients were put on anti-diabetic therapy to control hyperglycemia as required. Pregnant women, chronic smokers, individuals with excessive alcohol intake or a history of a recent (<6 months) cardiovascular event or with symptomatic heart disease (NYHA Class III, IV) and those with clinical infection, inflammatory or malignant disease were excluded from the study. Medical history of all individuals was noted, and each subject underwent a standardized physical examination for the measurement of body weight, height, waist-to-hip ratio, blood pressure and electrocardiogram (ECG). The study protocol was approved by the Institutional Ethics Committee, KEM Hospital and Research Centre, Pune. An informed consent was obtained in writing from all individuals upon explaining the nature of the study and its purpose.

Sample preparation. Blood samples were centrifuged at 4000 rpm (2500 g) for 10 min to separate the plasma. Plasma glucose concentrations were measured by glucose oxidase method using standard kits on an autoanalyser (Hitachi 902, Japan). HbA1c was measured by using an HPLC cation exchange column on D-10 HbA1c analyser (Bio-Rad Laboratories, Hercules, CA). The D-10 HbA1c Program is certified by the NCSP, and produces high-precision results.

Nonlinear model of the relation between FPG and HbA1c. The kinetics of glycosylation were first obtained by Higgins and Bunn (1981), and later others (Beach, 1979; Osterman-Golkar and Vesper, 2006; Svacina et al., 1990; Hamren et al., 2008; Moller et al., 2013). Here we construct a model modified from the Higgins–Bunn scheme and derive its steady-state solutions.

During glycosylation, the aldehyde of glucose binds with the amino groups of HbA and is transformed to an intermediate Schiff base, preA1c, which undergoes a further change to a more stable ketoamine HbA1c. We modify the kinetics proposed by Higgins and Bunn (1981) by incorporating a production of hemoglobin, at a constant rate α (mmol/hr), and decay rates for all three intermediate species. The decay term is assumed proportional to the concentrations of the species with rate γ (h⁻¹). The reaction schematic is thus

\[
\text{HbA} + \text{Glucose} \stackrel{k_1}{\rightleftharpoons} \text{preA}_{1c} \stackrel{k_2}{\rightleftharpoons} \text{HbA}_{1c},
\]

where \( k_1 \) (mM⁻¹h⁻¹) is the rate constant of the first reaction in the forward direction, \( k_2 \) (h⁻¹) is the rate constant of the reverse reaction. The first reaction is rapid; the second reaction is somewhat slow and occurs mostly in the forward direction with a rate constant is \( k_2 \) (h⁻¹).

The steady state FPG–HbA1c solution to this model is

\[
[HbA_{1c}] = \frac{\nu [\text{Glucose}]}{K + [\text{Glucose}]},
\]

with

\[
v = \frac{k_2 \alpha}{\gamma (k_2 + \gamma)} K = \frac{\gamma (k_3 + k_2 + \gamma)}{k_1 k_2 + k_1 \gamma}.
\]

Eq. (2) is the basis of the hyperbolic FPG–HbA1c relationship we use for nonlinear regression analysis.

Statistical analysis. Two regression analyses, one with a linear model and another with a nonlinear, hyperbolic relation were carried out on the FPG–HbA1c data. The nonlinear regression equation was adapted from Eq. (2), that is,

\[
[HbA_{1c}] = \frac{\nu [\text{FPG}]}{K + [\text{FPG}]},
\]

To estimate parameters of the nonlinear fit, linear regression was carried out between 1/HbA1c and 1/FPG. Goodness-of-fit was measured via the coefficient of determination, \( r^2 \). Regression analyses were carried out in MATLAB.

HbA1c correction to 4- and 8-week samples. We propose correcting each measured HbA1c value in such a manner that upon transforming to equivalent FPG values through the regression curves we get a distribution that is statistically consistent (up to the first moment) with the measured FPG distribution. In other words, we want

\[
\int_{–\infty}^{\infty} g(HbA_{1c}) = \frac{1}{FPG} \int_{–\infty}^{\infty} f(FPG) \, df
\]

where \( HbA_{1c} \) is the HbA1c value of \( i \)th subject, \( FPG \) is the corresponding FPG value. We choose to apply a constant shift to each HbA1c, uniformly, that is, \( g(HbA_{1c}) = HbA_{1c} - \beta \). Given a (linear or hyperbolic) regression curve \( HbA_{1c} = f(FPG) \), an HbA1c value inverted through \( f^{-1} \) yields a unique FPG value. Estimates of \( \beta \) were obtained numerically.

