The Analytical Goals for Hemoglobin A1c Measurement in IFCC Units and National Glycohemoglobin Standardization Program Units Are Different

To the Editor:

The variation of a biological measurement can be expressed in the units of the measured concentrations or as a percentage of the absolute variation relative to the mean concentration. For example, given that different metrologic systems are in use for the measurement of human body temperature, this parameter can be expressed in degrees Celsius (Europe), degrees Fahrenheit (US), or degrees Kelvin (scientists). The equivalent unitary variation is 1.0 °C, 1.8 °F, or 1.0 K, respectively. Expressed as a percentage of the mean body temperature, this variation corresponds to 2.7% (1/37 × 100) for degrees Celsius, 1.8% (1.8/99 × 100) for degrees Fahrenheit, and 0.3% (1/310 × 100) for degrees Kelvin. From these results, one might conclude that temperature variation is lowest for scientists and highest for Europeans. Of course, that is nonsense. This wrong conclusion derives from the fact that variation across metrologic systems cannot merely be compared in terms of relative percentages when the y intercept (b) in the generic conversion equation \( y = ax + b \) is not equal to zero. A higher y-intercept value will have a greater impact, as is illustrated by the example of the temperatures, where \( ^\circ F = 1.8 \, ^\circ C + 32 \), and \( K = ^\circ C + 273 \).

These mathematical considerations related to temperatures in different units also apply in laboratory medicine when the results of one measurement system are converted to another according to a conversion equation (i.e., \( y = ax + b \)) in which the y intercept is not equal to zero. From the analytical point of view, a y intercept significantly different from zero usually reflects a difference in specificity between the 2 systems. Hemoglobin A1c (Hb A1c) is a typical example. The “master equation” for converting to National Glycohemoglobin Standardization Program/Diabetes Control and Complications Trial (NGSP/DCCT) results from the IFCC results is: NGSP/DCCT = (0.0915 × IFCC) + 2.15, where the positive y-intercept value reflects the different specificity of the NGSP/DCCT method (the “Hb A1c” peak after chromatography with Bio-Rex 70 resin contains about 2% non–Hb A1c hemoglobin fractions, including Hb F and carbamylated hemoglobin) (1). The implication is that the expression of biological variation as a CV will be different, depending on the unit of measure used (IFCC, millimoles per mole; NGSP/DCCT, percentage). In addition, given that biological variation is the basis for their derivation, the allowable analytical goals, and the interpretation of serial measurements will differ when the concept of reference change value is used.

This consideration is summarized in Table 1. Biological variation, derived reference intervals, and analytical goals (based on either biological variation or outcome) are expressed in measurement units and as a relative percentage of the measured amounts. Data regarding the biological variation in Hb A1c vary in the literature (2). In the context of this Letter, however, which experimental data are selected is not relevant. For our example, we have chosen data published by Rohlffing et al. (3). As measured in NGSP units, they found values for intra-individual and interindividual Hb A1c variation (expressed as the SD) of 0.08% and 0.20%, respectively. Dividing these values by the mean of the measured Hb A1c values (4.90%), one obtains the corresponding intraindividual CV (CVI) and interindividjual CV (CVG) values of 1.6% (0.08/4.90 × 100) and 4.1% (0.20/4.90 × 100), respectively. In IFCC units, the corresponding intraindividual variation (SD) is 0.88 mmol/mol (2.9% as the CVI), and the interindividual variation is 2.20 mmol/mol (7.3% as the CVG). According to the mathematical premises described above, the biological variation appears lower when it is expressed in NGSP/DCCT units, owing to the substantially y intercept (2.15) in the master equation. Consequently, the calculated reference interval is narrower with NGSP data (92%–108%) than with IFCC data (85%–115%), and the analytical goals for imprecision, bias, and total error are likewise smaller. Similar calculations can be made for analytical goals derived from patient outcome. In Table 1, we present an example with data published by Mosca et al. (4). At an Hb A1c concentration of 58 mmol/mol (7.5%), the maximum total allowable error is 8.6% for Hb A1c expressed in IFCC units and 6.7% for Hb A1c expressed in NGSP units. The corresponding goals for imprecision are 2.8% and 2.0%.

In conclusion, the analytical goals for Hb A1c derived from the same source (either biology or clinical outcome) are different when results are expressed in IFCC or NGSP units. These differences are important when routine Hb A1c assays are evaluated: Allowable goals and estimated performance will depend on the units in which Hb A1c is expressed. CVs and total errors in external quality-assessment schemes will also be different. Al-

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1 Nonstandard abbreviations: Hb A1c, hemoglobin A1c; NGSP, National Glycohemoglobin Standardization Program; DCCT, Diabetes Control and Complications Trial; CV, intraindividual CV; CVG, interindividual CV.
Alternatively, SD units could be used, but this usage is very uncommon and therefore not a realistic option.

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