

The proposed terminology ‘A_{1c}-derived average glucose’ is inherently imprecise and should not be adopted

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Abstract The proposed use of a more precise standard for glycated (A_{1c}) and non-glycated haemoglobin would lead to an A_{1c} value, when expressed as a percentage, that is lower than that currently in use. One approach advocated to address the potential confusion that would ensue is to replace ‘HbA_{1c}’ with a new term, ‘A_{1c}-derived average glucose.’ We review evidence from several sources suggesting that A_{1c} is, in fact, inherently imprecise as a measure of average glucose, so that the proposed terminology should not be adopted.

Keyword Glycated haemoglobin

Abbreviations

A _{1c}	glycated haemoglobin
ADAG	A _{1c} -derived average glucose
CGM	continuous glucose monitoring
EDIC	Epidemiology of Diabetes Interventions and Complications
IFCC	International Federation of Clinical Chemistry
MPG	mean seven-point glucose
NGSP	National Glycohemoglobin Standardization Program

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In use since the 1980s, glycated haemoglobin (A_{1c}) levels have become an invaluable tool for tracking glycaemic control in diabetes. All relevant clinical trials of antihyperglycaemic therapy have employed this widespread metric. Moreover, because of educational efforts directed at the lay audience, ‘A_{1c}’ is also emerging within the lexicon of our diabetic patients. An important debate is developing, however, regarding the manner in which A_{1c} should be measured in the management of patients with diabetes.

The International Federation of Clinical Chemistry (IFCC) has proposed a new approach to A_{1c}, using a synthetic standard for glycated and non-glycated haemoglobin [1]. Existing normative ranges based on actual patient samples would be replaced with a more precise standard in which a specific chemical moiety representing a species of glycated A_{1c} is used, the substance fraction of the haemoglobin β-chain containing a stable hexose adduct on its N-terminal amino acid valine [2]. Comparison of assays using the standardisation methodology currently endorsed in the USA, Japan and Sweden with assays using the new approach suggests that the latter consistently generate lower A_{1c} levels [3]. The National Glycohemoglobin Standardization Program (NGSP) suggests that A_{1c} results be reported using these new more precise metrics, in IFCC units (as mmol A_{1c}/mol haemoglobin) [4], which would give a range in non-diabetic persons of ~25–42. Based on these results, derived NGSP units could also still be reported as the more familiar percentage, similar to that currently in use, giving a non-diabetic range of 2.5–4.2%. Of note, however, the introduction of an A_{1c} assay giving lower results in Sweden in the 1990s appeared to cause patients and clinicians to allow glycaemic control worsen [5]. This would certainly be undesirable, and so the use of the entirely new IFCC units, which do not overlap numerically with current A_{1c} percentages, appears reasonable.

The IFCC approach would, admittedly, cause significant confusion in the medical community. Two alternatives have been proposed. A_{1c} levels could simply be converted back to DCCT-like A_{1c} levels, which would have the advantage of continuity, but the conceptual disadvantage of providing a result that is factually incorrect. Another approach, suggested by a consensus committee representing the American Diabetes Association, the European Association for the Study of Diabetes, the International Federation of Clinical Chemistry and Laboratory Medicine and the International Diabetes Federation would be to abolish the term A_{1c} entirely, replacing it with a new name, the ‘ A_{1c} -derived average glucose’ (ADAG). The purpose of the present essay is to summarise a number of recent lines of investigation suggesting that it may not be possible to predict true mean or average glucose with a high degree of accuracy in a given person based on his or her A_{1c} result.

