

## Variation in parathyroid hormone immunoassay results—a critical governance issue in the management of chronic kidney disease

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### Abstract

Renal physicians strive to maintain parathyroid hormone (PTH) concentrations for patients with chronic kidney disease (CKD) within guideline limits, but poor method comparability means there is currently serious risk of clinical misclassification. The potential for under- or over-treatment is significant, representing a major challenge to patient safety. In the short-term, raising awareness of clinical implications of method-related differences in PTH is essential. Agreeing and adopting assay-specific PTH action limits for CKD patients as an interim measure is highly desirable and has been achieved in Scotland. Establishing pre-analytical requirements for PTH is also a priority. In the longer term, re-standardization of PTH methods in terms of an appropriate International Standard is required. Provided commutability can be demonstrated, the recently established IS 95/646 for PTH (1-84) is a suitable candidate. Establishment of a well-characterized panel of samples of defined clinical provenance to enable manufacturers to determine appropriate reference intervals and clinical decision points is also recommended and will provide an invaluable clinical resource. Recent developments in mass spectrometry mean that a candidate reference measurement procedure for PTH is now achievable and will represent major progress. Concurrently, evidence-based recommendations on clinical requirements and performance goals for PTH are required. Improving the comparability of PTH results requires support from many stakeholders but is achievable.

worldwide [5]. In the UK, the annual incidence of CKD is estimated to be between 132 and 148 per million population and >100 people per million population begin renal replacement therapy each year [6]. CKD-MBD is common in CKD and almost universal in Stage 5 disease [7]. Significant clinical effort is invested to minimize the risk of progression by attempting to maintain circulating calcium, phosphate and PTH levels within recommended target ranges.

Kidney Disease: Improving Global Outcomes (KDIGO) [8] and Renal Association [9] guidelines both now recommend plasma PTH target ranges expressed as multiples of the upper reference intervals (two to nine times for dialysis patients). UK National Institute for Health and Clinical Excellence (NICE) guidelines for cinacalcet, a relatively costly calcimimetic drug, state that it should be prescribed only for CKD patients with plasma PTH concentrations > 85 pmol/L (equivalent to 800 ng/L) [6]. Such recommendations place a major responsibility on clinical laboratories and diagnostic manufacturers, not only to ensure that results obtained using different PTH immunoassays are comparable, but also that reference intervals and clinical decision limits are appropriate [5, 10, 11]. However, this is not a simple challenge, and unless clinicians are aware of the substantial differences in results obtained by currently available assays and laboratories make efforts to ensure assay specific ranges are readily available, the potential for mismanagement of CKD-MBD is considerable.

In September 2010 the clinical governance issue of non-comparability of PTH results was debated at a meeting of interested parties at the Royal College of Pathologists in London. Current clinical practice in PTH measurement and interpretation was reviewed. Actions required for short-term improvement and for longer term progress towards national and international consensus and standards were identified and prioritized.

### Introduction

Parathyroid hormone (PTH) is a major regulator of bone metabolism and participates in control of the homeostatic response to alterations in plasma calcium concentrations [1, 2]. In patients with chronic kidney disease (CKD), PTH measurements are widely used as a surrogate marker in the assessment of the skeletal and mineral disorders associated with CKD or CKD-mineral and bone disorders (CKD-MBD) [3, 4]. CKD currently affects 11% of the adult population in the USA and represents a major health issue

### Factors contributing to variability in PTH results

Factors contributing to the variability described include those that affect immunoassay procedures for any analyte. They include pre-analytical factors (e.g. specimen type and stability), method design (choice of antibodies and how the

immunoassay is constructed), accuracy of calibration, imprecision and reproducibility [12].

#### *Pre-analytical factors specifically affecting PTH measurements*

PTH is a relatively unstable hormone, which is broken down in blood after venepuncture [10]. Stability varies depending on sample type, whether serum or plasma [ethylenediaminetetraacetic acid (EDTA) or heparin] [13], whether fresh frozen or lyophilized etc. Sample type (serum or EDTA plasma) may also affect the PTH concentration reported with some assays [14]. It is therefore essential to specify the preferred specimen type and to provide clear advice about storage if specimens are not assayed immediately.

### **Measurement of PTH by immunoassay**

PTH is a peptide hormone circulating in different molecular forms, including the intact molecule (PTH 1-84) and various truncated forms (e.g. PTH 7-84). These forms may be differently recognized by the various antibodies used in PTH immunoassays. The first generation radioimmunoassays for PTH that were developed in the 1960s and 1970s had relatively poor sensitivity and specificity as they frequently detected inactive fragments [15].

In the 1980s, second generation immunoradiometric assays were developed and were termed 'intact' PTH assays, as in these assays one antibody is directed to the C-terminal region and the second to the N-terminal region (amino acids 1-34) [16]. This configuration was thought to confer specificity for intact PTH (1-84) [17] but it was subsequently demonstrated that these assays also recognize other circulating fragments [15]. Many of these fragments are inactive, but some, such as PTH (7-84), may actually be inhibitory [15].

