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The Analytical Goals for Hemoglobin A_{1c} Measurement in IFCC Units and National Glycohemoglobin Standardization Program Units Are Different

To the Editor:

The variation of a biological measurand 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 °F = 1.8 °C + 32, and K = °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 substantially different from zero usually reflects a difference in specificity between the 2 systems. Hemoglobin A_{1c} (Hb A_{1c})[1] 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 A_{1c}" peak after chromatography with Bio-Rex 70 resin contains about 2% coeluting non–Hb A_{1c} 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 widths of reference intervals, 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 A_{1c} 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 Rohlfing et al. *(3)*. As measured in NGSP units, they found values for intraindividual and interindividual Hb A_{1c} variation (expressed as the SD) of 0.08% and 0.20%, respectively. Dividing these values by the mean of the measured Hb A_{1c} values (4.90%), one obtains the corresponding intraindividual CV (CV_I) and interindividual CV (CV_G) 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 CV_I), and the interindividual variation is 2.20 mmol/mol (7.3% as the CV_G). According to the mathematical premises described above, the biological variation appears lower when it is expressed in NGSP/DCCT units, owing to the substantial y intercept (2.15) in the master equation. Consequently, the calculated reference interval is narrower with NGSP data (92%–108%) than with

[1] Nonstandard abbreviations: Hb A_{1c}, hemoglobin A_{1c}; NGSP, National Glycohemoglobin Standardization Program; DCCT, Diabetes Control and Complications Trial; CV_I, intraindividual CV; CV_G, interindividual CV.

Table 1. Biological variation in Hb A_{1c} and estimated analytical goals related to the NGSP and IFCC measurement systems, as expressed in the Hb A_{1c} concentration unit of measure (percentage and millimoles per mole, respectively) and as a percentage of the Hb A_{1c} measured.

	NGSP system		IFCC system	
Parameter	Unit of measure, %	Percentage	Unit of measure, mmol/mol	Percentage
Biological variation				
Mean Hb A_{1c}	4.90		30.0	
Intraindividual variation	0.08 (as SD)	1.6%	0.88 (as SD)	2.9%
Interindividual variation	0.20 (as SD)	4.1%	2.20 (as SD)	7.3%
Reference interval (95% central interval)	4.50–5.30	92%–108%	25.6–34.4	85%–115%
Analytical goals (biological variation)[a]				
Imprecision	0.04	0.8%	0.44	1.5%
Bias	0.05	1.1%	0.59	2.0%
Total error	0.12	2.4%	1.32	4.4%
Analytical goals (outcome based)[b]				
Imprecision	0.15	2.0%	1.6	2.8%
Total error	0.50	6.7%	5.0	8.6%

[a] Calculated according to Fraser et al. *(5)*.
[b] Calculated according to Mosca et al. *(4)*.

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 A_{1c} concentration of 58 mmol/mol (7.5%), the maximum total allowable error is 8.6% for Hb A_{1c} expressed in IFCC units and 6.7% for Hb A_{1c} expressed in NGSP units. The corresponding goals for imprecision are 2.8% and 2.0%.

In conclusion, the analytical goals for Hb A_{1c} 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 A_{1c} assays are evaluated: Allowable goals and estimated performance will depend on the units in which Hb A_{1c} is expressed. CVs and total errors in external quality-assessment schemes will also be different. Alternatively, SD units could be used, but this usage is very uncommon and therefore not a realistic option.

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Serum Parathyroid Hormone Is Not an Accurate Predictor of Postthyroidectomy Hypocalcemia in Vitamin D–Deficient Patients: A Pilot Study

To the Editor:

Transient hypoparathyroidism resulting in temporary hypocalcemia is the most frequent complication of total thyroidectomy and affects up to one third of patients. The ability to accurately predict hypocalcemia after thyroidectomy allows timely intervention and facilitates early discharge of patients. The postoperative decline in serum parathyroid hormone (PTH) is currently regarded as the gold standard biochemical predictor of postthyroidectomy hypocalcemia. Although the value of PTH in predicting postthyroidectomy hypocalcemia has been extensively studied, its predictive accuracy in vitamin D–deficient patients is unclear. This is of particular importance because there is a high prevalence of vitamin D deficiency in patients with thyroid nodules, malignancy, and Graves disease, the major indications for thyroidectomy *(1, 2)*. We retrospectively examined the value of serum PTH as a predictor of postthyroidectomy hypocalcemia in patients with and without vitamin D deficiency.

