Need for Revision of Diagnostic Limits for Medullary Thyroid Carcinoma with a New Immunochemiluminometric Calcitonin Assay

To the Editor:

Calcitonin is the most sensitive tumor marker for both diagnosis and postoperative surveillance of medullary thyroid carcinoma (MTC).1 Healthy control individuals virtually always have a serum calcitonin concentration <10 ng/L, and patients with higher basal calcitonin concentrations are recommended to undergo a pentagastrin-stimulation test (PGT) to exclude the presence of MTC. Stimulated peak serum calcitonin concentrations >100 ng/L are >90% specific for a diagnosis of C-cell disease, either C-cell hyperplasia or MTC (1). These diagnostic limits were established on the basis of data from studies that used the manual Cisbio immuno-radiometric calcitonin assay and were subsequently validated for the Nichols calcitonin assay (2).

Many centers now use the Liaison assay (Diasorin) as an alternative to the discontinued Nichols assay. Bieglmayer et al. have shown that the Liaison calcitonin assay is positively biased compared with the Nichols assay (3). The manufacturer’s product insert for the Liaison assay currently recommends a basal calcitonin concentration of >10 ng/L as the diagnostic limit for further investigation for MTC, despite the fact that the upper reference limit for males (18.6 ng/L) exceeds this limit. A recent study published in Clinical Chemistry proposed revision of the 10-ng/L limit for measuring basal calcitonin with the Liaison assay (4).

The Liaison assay is a 1-step direct, 2-site immunochemiluminometric assay that uses specific affinity-purified mouse monoclonal antibody–coated magnetic microparticles and an alternative affinity-purified mouse monoclonal antibody conjugated to an isoluminol derivative. The functional sensitivity (defined as the concentration with a CV ≤20%) reported by the manufacturer is 8 ng/L; however, when calculated in our laboratory with 90 paired samples, we obtained a functional sensitivity of 4 ng/L.

We measured basal serum calcitonin and stimulated calcitonin with the Liaison assay in 83 healthy volunteers [43 females (age range, 18–59 years; mean, 32 years) and 40 males (range, 22–72 years; mean, 39 years)] who were recruited to the study. The study participants provided informed consent. Nonfasting 5-mL blood samples were collected into plain serum Vacutainer® tubes (Becton Dickinson). Ten of the 43 women (age range, 27–36 years; mean, 32 years) and 12 of the 40 men (range, 25–48 years; mean, 33 years) underwent a PGT, which was performed in the nonfasting state. A 5-mL blood sample was collected at 0 min and at 1, 2, 3, 5, and 10 min after a single intravenous bolus of pentagastrin (0.5 μg/kg). In these volunteers, the 0-min sample was used to determine the basal calcitonin reference intervals. All blood samples were allowed to clot and were centrifuged within 20 min of collection. Serum aliquots were stored at −20 °C and assayed in batches.

A rank-based nonparametric method was used to calculate reference intervals. The fifth-percentile values were lower than the functional sensitivity of the assay (4 ng/L) for both males and females. The 95th percentile (and hence the upper limit of the reference interval for basal calcitonin) was 21.9 ng/L (median, 9.8 ng/L) for males and 11.1 ng/L (median, 5.7 ng/L) for females (Fig. 1). Basal calcitonin values for 0-min samples obtained via a cannula for the PGT were similar to those of the remaining basal calcitonin samples. The median peak stimulated calcitonin concentration was 28.2 ng/L in males (range, 19.5–110.0 ng/L) and 11.0 ng/L in females (range, <4 ng/L to 38.6 ng/L).

In our study, the upper limit of the reference interval in healthy males was similar to that recom-

1 Nonstandard abbreviations: MTC, medullary thyroid carcinoma; PGT, pentagastrin-stimulation test.

Fig. 1. Basal serum calcitonin concentrations in males (n = 40) and females (n = 43).
Indicated are the current diagnostic limit of 10 ng/L (solid line) and the manufacturer’s upper reference limits for males (dashed line) and females (dotted line).
mended by the manufacturers of the Liaison calcitonin assay; however, the upper limit for healthy females is twice the manufacturer’s recommended value of 5.5 ng/L. Thirteen percent of healthy male volunteers and 19% of healthy female volunteers had basal calcitonin concentrations that exceeded the manufacturer’s recommended upper reference limit. When a basal calcitonin diagnostic limit of 10 ng/L was used to indicate the need for further assessment with the PGT (1), 48% of healthy males and 19% of healthy females had a basal calcitonin value greater than this limit. After pentagastrin stimulation, 1 individual had a peak stimulated calcitonin value >100 ng/L (basal, 16.6 ng/L; peak, 110 ng/L).