4. Results

A total of 51 diabetic patients and 50 non-diabetic control subjects were included in the analysis. FPG and HbA1c data were measured from diabetic patients at the beginning of treatment, i.e. at 0 weeks, at 4 weeks following the start of therapy, and at 8 weeks. A summary of the FPG and HbA1c of diabetic patients is presented in Table 1. Data was measured from nondiabetic subjects (n=50) once, and then again after 8 weeks (n=49).

4.1. Linear and nonlinear regression between HbA1c and FPG

We tested two regression models of the relationship between FPG and HbA1c: linear regression, and a nonlinear, hyperbolic regression model, Eq. (4).

Diabetic patients before treatment and non-diabetic subjects represent a "steady-state" group, that is, FPG and HbA1c are presumed stable over the previous three months. Using linear regression to fit this data we obtained the relation HbA1c = 0.64 FPG + 2.60, with a coefficient of determination, \( r^2 = 0.81 \). We then tested to what extent can linear regression, in addition to the steady-state data, also explain FPG and HbA1c data of diabetic patients at 4 weeks, and at 8 weeks. In each of the two cases the correlation weakens, \( r^2 = 0.76 \). Thus, linear regression between steady-state FPG and HbA1c cannot adequately describe data following intensive glucose control, i.e. at neither 4 nor 8 weeks.
A similar result was observed with the nonlinear regression model. The steady-state data is described by $\text{HbA}_{1c} = 26.32 \text{ FPG} / (18.20 + \text{ FPG})$ with $r^2 = 0.84$; when the diabetic patient data at 4 or 8 weeks is included $r^2$ values drop somewhat, to 0.825 and 0.81 respectively.

Although neither the linear nor nonlinear model is able to fully represent 4-week and 8-week data as well as the steady-state data, the nonlinear model performs slightly better than the two; the hyperbolic model has a somewhat higher coefficient of determination than the linear model in each case.

### 4.2. Regression models underestimate HbA$_{1c}$ by less than 0.7% (8 mmol/mol) at 4 weeks

HbA$_{1c}$ sampled at 4 and 8 weeks cannot be expected to have relaxed to steady-state; this is reflected in the HbA$_{1c}$ lying above the regression curves in Fig. 1. We used FPG measured at 4 and 8 weeks to predict corresponding HbA$_{1c}$ from the linear and hyperbolic models. At 4 weeks sampled mean HbA$_{1c}$ is $8.7 \pm 1.4\%$ (72 ± 15 mmol/mol) and mean FPG is 8.3 ± 2.3 mM. For this FPG data, linear regression predicts HbA$_{1c}$ to be 8.0% (64 mmol/mol) while nonlinear regression predicts an HbA$_{1c}$ of 8.2% (66 mmol/mol). At 8 weeks sampled mean HbA$_{1c}$ is 7.7% (61 mmol/mol) and mean FPG is 7.5 mM; mean HbA$_{1c}$ predicted by linear and nonlinear regression are 7.4 and 7.6% (57 and 60 mmol/mol), respectively. The differences of predicted HbA$_{1c}$ from sampled HbA$_{1c}$, together with $p$-values testing for the significance, are summarized in Table 2.

### 4.3. Corrections to measured HbA$_{1c}$ that reflect actual FPG at 4 and 8 weeks

A single blood sample collected at 4 weeks provides an HbA$_{1c}$ reading and one FPG reading. If more than one FPG measurements are collected, say over three successive days, the average of those measurements will better reflect actual FPG. If HbA$_{1c}$ is used to estimate FPG from regression models, it will reflect a value higher than actual FPG (because HbA$_{1c}$ sampled at 4 weeks is underestimated by the regression curves).

