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LETTER

The proposed terminology 'A_{1c}-derived average glucose' is inherently imprecise and should not be adopted. Reply to Bloomgarden ZT, Inzucchi SE, Karnieli E, et al. [letter]

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Abbreviations
A_{1c} glycated haemoglobin
ADAG A_{1c}-Derived Average Glucose

To the Editor: It has been argued that glycated haemoglobin (A_{1c}) does not adequately reflect mean plasma glucose, and therefore any attempt to convert A_{1c} into a surrogate for the unknown mean plasma glucose for an individual would not be valid. Here we discuss the limitations of measuring the true average plasma glucose, and suggest that much of the variation in A_{1c} that is not explained by the mean plasma glucose level may easily be explained by imprecision in the measurement of mean plasma glucose.

Bloomgarden et al. have argued against using A_{1c} as a precise marker of average plasma glucose [1]. Essentially, the authors stressed that the agreement between the measurement of mean plasma glucose and A_{1c} in the DCCT was only approximately 50% according to a subsequent analysis [2], although the original data reported an agreement of 67% [3]. They presented well-known evidence that different treatment modalities for diabetes may have an impact on the agreement between mean plasma glucose and A_{1c}. In addition, the possible influence of race, renal function, anaemia and other factors on the precision of A_{1c} as a measure of the true mean plasma glucose was highlighted. Here we will take the opposing position and argue that the influence of the inherent imprecision of the measurement of mean plasma glucose, the gold standard against which the accuracy of A_{1c} is determined, should be evaluated.

The DCCT used a seven-point glucose measurement per day on a quarterly basis to evaluate the correlation with A_{1c} [3]. Only four studies have implemented continuous glucose measurements [4–7]. It is striking that the DCCT reported a correlation of r=0.71, representing 50% agreement between the seven-point glucose measurement and A_{1c}, whereas a study using continuous glucose measurements reported a correlation of r=0.89, representing 80% agreement between the gold standard of estimating the true mean plasma glucose and A_{1c} [5]. Very recently, the A_{1c}-Derived Average Glucose (ADAG) Study achieved an agreement of 84% (R^2) between weighted average glucose level and A_{1c} by applying near continuous measurement of glucose levels, i.e. obtaining 2,700 glucose measurements during the 3 months preceding an A_{1c} measurement in each of 507 participants, who were primarily white diabetic patients with a typical A_{1c} ranging from 6% to 9% [6]. Moreover, the relationship between average glucose level and A_{1c} was best described by a linear equation. As A_{1c}

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measurements were performed equally rigorously in the DCCT and the ADAG Study, it follows that more than 50% of the disagreement between A_{1c} and the estimated 'mean plasma glucose' in the DCCT may be explained by shortcomings in the estimation of the true mean plasma glucose by the method used in the DCCT. In the DCCT participants provided capillary blood haemolysates: this adds imprecision to the estimate of blood glucose because of the inherent difficulty in obtaining capillary blood that is representative of circulating blood. Moreover, technical problems in obtaining these samples and glycolysis in some of the samples may be additional factors that contributed to the rather low agreement between A_{1c} and the estimate for mean plasma glucose in the study.

How much of the imprecision in the 'mean plasma glucose' value [demonstrated by the range of plasma glucose of 10.0–16.7 mmol/l (180–310 mg/dl) at an A_{1c} of 9% reported in the DCCT] can be explained by the imprecision of glucose measurements in an optimal setting in which blood glucose is measured by a gold-standard bedside glucose monitor? We should obtain CVs for within-run, between-day and between-analyser precision at relevant glucose levels for such monitors. One of the best evaluated and validated bedside glucose monitors is the HemoCue B-Glucose meter (HemoCue, Angelholm, Sweden). In Table 1 we present the CVs for within-run and between-day precision as provided by the manufacturer. We also present our own measurements of between-analyser precision for 52 individuals (four women and 48 men, of whom two had diabetes) undergoing a hyperinsulinaemic–euglycaemic clamp preceded by an intravenous glucose tolerance test, representing 1,682 pairs of simultaneous glucose measurements at various blood glucose levels [8]. (All study participants gave informed consent, the protocol was approved by the local ethics committee and the study was carried out in accordance with the Declaration of Helsinki as revised in 2000.) It is evident that these inherent causes of imprecision in glucose measurement amount to an expected SD of 4–5% of the actual blood or plasma glucose level. This can be translated into a 95% CI of ±8–10% (2 SD) or a range of ±12–15% (3 SD). Thus, the imprecision inherent in the glucose measurement itself in this setting could easily account for a range of glucose levels of 11.6–15.0 mmol/l (210–270 mg/dl) at an A_{1c} of 9%. It should be emphasised that the three precision tests on the HemoCue meters were performed under research study/laboratory conditions, and thus the values for the CVs in Table 1 will be lower than the values for blood glucose measurements assessed in patients in their daily lives.