Our data show an upper reference limit for males that is almost twice that for females. This result is supported by postmortem studies demonstrating that men have twice the number of C cells than females (5). Therefore, the validity of applying a single diagnostic limit for basal and stimulated calcitonin for both males and females remains questionable.

The information gained from this study is insufficient to make any definite recommendation regarding changes to the currently used cutoff limits for stimulated calcitonin concentrations, and further studies are needed. This study offers strong evidence, however, to suggest that the current diagnostic limits of >10 ng/L for basal concentrations are too low when the Liaison assay is used. Extrapolating these cutoffs obtained with the Cisbio assay to the Liaison assay has the potential to lead to unnecessary thyroid biopsies. Thus, our data support calls for a revision of the diagnostic limits for basal serum calcitonin with the Liaison assay (4).

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Lack of Transferability of Results between Procalcitonin Assays

To the Editor:

In a recent issue of Clinical Chemistry, De Wolf et al. described an evaluation of the new Procalcitonin (PCT) assay from Roche, performed according to CLSI (Clinical and Laboratory Standards Institute) recommendations, compared with the widely accepted PCT assay on the Brahms Kryptor analyzer (Brahms) (1). We recently carried out an analogous study on a Cobas e411 (Roche Diagnostics) (2) and reached some different conclusions. We found no transferable results between the Elescsys Brahms PCT (Cobas) and PCT-TRACE (Kryptor) when we
Letters to the Editor

In Reply

Prieto and Alvarez point out a lack of transferability between the PCT assay for use on a routine immunochemistry analyzer family and the PCT assay on the Brahms Kryptor analyzer.

Compared to our study, the study by these authors revealed a more pronounced tendency toward lower concentrations on the Cobas analyzer. This was especially true when PCT values covering the entire concentration range were included (0 to >50 µg/L). The regression lines were: $y = 0.86x - 0.002$ and $y = 0.95x - 0.09$ for their and our study, respectively. Besides interlaboratory differences in sample handling and calibration procedures, the use of different orthogonal regression methods likely contributed to the difference in proportional bias. The same holds true for the inclusion by Prieto and Alvarez of more high-concentration PCT samples, which acted as leverage points on the regression line.

In our study, we focused on the PCT range relevant for diagnostic purposes. Concordance at the clinical cutoff points (0.25 and 0.5 µg/L) was high in both the study by Prieto and Alvarez (97% and 94%) and our study (99% and 98%). We performed a Bland-Altman difference analysis within the clinically important interval. The distribution of the differences (Fig. 1) demonstrates a mean bias of $-0.02\ \mu g/L$ that is randomly

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compared 152 samples from the same number of different patients. A regression analysis demonstrated the heteroscedasticity of the results as well as the lack of normality of the residuals. Passing-Bablok nonparametric analysis showed a proportional tendency toward lower PCT concentrations on the Cobas than the Kryptor analyzer. The regression equation was: PCT Cobas = −0.0024 + 0.8586 PCT Kryptor (intercept 95% CI, −0.0061 to 0.0051; slope 95% CI, 0.84–0.87). We created a folder empirical cumulative distribution plot (mountain plot) to compare both methods, following the CLSI-EP21A recommendation for situations in which differences do not follow a gaussian distribution. The mountain plot was not fully included among the specification lines, the graph was biased toward positive differences between methods, and an outlier was detected (2). Less than 95% of the differences were included within the tolerance limits (defined by the 2.5th and 97.5th percentiles, respectively), and on the basis of these results we concluded that there was not transferability between both methods. Because the same analytical handling conditions were followed in both studies, this point could not explain the discrepant results. A similar range of concentrations were compared in both studies, but a different percentage of low concentration samples were assayed (70% of the PCT values were ≤0.25 µg/L in the study by de Wolf et al. compared to 28% in our study), probably due to the fact that de Wolf et al. included only patients with lower respiratory tract infections, whereas we also included patients with sepsis who were hospitalized in the intensive care unit. In our study the tendency toward lower values on the Cobas analyzer was confirmed over the entire measuring range. With regard to concordance between the 2 assays, de Wolf et al. found 99% and 98% at cutoff values of 0.25 µg/L and 0.5 µg/L, respectively, whereas we found a slightly lower grade of concordance of 97% and 94% for the same cutoff values.