To address this inconsistency we propose the following: We correct each HbA$_{1c}$ value at 4 weeks in such a manner that the regression models then predict FPG that is statistically consistent with measured FPG (see Section 3). The correction factor is dependent on the regression model used; we first describe this using the nonlinear regression model. Each HbA$_{1c}$ reading measured at 4 weeks, when decreased by 0.5% (5 mmol/mol) and inverted via the hyperbolic regression curve yields a corresponding FPG value; the mean of FPG values obtained in this manner agrees with 4-week sampled FPG. In other words, a 4-week HbA$_{1c}$ sample must be corrected by decreasing it 0.5% (5 mmol/mol) in order to obtain a good estimate of actual FPG at that stage. In a similar manner, if linear regression is used, the HbA$_{1c}$ correction factor is 0.7% (8 mmol/mol).

A similar estimate can be obtained for 8-week HbA$_{1c}$ sampling. We propose an 8-week HbA$_{1c}$ correction of 0.1% (1 mmol/mol) for the hyperbolic model and 0.3% (3 mmol/mol) for the linear model.

To validate the proposed correction factor we compared the FPG distribution obtained from adjusting the HbA$_{1c}$ values and inverting through the linear and nonlinear regression curves, with sampled FPG. The distributions agreed in the mean (as expected), and s.d.’s were comparable as well.
5. Discussion

In type 2 diabetes FPG and HbA1c correlate very reliably with each other, although establishing a precise relationship between the two is difficult. Nevertheless, clinical practice invariably follows the ADA recommendation of measuring FPG or HbA1c to diagnose and treat diabetes (American Diabetes Association, 2014). In some cases it is easy to measure FPG directly, such as when self-monitoring using a glucometer; however, daily variability is confounded with the limited accuracy of that test. A high-quality HbA1c measurement is therefore desirable. Here we have proposed that HbA1c measurements alone are sufficient to provide an accurate estimate of FPG as early as within 4 weeks of starting antidiabetic therapy.

We prescribe the following: An HbA1c measurement collected at 4 weeks of antidiabetic treatment must be decreased by 0.7% (8 mmol/mol), and if required, this corrected HbA1c can be used, using the steady-state regression curve, to obtain an excellent estimate of the FPG at 4 weeks. By 8 weeks the corrections to HbA1c are as low as 0.3% (3 mmol/mol). We note that the 8-week corrections may not be significant \( p = 0.15 \) (Table 2) because our study is limited in its power to detect this small a difference. We can refine these corrections further still: We propose that a nonlinear, hyperbolic relation between FPG and HbA1c is even more accurate in relating the two. If the nonlinear regression model is used HbA1c needs to be corrected by 0.5% at 4 weeks, and barely needs to be corrected at 8 weeks. We recommend the adoption of these new, refined values of HbA1c in clinical practice to enable the use of HbA1c measurement in antidiabetic treatment as early as within one month.

Apart from the clinical relevance of these results, our analysis has implications for understanding the physiology of glycation of hemoglobin as well. Both, theoretical considerations based on the slow timescales of glycation of hemoglobin as well as experimental studies have showed that FPG–HbA1c correlations are best effective in those circumstances when average glucose changes relatively slowly compared to the timescale of HbA1c equilibration (Paisey et al., 1980; Bouma et al., 1999). In other words, when diabetic patients are placed on antidiabetic therapy glucose changes continuously and HbA1c cannot be expected to be in a good equilibrium relative to FPG, especially at the start of treatment. As a rule of thumb this period is usually taken to be roughly the lifetime of a red blood cell, about 120 days. Sometimes the HbA1c equilibration period is taken to be closer to 3 months: Clinical recommendations, for example, assert that HbA1c monitored at 3-month intervals reflect plasma glucose consistently. We followed HbA1c and FPG of newly diagnosed diabetic patients that had just began therapy over the subsequent two months, sampled at 4 and 8 weeks. We validate the following picture. As therapy is initiated glucose begins to change rapidly hence measured HbA1c overestimates actual FPG for several weeks after. By eight weeks, however, HbA1c, and FPG are in excellent quasi-equilibrium. This implies that the effective timescale of glucose control is longer than 2 months, while HbA1c, equilibrium has a relaxation constant considerably less than 120 days (hence 8 weeks are sufficient for HbA1c to attain quasi-equilibrium with glucose). Our analysis therefore predicts that the steady-state regression curves are excellent estimators of the FPG–HbA1c relationship beyond 8 weeks even while glucose continues to change. In other words, clinical data echoes what is expected from the physiology described in the kinetic model of glycosylation: An abrupt change in plasma glucose leads to a temporary misalignment of FPG and HbA1c measurements; after about 8 weeks, quasi-equilibrium is established and FPG and HbA1c evolve together in close agreement.