The ADAG Study showed that repetitive multipoint measurements of blood glucose performed as well as continuous glucose monitoring, each providing 82% (R^2) agreement with A_{1c} [6]. Obtaining plasma glucose measurements on a continuous basis may be associated, however, with considerable imprecision, with mean absolute relative

Table 1 Imprecision inherent in blood glucose measurements

Precision	Pairs of determinations (*n*)	Blood glucose measured by HemoCue B-Glucose meter (mmol/l)				
		Minimum	Maximum	Mean	SD	CV (%)
Within-run[a]	20	4.0	4.6	4.3	0.15	3.5
	20	7.2	7.9	7.7	0.20	2.6
	20	12.1	12.8	12.5	0.24	1.9
	20	17.7	18.6	18.3	0.28	1.6
	20	20.6	22.1	21.1	0.45	2.2
Between-day[b]	21	2.5	2.7	2.6	0.07	2.7
	21	5.3	5.7	5.6	0.14	2.5
	21	10.3	11.2	10.8	0.20	1.9
Between-analyser[c]	1,119	2.8	6.0	4.6	0.16	3.3
	258	6.1	9.9	7.9	0.19	2.3
	307	10.0	21.9	12.8	0.48	3.7

Data on within-run and between-day precision were provided by the manufacturer (HemoCue, Angelholm, Sweden)
To convert glucose values in mmol/l to mg/dl multiply by 18

[a] Within-run precision was determined at five different blood glucose levels (different amounts of glucose were added to a venous EDTA-blood sample to give five blood glucose levels). Twenty consecutive measurements were performed for each level. The study was performed in the shortest possible time to minimise the effect of glycolysis

[b] Between-day precision was determined at three different glucose levels. Commercially available freeze-dried plasma control samples were used. A new vial for each level was reconstituted each day according to the manufacturer's recommendation and one single HemoCue B-Glucose meter determination was performed each day. The study was performed over 21 consecutive working days

[c] Between-analyser precision was determined simultaneously on two different HemoCue B-Glucose meters during a fast-sampling intravenous glucose tolerance test and a hyperinsulinaemic–euglycaemic clamp [8]. Fifty-two patients had 1,684 pairs of samples taken for analysis

differences of 15–21% in the range of blood glucose of 3.9–10.0 mmol/l (70–180 mg/dl) [9]. Thus, a combination of frequent multipoint and continuous measurement of plasma glucose appears to be the most feasible approach to obtain reliable mean plasma glucose values.

Awareness of the limitations of obtaining the average glucose level by multipoint plasma glucose monitoring and/or by continuous glucose monitoring, and of the A_{1c} determination itself, should be imperative in decisions based on these variables, as neither method is likely to give a true picture of the average plasma glucose of a given patient. Anaemia, sex, race, age, obesity, glucose level, type and treatment modality of diabetes, renal and hepatic impairment, blood loss, blood transfusion, pregnancy and medication factors (such as iron, erythropoietin, thiamine and some antiretroviral drugs) may each require a correction factor to enable A_{1c} to reflect true mean plasma glucose. These factors could be determined in studies using multipoint glucose monitoring on a 'low-frequency' basis as performed, for example, in the DCCT. However, a specific equation for the exact relationship between A_{1c} and mean plasma glucose can only be obtained on the basis of a combination of frequent multipoint and continuous monitoring of plasma glucose. Further such studies are eagerly awaited.

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