It is beyond the scope of this communication to state whether a reappraisal of the cutoff is necessary, because this was not a clinically based study. However, if the present lack of transferability is confirmed in the clinical management of the patients, it would be interesting to open up further discussion about the best cutoff points of the new Elecsys Brahms PCT method, not on the basis of calculated predictions but rather clinical findings.

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scattered; >95% of the differences were within the levels of agreement (defined by bias ± 1.96 SD).

Recently, decision-making regarding PCT results has been based on relative PCT concentrations rather than absolute cutoff points, taking into account patient day-to-day variations (1). With this shift toward PCT trend analysis, precision criteria might ultimately outweigh criteria for accuracy, putting the current discussion on interassay differences into another perspective. We conclude that method comparison should focus on concentration intervals relevant for clinical purposes and that the observed differences in interassay transferability should not withhold introduction of the PCT assay on a routine immunochemistry analyzer family.

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Fig. 1. Difference plot of procalcitonin concentrations (Roche Modular E170 assay, Brahms Kryptor) at the clinically important range of 0–1.0 μg/L. Solid line, mean bias (−0.019 μg/L); dashed lines, 95% limits of agreement (−0.106 to 0.068 μg/L, n = 187).

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Inaccuracies in Free Thyroid Hormone Measurement by Ultrafiltration and Tandem Mass Spectrometry

To the Editor:

We have read with interest recent reports of the measurement of free thyroxine and free triiodothyronine by ultrafiltration and tandem mass spectrometry (1–4). There is, however, a fundamental flaw in these studies that we wish to bring to general attention. Ultrafiltration of serum was routinely carried out close to room temperature (25 °C) (1–4). Ross and Benraad (5) and van der Sluis Veer and coworkers (6) have demonstrated that the free analyte concentrations typical of serum at body temperature (37 °C) are not maintained in other environments. Crucially, the above workers and others (7) have shown that the binding affinity of thyroxine-binding globulin for thyroid hormones is very sensitive to temperature variations, undergoing drastic changes, both in absolute terms and relative to the other thyroxine-binding proteins, which are less affected (5,6).

Hence, one can no longer regard the reported results (1–4) as accurate. All studies, including those with study populations of pregnant and nonpregnant euthyroid individuals (1–4), should be repeated at 37 °C, when we suspect that different conclusions may be drawn.

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In Reply

In our earlier studies ultrafiltration (UF) was performed at 25 °C and not at room temperature or 37 °C. This was done to provide the endocrinologists at Children’s National Medical Center with results that were essentially identical to those obtained by the then gold standard equilibrium dialysis immunoassay (EDIA) method marketed by Nichols. Comparison between these 2 approaches, EDIA and UF tandem mass spectrometry (UFMSMS) yielded the regression equation: EDIA = 0.971 (UFMSMS) + 0.041, r = 0.954 (1, 2), and we observed close agreement between the 2 methods (1, 2).

The UF temperature used in the recently reported studies (3, 4) was also 25 °C. Clearly the fact that this UFMSMS method yielded results that correlated well with both the gold standard EDIA method (performed at 37 °C) and with log thyroid-stimulating hormone is a measure of the veracity and clinical utility of the UFMSMS method. Note that the direct analog IA correlation with EDIA/UFMSMS and log thyroid-stimulating hormone was poor (1–4). In the study population of pregnant women a correlation of r = 0.898 was also observed between the EDIA gold standard method and UFMSMS at 25 °C (3).

Our initial studies (1, 2) reflecting the effect of UF temperature on free thyroxine (FT4) and free triiodothyronine (FT3) measured by UFMSMS have been extended and were recently published (5). The regression equations obtained for FT4 and FT3 were: [37 °C] = 1.514 [25 °C] – 0.097 (r = 0.974) and [37 °C] = 1.495 [25 °C] + 0.038 (r = 0.964), respectively, and were tightly correlated (5). The Nichols kit is no longer available, and some commercial laboratories have developed EDMMS methods that are performed at 37 °C and use different membranes from those employed in the Nichols approach. These methods provide results approximately 1.5 times higher than the original Nichols gold standard method.

At Georgetown University (Washington, DC) and NMS Laboratories (Willow Grove, PA) we have recently changed the temperature of the UF step to 37 °C to both perform UF at the physiologically relevant temperature and harmonize our results to those from other commercial laboratories. This move from 25 °C to 37 °C increases the results and reference intervals by a factor of approximately 1.5 (5) but in no way affects data interpretation. Finally, it is noteworthy that the Endocrine faculty at Children’s National Medical Center are happy with the FT4/FT3 results they have routinely been getting over the past 3 years (>30 000 samples), measurements obtained with UFMSMS in which the UF is performed at 25 °C. The Children’s National Medical Center has refused to allow us to change the UF temperature to 37 °C. The direct analog IA methods previously used at Children’s National Medical Center have been discontinued because of their lack of credibility, and only UFMSMS FT4 and FT3 results are available.