More recently, third generation assays have become available [15]. Analytically, these assays are thought to be specific for PTH (1-84), as the second antibody is directed to amino acids 1-4 [18, 19]. However, improved clinical specificity of third generation assays (as compared to second generation assays) in the management of CKD-MBD has not yet been established [15] and they are not yet in widespread use.

#### *Antibody specificity and method design*

Despite major progress in improving the specificity of PTH methods for the holo-molecule, the problem of recognition of other PTH fragments such as PTH (7-84) (which tend to accumulate in the circulation with increasing severity of CKD stage) [4, 5] is an issue for many of the second generation PTH immunoassays in current use. Whether this compromises their clinical utility is not yet clear [8]. However, variable recognition of such fragments undoubtedly presents challenges for assay standardization. Reflecting specificity differences in the antibodies used [20], as well as method design, PTH (7-84) is known to contribute to the variability observed in different second generation intact PTH assays. In a survey of manufacturers' data, information regarding cross-reactivity of PTH (7-84) was provided for only 11 of 27 methods [21]. As expected, PTH (7-84) was not

detected by five 3rd generation PTH methods that are available from a single supplier. In the other six methods for which cross-reactivity was stated, figures varied from 44.8 to 100%. These data agree with studies on the recovery on synthetic PTH (7-84) which show that, excluding third generation methods which do not recognize PTH (7-84), recognition can vary by up to 2.7 [22] or 3-fold [23] for different groups of assays.

#### *Accuracy of calibration*

Similar variability to that described for patient specimens is observed in recovery experiments in which known amounts of highly purified synthetic PTH (1-84) are spiked into pools of normal human sera or plasma. Recoveries of added PTH (1-84) reported in two of the studies described above ranged from 63.1 to 215.6% (a 3.4-fold difference) [22] and from 95.9 to 191.0% (a 2-fold difference) [23]. In the latter study, the correlation observed between recovery and bias from EQA consensus target values strongly suggests that accurate method calibration in terms of a common standard should improve comparability of PTH results [23], provided the standard is commutable [24]. The newly established first International Standard (IS) for PTH (WHO IS 95/646) [25], a recombinant preparation, is a suitable candidate if its commutability can be confirmed, i.e. if the IS can be demonstrated to have the same characteristics as PTH in patient samples when measured in immunoassays.

#### *Imprecision and reproducibility*

Within-method between-laboratory imprecision (i.e. coefficient of variation) as assessed by EQA schemes is low, varying from 5 to 9% [15, 23], reflecting the excellent performance achieved by automated immunoassay analysers. These figures are likely to over-estimate imprecision within-laboratory. Low imprecision is desirable when establishing performance goals. EQA data for pools distributed on more than one occasion suggest that this is also generally very good [23], which is important when serial measurements are clinically relevant, as for PTH.

#### *Method-related variability of PTH results*

Lack of comparability of PTH results has been convincingly demonstrated by method comparison studies in which PTH concentrations have been determined for similar specimens (individual and/or pooled patient samples) using different commercially available immunoassays [22, 26-29]. In a study of 47 serum pools from dialysis patients, results obtained in 15 assays varied almost 4-fold, ranging from 8.7 to 34.0 pmol/L (83 to 323 ng/L) for one pool [22]. Variations of 2.7-fold were reported by Cantor *et al.* [26] for 46 specimens from Stage 5 CKD patients when measured by seven different PTH methods, with results ranging from 12.8 to 34.5 pmol/L (122 to 328 ng/L) for one specimen. PTH results for lyophilized pools of plasma from patients with CKD distributed by the UK National External Quality Assessment Service (UK NEQAS) typically vary by at least 2-fold for six commonly used methods [23]. Similar variability in results has been reported in an independent study of 99 single dialysis patient plasma specimens assayed using the same six methods [28].

## PTH variability implications for clinical practice

Method-related differences in PTH results make reliable implementation of clinical guideline recommendations highly problematic and potentially seriously decrease their intended benefit to the patient. The true serum or plasma PTH concentration may be under- or over-estimated depending on the assay used, potentially leading to under- or over-treatment and even, in some cases, unnecessary parathyroid surgery [4]. Expressing decision limits in relation to assay-specific upper limits of the reference interval could be an improvement over absolute concentrations, but only if appropriate reference interval data are available for all methods used. However the reference intervals currently provided by manufacturers are often remarkably similar [lower limits ~1.1 pmol/L (10 ng/L), upper limits ~7.4 pmol/L (70 ng/L)] [10, 21] and do not necessarily reflect reported method-related differences in PTH results. There is therefore major cause for concern. The potential impact of inaccurate reference intervals is sharply illustrated by Almond *et al.* [28] who demonstrate that such variation can be enough to prompt treatment regimens with completely opposite aims, depending on which assay is used. When PTH was determined using six different immunoassays in plasma specimens obtained from 98 patients with CKD, the difference in results between the lowest and highest reading methods ranged from 1.2- to 2.7-fold. Fifty-two patients (53%) would have been treated differently according to the highest or lowest reading assay if manufacturers' reference interval data were used [28]. These differences in classification could be decreased to 12% by applying assay-specific targets [28].

