Caveats regarding the use of HbA_{1c} for prediction of mean blood glucose

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To the Editor: In a recent article, Nathan et al. [1] confirm a strong linear relationship between mean blood glucose (MBG) derived from continuous glucose monitoring (CGM) and HbA_{1c} in 25 selected individuals observed for 12 weeks. The published study was conducted using CGM to eliminate variation in the relationship between HbA_{1c} and MBG that might be due to non-representative glucose sampling. Based on the strong association between CGM-derived MBG and HbA_{1c}, the authors advocate that an individual's HbA_{1c} level is interchangeable with and can be safely interpreted as the estimated MBG based on the population regression equation. They further imply that the high degree of correlation supports the idea that HbA_{1c} should be 'used universally to adjust therapy'. After carefully reviewing both the authors' data and similar data presented at the European Association for the Study of Diabetes (EASD) annual meeting [2], we wish to offer an alternative perspective to this 'one size fits all' concept.

The authors' Fig. 1 is a scattergram depicting the relationship between CGM-derived MBG and HbA_{1c}. A horizontal line across the graph at a MBG of 8 mmol/l identifies two patients with HbA_{1c} of about 6.5 and 8.0%, respectively [1]. Two patients, same MBG, yet one has a near normal HbA_{1c}

while the other has an unacceptably high HbA_{1c}. Other examples of between-patient variation in HbA_{1c} at the same MBG are apparent elsewhere in the figure and in the data presented at the EASD meeting [2]. Nathan et al. had faulted prior studies [3, 4] of the relationship between MBG and HbA_{1c} for inadequate glucose sampling protocols that may have led to over- or underestimation of the patient's true MBG. In the present study, Nathan et al. overcame the problem of non-representative glucose sampling by using a more intensive glucose sampling protocol over 12 weeks, which would have allowed them to achieve the best possible estimate of a patient's true MBG. Thus, the between-patient variation in HbA_{1c} at the same MBG found in the data of Nathan et al. is unlikely to be due to inaccurate MBG caused by inadequate sample size or sampling biased to certain times of day. In this respect, the authors' data resemble those reported by the Diabetes Research in Children Network (DirecNet) investigators, who also used CGM and observed between-patient variation in HbA_{1c} independent of MBG [5]. Between-patient differences in HbA_{1c} not due to MBG have been well documented in the literature, using less sophisticated glucose sampling protocols but with similar results (citations in [3] and [6]). In longitudinal studies evaluating repeated measures of MBG and HbA_{1c} within individuals over time, we have shown that between-patient differences are not due to random variation, but instead track consistently through time and with changes of MBG [3, 6]. Furthermore, these between-patient HbA_{1c} differences appear to be unrelated to erythrocyte longevity [3]. The widely cited DCCT study followed more than 1400 patients with repeated measures of MBG and HbA_{1c} every 3 months for up to 9 years [7]. Albeit with a simple glucose sampling protocol, the DCCT also reported an impressive linear association between HbA_{1c} and MBG [4]. However, large, non-random, consistently repeatable between-patient differ-

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ences in HbA_{1c} were readily apparent in the DCCT data at the same MBG [4, 6].

The demonstration of between-patient HbA_{1c} differences at the same MBG, whether derived by CGM [1, 2, 5] or other methods, suggests that factor(s) other than blood glucose concentration may also play a role in determining HbA_{1c} levels [3, 6]. These between-patient differences have additional relevance, since patients with higher than average HbA_{1c} levels at any given MBG have greater risk for development of microvascular complications in patients with type 1 [6] or type 2 diabetes. Thus the most comprehensive interpretation of HbA_{1c} for an individual patient should ideally take into account not only the patient's MBG, but also the patient's idiosyncratic characteristics, which cause consistent HbA_{1c} variance from the mean of the linear regression relationship between HbA_{1c} and MBG within the population [3, 6].

The practice of using a patient's HbA_{1c} as an interchangeable and universally applicable estimate of MBG evolved during the DCCT era. Patients today, however, have ready access to CGM and other sophisticated methods of direct glucose measurement, data storage and calculation of MBG at home that were not available at the time of the DCCT. If the between-patient differences in HbA_{1c} apparent in the data of Nathan et al. really are due to biological differences between patients, then we predict that there will be large numbers of patients in every diabetes clinic who will repeatedly have major discrepancies between their self-monitored MBG and the estimated-MBG based on HbA_{1c}, even if CGM is used to establish the population regression equation. This dissonance will probably be extremely confusing to both patients and their diabetes management team. Furthermore, if HbA_{1c}-estimated MBG is used as the primary guide for adjusting therapy, patients whose true MBG are overestimated by this equation will be at risk for more frequent episodes of life-threatening hypoglycaemia induced by needlessly aggressive glucose-lowering therapy.

As hypoglycaemia is a major complication of intensive diabetes management [7], ignoring the possible presence of between-patient variation in the relationship between HbA_{1c} and MBG is likely to be perilous.

To achieve the most comprehensive and safest interpretation of HbA_{1c} for patient care, clinicians must recognise that HbA_{1c} may not be a fully reliable surrogate for MBG. In this case, both patients and clinicians will need to learn how to individualise treatment decisions by taking into account the patient's HbA_{1c} and preceding self-monitored MBG, as well as idiosyncratic between-patient differences that also contribute to the level of HbA_{1c}.

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