The phenomenon of person-to-person variability in the degree of haemoglobin glycation has been described by a number of authors. The use of measures reflecting the difference between the measured A_{1c} and that predicted from home capillary glucose profiles has been employed in several studies. In one investigation of 128 type 1 diabetic children almost one-third showed a significant and clinically relevant difference between the two measures [6]. Others have analysed a publicly available DCCT database that includes 247,717 glucose measurements obtained by analysis of seven-point home capillary blood specimens with laboratory methods and approximately 72,000 accompanying A_{1c} values. One regression analysis indicated that the glucose profile explains just half of the variance in A_{1c} [7]. The authors of the analysis suggested that those persons with high haemoglobin glycation might be at increased risk of microvascular complications. An independent investigation supported this hypothesis by demonstrating that A_{1c} levels were higher in patients with type 1 diabetes who had developed retinopathy vs those who had not, after correction for fructosamine, another measure of mean glucose levels. This further suggested that glycation may have determinants other than prevailing glycaemia [8]. DCCT investigators have taken exception to aspects of this interpretation [9], arguing with some reason that the seven-point capillary blood sample set might not be considered sufficiently representative of an entire 3 month period of glycaemia [10]. It is noteworthy, however, that another analysis using this same database showed that the conventional treatment group in the DCCT had consistently higher mean glucose concentrations than intensively treated patients at any given A_{1c} value, with a mean difference of 1.6 mmol/l (29 mg/dl) at an A_{1c} of 7%, increasing to 2.8 mmol/l (52 mg/dl) at an A_{1c} of 11% [11]. Furthermore, mean seven-point glucose (MPG), but not A_{1c} , predicted cardiovascular events during the DCCT study itself [12], while it was not until a decade

later, in the Epidemiology of Diabetes Interventions and Complications (EDIC) follow-up of the DCCT, that a difference between the intensive and conventional treatment groups in cardiovascular disease rates could be demonstrated [13]. The predictive power of the MPG appears to be strong biological evidence of the validity of the methodology. Notably, in a separate investigation, it was found that an individual whose MPG was 10 mmol/l (180 mg/dl) could have A_{1c} levels ranging from 6–11% [14]. One may independently observe this from examination of reports from the DCCT investigators themselves (Fig. 1), which reveal that patients with an A_{1c} of 9% had mean plasma glucose ranging from ~10–16.7 mmol/l (180–300 mg/dl) [15]. Taken together, these data suggest that the relationship between mean blood glucose and A_{1c} is not constant, differing depending on factors other than glycaemia. As a result, the concept of different diabetic individuals having different degrees of glycation for a given glucose level appears attractive [16].

Certainly, it is well-recognised that a variety of haematological conditions, including persistent fetal haemoglobin, haemoglobin variants, the presence of carbamylated haemoglobin in uremic patients, and conditions with decreased erythrocyte survival, such as hemolysis, are associated with altered A_{1c} concentrations [17, 18]. Low A_{1c} levels are not uncommon in normal persons, and may be associated with haemoglobin S, C, or D, with various forms of anaemia, and with pregnancy, dyslipidemia, malignancy, cirrhosis, and acetylsalicylic acid use [19]. One therefore must presume that among persons with diabetes such conditions would be equally likely to lower A_{1c} below the level which might be

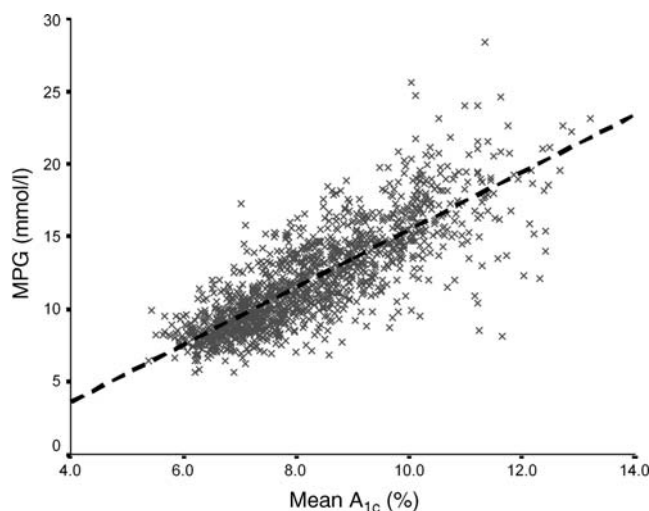


Fig. 1 Relationship between A_{1c} and MPG, using capillary blood haemolysates collected before meals, 90 min after meals, and at bedtime, by DCCT participants in the home. Observe that patients with an A_{1c} of 9% had MPG ranging from ~10–16.7 mmol/l (180–300 mg/dl). Copyright © 2002 American Diabetes Association. From [15]. Reprinted with permission from The American Diabetes Association

predicted from the actual average glycaemia. This is well recognized to occur during the third trimester of pregnancy in women with type 1 diabetes [20], and there is evidence that diabetic persons with nephropathy have levels of A_{1c} differing from those would be predicted from the simultaneously measured serum fructosamine level [21]. Further studies are in progress of interrelationships between A_{1c} and erythrocyte survival, and between A_{1c} and the presence of renal and hepatic disease [22]. Interestingly, there is some evidence that high A_{1c} may itself be associated with reduced erythrocyte survival, so that A_{1c} might at high levels particularly underestimate the true degree of hyperglycaemia [23], further implying need to closely examine factors affecting A_{1c} rather than assuming that it directly represents average glucose concentrations [24].