While most physicians are familiar with clinical guidelines recommending target PTH values, the large and unacceptable variability in current PTH measurements have until recently been less well publicized [4]. The potential clinical and economic consequences—with respect to inappropriate parathyroid surgery and prescribing of expensive calcimimetic medication—are significant [4] and represent a major challenge to patient care and safety. They also raise serious concerns about the validity of any comparative audit or unit bench marking involving PTH, a point already acknowledged by both the UK Renal Registry [30] and the Scottish Renal Registry [31].

## Improving the comparability of PTH results

The PTH standardization meeting in September 2010 brought together experts from renal and laboratory medicine and most global companies currently marketing PTH immunoassays (see Appendix for attendees). Consensus on how to address the issues outlined above was reached.

### Short-term priorities

It was agreed that raising awareness of the clinical implications of assay-related differences in PTH results is the first priority (Table 1).

A systematic review of the literature relating to pre-analytical requirements for PTH should be undertaken with the aim of publishing good practice guidelines to minimize

**Table 1.** Short-term actions to improve the international comparability of PTH results

Priority Action	
1	Raise awareness of the shortcomings of current PTH assays in the management of renal patients with renal physicians and clinical biochemists through published articles in key journals and posters and/or presentations at conferences.
2	Following a systematic review of the literature, prepare good practice recommendations for the optimal pre-analytical handling of patients and samples to reduce variability in PTH results due to pre-analytical factors including anti-coagulant used, time of sampling, sample handling and storage and sample stability.
3	Under the auspices of UK NEQAS in collaboration with other EQA providers, extend the Scottish single-patient study [28] by distributing single patient samples from defined subjects (normal, hypercalcaemic and renal) to a number of labs in order to acquire data on performance of all assays in common use.
4	Recommend adoption of assay-specific PTH action limits for managing renal patients pending re-standardization of methods in terms of a common standard. This should include reaching agreement (ideally internationally but realistically nationally) on units for reporting PTH results.

variability associated with differences in patient preparation, sample handling and storage. Achieving national (or ideally international) agreement about the units in which PTH results are reported would also be highly desirable to minimize the risk of confusion. Molar units have already been accepted and implemented as the preferred unit in Scotland, with adoption throughout the UK recommended [32].

Achieving agreement on and then adopting assay-specific PTH action limits for CKD patients will improve comparability of clinical practice with respect to the use of PTH results produced by current assays, pending a re-standardization of PTH methods using the newest IS. The Scottish Renal Registry, in collaboration with the Scottish Clinical Biochemistry Managed Diagnostic Network, has now proactively implemented the assay-specific target values derived in the study by Almond *et al.* [28] across Scottish renal units. Confirming results of this study in a larger cohort of clinically well-defined subjects (healthy, hypercalcaemic and CKD)—and extending it to include all assays in common use—is desirable and would provide additional support for development and implementation of assay-specific target values nationally and internationally, which is the final short-term priority.

### Longer term priorities

Universal availability and acceptance of assay-specific target values would represent major progress, but nevertheless should be regarded as an interim measure. PTH methods will only satisfactorily fulfil requirements for clinical practice and facilitate sound clinical decision-making—for patients with CKD as well as for those with other parathyroid disorders—when they are accurately calibrated against the same standard and the most clinically relevant forms to measure are defined. Re-standardization of all PTH assays in terms of a single internationally recognized standard such

as recombinant PTH IS 95/646 [25] must therefore be the long-term goal (Table 2). Such re-standardization of commercial methods is complex and time consuming and at least 2–3 years may be required to achieve this. Since well-coordinated international collaboration among clinical and laboratory organizations and the diagnostic companies that provide PTH methods is a pre-requisite for success, it is very encouraging that there is already considerable support for such an initiative from these groups. The International Federation of Clinical Chemistry and Laboratory Medicine (IFCC) has established a Working Group to undertake this.