We identified 74 consecutive patients who had undergone total/completion thyroidectomy. Serum 25-hydroxyvitamin D concentration was measured preoperatively, and serum PTH and calcium concentrations were measured in all patients 8–10 h after surgery. Serum calcium and albumin were measured by using standard automated assays (Abbott Architect, Abbott Diagnostics). PTH was measured by using an automated immunoassay (Abbott Architect, Abbott Diagnostics). The CV for this assay was <8% across the diagnostic range.

Serum 25-hydroxyvitamin D was measured by using the automated Liaison assay (Diasorin) with a CV of <11% across the diagnostic range. A 25-hydroxyvitamin D concentration <25 nmol/L was used to indicate vitamin D deficiency, as suggested by the manufacturer's reference range.

The definition of temporary hypocalcemia after thyroidectomy in the literature varies between different studies. In one prospective study of hypocalcemia developing after thyroidectomy, patients were treated if they were symptomatic or had serum calcium <1.95 mmol/L *(3)*. We used similar criteria and defined temporary hypocalcemia as a corrected serum calcium of ≤1.95 mmol/L or the presence of hypocalcaemic symptoms.

Patients were divided into 2 groups according to their preoperative serum 25 hydroxyvitamin D concentrations. Of 58 patients with 25-hydroxyvitamin D concentrations >25 nmol/L, 23 patients developed hypocalcemia requiring treatment. Six of 16 patients with vitamin D deficiency developed hypocalcemia requiring treatment. ROC curves for serum PTH were created for both groups (Fig. 1). The ROC curve reflects the effectiveness of a test in correctly establishing the diagnosis. The area under the ROC curve for serum PTH to predict hypocalcemia postthyroidectomy in patients with a 25-hydoxyvitamin D concentration >25 nmol/L was 0.93 (95% CI: 0.86–1.00; $P < 0.0001$). The area under the ROC curve for serum PTH in patients with vitamin D deficiency was 0.68 (95% CI: 0.39–0.97; $P = 0.23$). Our results show that serum PTH is a good predictor of postthyroidectomy hypocalcemia in the absence of vitamin D de-

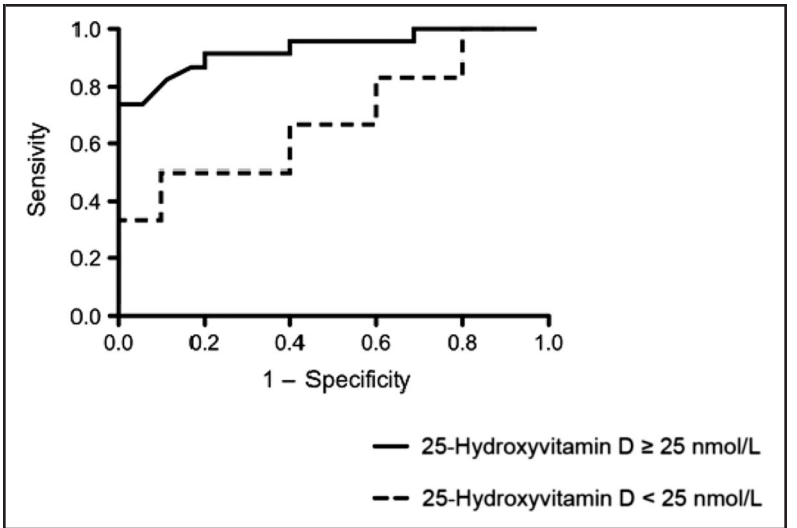

Fig. 1. ROC curves demonstrating the accuracy of serum PTH in predicting postthyroidectomy hypocalcemia in patients with a serum vitamin D concentration ≥25 nmol/L and those with a serum vitamin D concentration <25 nmol/L.