In summary, our laboratory has performed extensive comparisons between UFMSMS, performed at both 25 °C and 37 °C, and EDIA and EDMMS. In all studies the results were in close agreement. In contrast to ED, UF is a rapid procedure and the precision afforded by UF is also far superior to that of ED.

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In our earlier studies ultrafiltration (UF) was performed at 25 °C and not at room temperature or 37 °C. This was done to provide the endocrinologists at Children’s National Medical Center with results that were essentially identical to those obtained by the then gold standard equilibrium dialysis immunoassay (EDIA) method marketed by Nichols. Comparison between these 2 approaches, EDIA and UF tandem mass spectrometry (UFMSMS) yielded the regression equation: EDIA = 0.971 (UFMSMS) + 0.041, r = 0.954 (1, 2), and we observed close agreement between the 2 methods (1, 2).

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In summary, our laboratory has performed extensive comparisons between UFMSMS, performed at both 25 °C and 37 °C, and EDIA and EDMMS. In all studies the results were in close agreement. In contrast to ED, UF is a rapid procedure and the precision afforded by UF is also far superior to that of ED.

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Cardiac Troponin Scorecard

To the Editor:

The recent opinion paper by Apple (1) on a cardiac troponin assay scorecard has enlarged the conundrum on whether cardiac troponin assays are clinically usable or not. Apple has proposed a scorecard that evaluates cardiac troponin assays according to the total imprecision at the 99th percentile. The cited data include the concentrations at the 10% CV and whether the value is greater or less than the cited 99th-percentile value. No data for the 20% CV are presented, however, and all of the cited values are derived from separate independent studies.

Values for the 99th percentile of a healthy population have been reported to show considerable variation between assays and even within an assay (2), due to such factors as the reference population chosen, the skewness of the distribution, specimen type, exclusion criteria, and sample size. In addition, the selection of the zero-concentration calibrator can skew values for the 99th percentile by >3-fold (3). All of the variables used to define a healthy population remain nonstandardized among manufacturers, making comparisons difficult.

Likewise, the determination of the 10% or 20% CV value can be inconsistent, given the potential differences with respect to multiple variables, such as the number of days tested, the total number of replicates, the number of calibrations, and the number of reagent batches. Plotting the CV values thus yields a curve with multiple options for fitting the data, the choice of which could affect the estimated CV at specific concentrations.

We also note an inconsistency between the criteria used in the scorecard opinion paper (1) and those previously published by Apple et al. (4) and included in the recent National Academy of Clinical Biochemistry Laboratory Medicine Practice Guidelines on biomarkers of acute coronary syndromes (5). In these publications (4, 5), CV values as high as 25% at the 99th percentile do not lead to clinically important patient misclassification over serial measurements. The scorecard uses a 20% CV decision point.

Therefore, discussions and comparisons regarding the variables affecting 99th-percentile and CV values can be complex. Until uniform methods can be used to evaluate these variables, comparisons should be made with caution and be based on studies that use the same materials and testing procedures.

Historical data based on functional-sensitivity studies for the Abbott AxSYM Troponin-I ADV assay indicate that the 20% CV aligns with a concentration between 0.04 ng/mL and 0.05 ng/mL (95% confidence limits), which is in agreement with the reported value for 99th percentile of a healthy population, 0.04 ng/mL. More recently, Tate et al. (2) independently reported that the AxSYM Troponin-I ADV assay has a 20% CV at a concentration of 0.025 ng/mL. This concentration is less than the 99th-percentile value of 0.04 ng/mL, a finding that meets Apple’s criteria (1) for a clinically usable assay. Furthermore, this study used the same samples and procedure.
to compare 6 troponin-I assays and found that the performance of the AxSYM analyzer at the 20% CV (0.025 ng/mL) was comparable to the performance results for the Beckman Coulter Access (0.043 ng/mL), the Abbott Architect (0.023 ng/mL), the Siemens ADVIA Centaur (0.022 ng/mL), the Siemens Dimension (0.03 ng/mL), and the Johnson & Johnson Vitros (0.019 ng/mL) assays, all of which were considered acceptable or clinically usable according to the proposed criteria (1).

These findings indicate that the AxSYM Troponin-I ADV assay is clinically useful and that the results are comparable to those of other available assays.

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