While improved analytical comparability of PTH results is highly desirable, it is also critically important that reference intervals and clinical decision points are appropriate. The original KDOQI targets [33] were derived from systematic review of published data obtained in studies using the Nichols Allegro PTH method, which was regarded as the gold standard method at the time, but is no longer available. The establishment of a well-characterized panel of samples of defined clinical provenance to enable all manufacturers to determine appropriate PTH reference intervals and clinical decision limits represents a more rigorous approach and was proposed at the London meeting as the second longer term priority. Preparing a panel of plasma and/or sera in sufficient quantities will require detailed planning and adherence to best practice guidelines for biobanking [34] as well as requiring careful selection of donors. It has been recommended that, when establishing reference intervals, subjects with low serum 25-hydroxyvitamin D concentrations should be excluded and other determinants of PTH concentrations including age, glomerular filtration rate, calcium intake, serum magnesium, race and body mass index should also be taken into account [11, 14]. Although undoubtedly very challenging to establish, such a panel would provide an invaluable clinical resource, not

only for improving current clinical interpretation of PTH results but also for early evaluation of promising new CKD–MBD biomarkers such as fibroblast growth factor 23 (FGF23) [35].

Although the consensus mean (the mean of all results for a given specimen) provides a convenient estimate of the correct value for complex analytes [23, 36], where feasible reference measurements based on physicochemical techniques are almost always preferable and allow demonstration of metrological traceability. Recent the developments in mass spectrometry mean that the development of a candidate reference measurement procedure for PTH should now be achievable [37, 38]. This was therefore identified as the third longest term priority and will require significant funding and international support.

Finally, and running concurrently with the above, a group of clinical and laboratory professionals representing relevant clinical and laboratory organizations should be convened with the remit of producing evidence-based recommendations on the clinical requirements for the measurement of PTH and the performance goals (e.g. bias, imprecision, specificity) necessary to fulfil these.

## Conclusion

The clinicians' interpretation of currently available PTH assay results is fraught with significant governance issues hindering confidence in the appropriate clinical management of CKD–MBD. The activities described above should facilitate more equitable implementation of evidence-based recommendations that are essential for optimal care of patients with CKD. Meaningful comparison and interpretation of national and international audit data proactively collected by renal registries will also be possible, enabling better understanding of how PTH should be used in the management of CKD, to the benefit of patient care. These ambitious plans will require support from many stakeholders but there is no doubt that with sufficient participation and co-operation from the clinical and scientific communities, they are achievable.

*Acknowledgements.* We would like to thank Anne Dawney, John Seth, Keith Simpson and Robin Winney for their careful reading of this manuscript and most helpful comments. We would also like to thank all participants at the London meeting for their much appreciated contributions and support (For list of attendees, please see the Appendix).

*Conflict of interest statement.* None declared.

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**Table 2.** Longer term actions required to improve the international comparability of PTH results

Priority	Action
1	Confirm support for and then commence an international PTH assay re-standardization project based on IS 95/646. A detailed protocol should be produced as part of the process of gaining support. Funding and the resulting educational support will be incorporated in the project.
2	Establish a panel of samples of defined clinical provenance covering normal hypercalcaemic and CKD patients that could be used by all manufacturers to determine reference intervals and clinical decision points. Assign values to these samples—initially based on consensus means but subsequently based on a reference measurement procedure (see below).
3	Identify an expert group that could establish a candidate reference measurement procedure for PTH (probably based on mass spectrometry). Seek funding and international support to enable establishment and validation of the candidate reference measurement procedure.
4	Establish a group to examine existing and new evidence about the clinical requirements of a PTH assay and the performance goals to meet those requirements. Issues considered should include bias, imprecision, specificity (bio-intact versus intact) and biological variation.

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Received for publication: 25.7.11; Accepted in revised form: 16.9.11

## Appendix

Attendees at the London meeting in September 2010 were Alison Almond, Scottish Renal Registry; Gordon Avery, Abbott Diagnostics; Barth, Julian, UK Association of Clinical Biochemists (ACB); Graham Beastall; Frank Blocki, DiaSorin; Chris Burns, National Institute of Biological Standards and Control; Etienne Cavalier, University of Liège, Belgium; Anne Dawnay, UK Renal Registry; Laurence Demers, Pennsylvania State University College of Medicine and American Association of Clinical Chemistry (AACC); Craig Dixon, IDS; Agnes D'Souza, Roche Diagnostics; Andy Ellis, UK National External Quality Assessment Service [UK NEQAS (Edinburgh)]; Sherry Faye, Beckman Coulter Eurocenter, Switzerland; William

D. Fraser, University of East Anglia; Edmund Lamb, Kent and Canterbury Hospital; Ernst Lindhout, Future Diagnostics; Stefan Lorenz, Abbott Diagnostics; Stefaan Marivoet, Tosoh; Jonathan Middle; Alicia Racelis, Siemens Healthcare Diagnostics; Jean-Claude Souberbielle, Hôpital

Necker-Enfants maladies, Paris; Stuart Sprague (by teleconference), Division of Nephrology and Hypertension, NorthShore University HealthSystem, University of Chicago Pritzker School of Medicine, Illinois and Catharine Sturgeon, Royal Infirmary, Edinburgh.