Caveats regarding the use of HbA_{1c} for prediction of mean blood glucose. Reply to Chalew S, Hempe JM [letter]

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Abbreviations

HGI haemoglobin glycation index
MBG mean blood glucose
CGM continuous glucose monitoring

To the Editor: Chalew and Hempe [1] respond to our study in which we demonstrate, in a relatively small group of patients with type 1 and type 2 diabetes and non-diabetic individuals, a high degree of correlation between carefully measured mean glucose levels over a 3 month period and HbA_{1c} at the end of the 3 months [2]. They object to our suggestion that HbA_{1c} should be ‘used universally to adjust therapy’ [1]. (In fact, we didn’t suggest that HbA_{1c} be used universally for this purpose, although we believe it to be appropriate; rather, we only stated the fact that HbA_{1c} ‘is the basis of treatment guidelines, and is used universally to adjust therapy’ [2]). Chalew and Hempe further propose that the ‘between-patient variation in the relationship between HbA_{1c} and MBG (mean blood glucose)’ precludes its universal use to adjust therapy.

In the past, these same authors have tried to explain the variability in the relationship between MBG and HbA_{1c} on the basis of biological variability and, specifically, on inter-individual differences in glycation as represented by their haemoglobin glycation index (HGI) [3, 4]. While inter-individual differences in glycation (or, more likely, in de-

glycation, which is enzymatic) may be the source of variation between MBG and HbA_{1c}, an examination of the data used to establish the relationship between MBG and HbA_{1c} in the past, and in our study, suggests other more technical explanations.

The authors’ original suggestion that HGI explained the less than perfect relationship between MBG and HbA_{1c} was based on studies in which MBG was predicated on infrequent glucose sampling and in which the correlations between calculated MBG and HbA_{1c} were relatively weak ($R^2=0.49-0.67$) [3, 4]. In their current response they refer to the DCCT data [5], with MBG based on only seven glucose tests in each 3 month period, as demonstrating an ‘impressive linear association between HbA_{1c} and MBG’ (the R^2 in the DCCT was only 0.67). They now choose to attribute the remaining 51–33% unexplained variation in HbA_{1c} to each ‘patient’s idiosyncratic characteristics’. However, other studies, including our recent publication, that have used more frequent and more representative glucose sampling, have lead to substantially higher correlation coefficients between MBG and HbA_{1c}, and less residual variability to explain [2, 6, 7]. Thus, much of the variability in the relationship between MBG and HbA_{1c} levels disappears when MBG is measured more accurately.

The potential sources of variability in our recently published study, with a large number of glucose samples per individual, but with a small number of individuals studied, bears consideration [2]. The R^2 of 0.84, similar to that in other studies that have captured MBG more completely, means that 16% of the variance is not explained by the relationship between MBG and HbA_{1c}. What are the potential sources of this less than perfect correlation? First, each of the measures has error. Although continuous glucose monitoring (CGM) has improved in accuracy over

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time, it is not identical to a laboratory measure of glycaemia, and is generally accepted to be no better than within + 10% of laboratory values. Short of hospitalising patients for 2–3 months and performing laboratory-based measurements of blood glucose often enough to capture mean glycaemia, we can't realistically reduce the error implicit in CGM. The measurement of HbA_{1c} also has error. Second, although we made an effort to exclude patients who had conditions known to interfere with the measurement of glycated haemoglobin, changes in erythrocyte turnover because of periods of anaemia or other factors might have affected HbA_{1c} and its correlation with MBG.

It is difficult to imagine that we can limit these sources of variability much more than we have to date. While it is possible that HGI, or other biological factors, may explain the residual variance in the relationship between MBG and HbA_{1c}, HGI and other postulated inter-personal differences remain hypothetical in the absence of direct data. An ongoing international study that includes a relatively large number of diabetic and non-diabetic individuals and that also measures mean glycaemia as completely as is practical may shed more light on these issues.

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