We stress that a good kinetic model does not currently exist. The biochemical model \( \alpha \) extends that originally due to Higgins and Bunn (1981), and is built on minimal assumptions. In particular, the steady state equation of \( \alpha \) was derived under the assumption that the turnover rate of hemoglobin, \( \alpha \), is a constant. However, it is well known that the half-life of RBCs, which contain hemoglobin, is not constant: It varies with numerous factors like patient age, sex, and medical conditions such as inflammation. A more comprehensive kinetic model holds the promise of being able to explain individual deviations from the regression curve, perhaps in terms of pathophysiological differences between patients. Our preliminary investigation has shown that while it is possible to obtain good estimates of the kinetic parameters in the model described in the Methods (see reaction (1)), results from the model are no better (and at times, worse) than the regression analysis that we have presented. Another major limitation which prevents a detailed kinetic analysis is that we do not have a sufficiently good model of glucose changes during the course of treatment; although glucose changes are roughly linear in the first couple of weeks, it remains to be investigated to what extent patients respond to glucose control, and over what timescales. Kinetic models of plasma glucose, hemoglobin and HbA1c have been investigated by several authors since Higgins and Bunn (1981), Beach (1979), Osterman-Golkar and Vesper (2006), Svacina et al. (1990), Hamren et al. (2008), and many of the questions raised there continue to be important in developing a satisfactory understanding of the factors that influence glycation of hemoglobin in diabetes.

Finally, we discuss the potential generalization of these ideas to other populations. While the methodology we have employed is valid in general for use on other cohorts, we expect that the results, including the correction factors we obtain, will vary with the characteristics of each group. We have considered a population that represents a "typical" Indian patient on antidiabetic treatment with relatively few co-existing morbidities. However it is important to note that HbA1c varies significantly across populations depending on various factors. Thus, any study that is interested in investigating HbA1c, correction factors relative to specific features of a population must take into account epidemiological considerations that include racial backgrounds (Herman et al., 2009; Herman and Cohen, 2012; Venkataraman et al., 2012), sex, age (Lu et al., 2010) and RBC life span (Cohen et al., 2008). Further, the correction factors can also be influenced by the specific antidiabetic therapy used, because each particular combination of drugs will influence the HbA1c trajectory (Sherifali et al., 2010; Esposito et al., 2012). Our work thus represents a first step towards developing correction factors that enable a rapid interpretation of HbA1c in early therapy. Further work is needed to understand the underlying sources of variation in correction factors across different populations.

5.1. Conclusion

Both FPG and HbA1c are now widely used to diagnose type 2 diabetes mellitus and to assess the progress of antidiabetic treatment. In late-stage treatment the two variables are very well correlated. However, HbA1c is not used in the early phase of antidiabetic therapy (12 weeks or earlier), during which time glucose changes continuously. The FPG–HbA1c relation in early-stage treatment remains poorly investigated, although it is highly relevant clinically.

Using data obtained from Indian diabetic patients, we investigated a FPG–HbA1c relation valid in the initial stage of antidiabetic treatment. We studied linear regression as well as a nonlinear regression model derived on the basis of the biochemistry of glycosylation of HbA1c, to determine a relationship between FPG and HbA1c valid during the first two months of therapy. We provide an estimate of the correction that should be
applied to measured HbA1C values in order to avoid over-estimating the true glycemic status of the patient in early-stage therapy. We conclude that if measured HbA1C is decremented by 0.7% (8 mmol/mol) at 4 weeks and 0.3% (3 mmol/mol) at 8 weeks, this corrected HbA1C is a good predictor of the corresponding FPG through the steady-state linear regression curve.

On the basis of the corrections proposed here HbA1C measurements can be better interpreted in the early weeks of antidiabetic treatment, both clinically as well as in epidemiological studies.

Conflict of interest

The authors declare no potential conflict of interest related to this article.

Author contributions

A.B., J.A., P.G., and S.G. wrote the manuscript. J.A. and S.G. designed and carried out the experiment. A.B. and P.G. carried out modeling and statistical analyses.

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