
Parathyroid Hormone

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GUIDELINES

- a. For patients on dialysis, levels of intact-parathyroid hormone (iPTH) that are within or below the normal range of the assay are generally indicative of low bone turnover and levels of iPTH that are greater than 2–3 times the upper normal range of the assay are generally indicative of high bone turnover. (Level I evidence)
- b. For the non-invasive assessment of renal osteodystrophy, assays for iPTH and PTH(1–84) have similar diagnostic value. (Level II evidence)

SUGGESTIONS FOR CLINICAL CARE

(Suggestions are based on Level III and IV evidence)

- For patients on dialysis, normal bone turnover is generally associated with levels of iPTH that are 1–3 times the upper normal range of the assay. For bone, the suggested target iPTH is from 1–3 times the upper normal range of the assay, with most opinion favouring 2–3 times. (Opinion)
- Markedly elevated levels of iPTH are associated with an increased risk of cardiovascular mortality and sudden death. Values that are > 7 times the upper normal range of the iPTH assay should generally be avoided. (Level III evidence)
- When iPTH levels are below 7 times the assay upper range, therapies to achieve bone targets for PTH that compromise target levels of serum calcium, phosphate or the calcium x phosphate product should be used with caution. (Opinion)
- PTH levels determined using assays for iPTH and PTH(1-84) correlate closely. However, iPTH assays vary in their detection of C-terminal PTH fragments and values may differ between assays (Level III evidence). PTH(1–84) assays that measure the full length polypeptide are reported to be more directly comparable. (Level III evidence) For comparison of PTH values in multicentre clinical trials, the use of a PTH(1–84) assay may be preferable. (Opinion)
- In assessing bone turnover, the value of the PTH(1–84)/ non-PTH(1–84) ratio remains uncertain. (Opinion)

- **PTH levels should be checked monthly when changes of therapy that may influence PTH are introduced and 2–3 monthly in other patients on dialysis. (Opinion)**
- **PTH levels may respond rapidly to interventions that influence calcium, phosphate and vitamin D levels but bone and cardiovascular responses may take months to years. Bone and cardiovascular outcomes are more likely to correlate with PTH trends or averaged values than with isolated PTH values. (Opinion)**

BACKGROUND

Patients on dialysis commonly have abnormalities of PTH secretion, among the causes of which are disturbed regulation of serum phosphate, calcium, calcitriol, bone morphogenetic protein-7 and the use of medications that include calcium and aluminium-based phosphate binders and active vitamin D. Levels of PTH have a major influence on bone turnover and mineral metabolism and most patients on dialysis have regular PTH measurements. The possibility to modulate PTH levels has improved with the introduction of a calcimimetic drug, vitamin D analogues and newer phosphate binders. For PTH monitoring to provide the maximum benefit to patients, therapeutic targets are necessary and clinicians need to know the strengths and weaknesses of studies on which these targets are based.

Higher levels of serum calcium, phosphate and the calcium x phosphate product have been associated with coronary artery calcification and increased morbidity and mortality (Goodman et al 2000, Marco et al 2003, Block et al 2004, Stevens et al 2004). Bone turnover driven by PTH strongly influences these biochemical values and in some studies, markedly elevated levels of PTH are positively associated with all-cause and cardiovascular mortality (Ganesh et al 2001, Marco et al 2003, Block et al 2004, Young et al 2005). However, interactions of mineral metabolism, the cardiovascular system and bone are complex. Arterial calcification is reported to be more frequent in the presence of low bone turnover with mean iPTH levels at 7.5 pmol/L (71 pg/mL) (London et al 2004) and for patients with elevated levels of phosphate and calcium, mortality is reported to be higher when iPTH levels are < 3.6 times the upper normal range of the iPTH assay than for levels > 3.6 times the upper normal range (Stevens et al 2004). Mortality has also been reported to be higher if enrolment levels of iPTH are < 6.9 pmol/L (65 pg/mL), approximately the upper normal range of most assays, vs iPTH from 6.9–21 pmol/L and > 21 pmol/L (Avram et al 2001) or for unadjusted levels of iPTH < 16 pmol/L (Block et al 2004). These data possibly reflect an association of poor nutrition and lower iPTH and emphasise the need for PTH targets to be evaluated in the context of serum calcium, phosphate, the calcium x phosphate product, nutrition, other cardiovascular risk factors and variables that are positively correlated with levels of iPTH including female sex, younger age, absence of diabetes and, in studies from the USA, Afro-American race (Block et al 2004).

Because randomised controlled trials (RCTs) to assess therapeutic intervention are lacking, patient-based outcomes of PTH modulation remain uncertain. Prospective studies are needed to assess the role of therapeutic interventions on bone and the

cardiovascular system. In the meantime, these guidelines and Suggestions for Clinical Care describe some uses and limitations of PTH measurement in clinical practice and suggest target levels for iPTH that may improve patient outcomes. They should be read in conjunction with the CARI Biochemical Targets guidelines for calcium, phosphate and the calcium x phosphate product.