A recent report of the relationship between A_{1c} (performed with the new IFCC assay) and mean glucose levels determined from continuous glucose monitoring (CGM) showed that at an A_{1c} of 7%, the mean glucose varied between 7.5 and 9 mmol/l (135 and 162 mg/dl); at an A_{1c} of 8%, between 8 and 11 mmol/l (144 and 198 mg/dl); and at an A_{1c} of 9%, between 10.5 and 13.5 mmol/l (189 and 243 mg/dl), again suggesting that factors other than glycaemia may play a role in haemoglobin glycation [25]. In a similar analysis of a CGM database of children with type 1 diabetes, with A_{1c} measured using an assay referable to the DCCT standard, at an A_{1c} of 7%, mean glucose ranged from 7.6–10.5 mmol/l (138–189 mg/dl) [26].

Another line of evidence suggesting that A_{1c} may not predict glycaemia similarly across populations comes from comparison among various groups of persons without diabetes. The ‘glycation gap’ quantifies the relationship between the glycation of intracellular haemoglobin and that of extracellular plasma proteins. The former is additionally influenced by access of glucose to the intra-erythrocyte space, the non-enzymatic glycation rates of haemoglobin, and red blood cell survival. Studies of twins by Cohen et al. have suggested that almost 70% of the glycation gap is heritable and, therefore, genetically pre-determined [27]. In the Diabetes Prevention Program, which involved 3,234 patients with impaired glucose tolerance, the mean A_{1c} in non-Hispanic whites was 5.78%, whereas the corresponding values in Hispanic, Asian, American-Indian, and African-American individuals were 5.93%, 6.00%, 6.12% and 6.18%, respectively, after adjustments for both fasting and postprandial glucose, as well as other demographic and clinical features. These data strongly suggest an important ethnicity-related difference in the glycation of haemoglobin [28]. In a study comparing obese with non-obese South Asian men with neither hypertension nor diabetes, glycated haemoglobin was higher in the former, showing a correlation with the malondialdehyde level, suggesting that glycation may vary with lipid peroxide levels, perhaps reflecting oxidative

stress [29]. Finally, other lines of inquiry have suggested that one-quarter of diabetic patients have an A_{1c} 1 percentage point higher and that one-sixth have an A_{1c} 1 percentage point lower than the value that would be predicted from simultaneously measured glycated serum protein concentration [30].

Based on the above arguments, it seems that although the new advances represented by the IFCC methodology do offer the opportunity to introduce a more accurate approach to A_{1c} measurement, it would be a mistake to report the results of the new assay in terms such as ADAG. If change must occur (and reasonable arguments can be made to maintain the status quo), the best option might be to introduce the new measurement in its precise units, namely mmol/mol, with an entirely new normative range, also reporting A_{1c} in DCCT percentage equivalent units for a limited period of time. Although an accompanying intensive educational effort for both clinicians and patients would be necessary, a more complete understanding of the relationship between A_{1c} and glycaemia could then emerge. Although A_{1c} should continue to play a major role in diabetes management and should continue to remain the gold standard for groups of diabetic patients in clinical trials, it will undoubtedly be better applied to an individual patient when accompanied by a full understanding of their actual patterns of glucose control. Such patterns may be derived from analysis of glucose meter-derived home glucose patterns. As CGM becomes more readily available, this approach to determination of average glucose concentrations could prove to be particularly robust, and in some cases may be considered more useful than the A_{1c} measurement itself. Because, however, CGM requires considerably more effort to ascertain, the need for A_{1c} determination remains certain for the foreseeable future. The ultimate goal will be to develop and validate new approaches to the understanding of glycaemic exposure of persons with diabetes, and, as a result, their underlying risk of micro- and macrovascular complications.

Duality of interest The authors declare that there is no duality of interest associated with this manuscript.

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