Some factors for consideration when assessing PTH levels in patients with chronic kidney disease (CKD) include:

- PTH levels can respond rapidly to serum calcium, phosphate or calcitriol, but bone and cardiovascular responses to PTH are likely to occur over months to years. Therefore, PTH trends or averaged PTH values may be more useful than isolated measures.
- Heterogeneous study populations may influence association studies and present difficulties for setting PTH targets. Levels of PTH vary for patients with and without diabetes, are influenced by age, sex and race (Block et al 2004) and have been reported not to correlate with bone turnover in Afro-American subjects (Sawaya et al 2003).
- The parathyroid secretes both PTH(1–84) and C-terminal PTH, in a ratio that varies with the level of serum ionised calcium. C-terminal fragments are excreted via the kidney and accumulate in patients with CKD, contributing 40%–60% of PTH in CKD Stage 5 (Lepage et al 1998, Brossard et al 2000). C-terminal PTH fragments may influence PTH resistance; being implicated in PTH-1 receptor down-regulation and anticalcaemic effects via the C-terminal PTH receptor (Fig. 1). A PTH(1–84)/ non-PTH(1–84) ratio of < 1 has been reported to correlate with low bone turnover (Monier-Faugere et al 2001) but this association has not been confirmed in other studies (Goodman et al 2003).
- Recently developed assays for PTH(1–84) bind antigenic determinants in the N-terminal 1–4 region and the C-terminal region. On the other hand, standard assays for intact-PTH react with amino acids in the 14-34 and C-terminal regions, thus detecting PTH(1–84) and a mixture of long C-terminal PTH fragments, predominantly PTH(7–84). Depending on the N-terminal binding epitope, iPTH values using different commercial assays that detect C-terminal PTH fragments of varying lengths may not be directly comparable (Fig. 2).

Optimal PTH targets for bone (assessed by bone histomorphometry) may differ from those that are optimal for the cardiovascular system (Block et al 2000). Whereas a linear association has been reported for increasing mortality and levels of serum phosphate, adjusted calcium and the calcium x phosphate product, associations of iPTH and mortality are generally only significant for iPTH levels above 52-95 pmol/L (Ganesh et al 2001, Block et al 2004), with a trend to increased mortality also reported for iPTH levels below 3.5 pmol/L (Ganesh et al 2001) and 27 pmol/L (Stevens 2004). Therefore, therapeutic interventions to achieve PTH targets that compromise targets for calcium, phosphate or the calcium phosphate product may be counterproductive.

Few patients meet CARI or K/DOQI targets for levels of calcium, phosphate and PTH over a 12-month period, suggesting that successful implementation of these biochemical goals will require significant changes in management.

SEARCH STRATEGY

Databases searched: MeSH terms and text words for parathyroid hormone were combined with MeSH terms and text words for chronic kidney disease and renal replacement therapy. These were combined with MeSH terms and text words for bone disease, bone biopsy, bone histomorphometry, bone mineral density, bone turnover markers, biochemical markers and cardiovascular disease. The searches were carried out in Medline, Embase and the Cochrane Controlled Trial Register (in May 2005) and abstracts of scientific meetings were searched for randomised controlled trials.

Latest search date: May 2005.

WHAT IS THE EVIDENCE?

Guidelines

For patients on dialysis, levels of intact-PTH (iPTH) that are within or below the normal range of the assay are generally indicative of low bone turnover and levels of iPTH that are greater than 2–3 times the upper normal range of the assay are generally indicative of high bone turnover. (Guideline a)

Using the studies of Hutchison et al (1993), Qi et al (1995), Wang et al (1995), a paediatric study of Ziolkowska et al (2000) and a study that assessed intact, mid- and C-terminal PTH assays (Solal et al 1991), receiver-operator characteristics (ROC) curves were constructed for the association of serum PTH values and bone histomorphometry. This analysis in the 2003 K/DOQI bone guidelines (National Kidney Foundation 2003) can be considered a diagnostic meta-analysis (Level I evidence). A threshold for iPTH between 15.9–21.2 pmol/L (150–200 pg/mL) was 93% sensitive (95% CI: 87–97%) and 77% specific (95% CI: 62–87%) for the presence of high turnover bone disease. An iPTH threshold < 6.3 pmol/L (60 pg/mL) was 70% sensitive and 87% specific for the presence of low turnover bone disease. There are a number of limitations to these analyses. Data for adult dialysis patients used in the meta-analyses date from 1991–95 and changed dialysis practices and medical management may have altered these associations. Unfortunately, prospective studies have not been performed to assess the effect of modulation of PTH levels on bone histomorphometry.

Couttenye et al (1996) reported a study of 103 patients on haemodialysis, having a bone biopsy and serum collected for iPTH, bone specific alkaline phosphatase and osteocalcin levels. Adynamic bone disease was present in 37% of patients. Constructing ROC curves, an iPTH < 150 pg/mL (15.9 pmol/L) was the optimal cut-off level for a diagnosis of low bone turnover, with lower levels 80.6% sensitive and 76.2% specific for adynamic bone disease. Applying Bayes' theorem and with an estimated prevalence of adynamic bone disease in the dialysis population of up to

35%, the iPTH cut-off value was calculated to have a positive predictive value of 65% (Level II evidence).

Canavese et al (1998) reported a study that assessed the association of serum PTH, alkaline phosphatase, osteocalcin, calcitonin, baseline and post-deferrioxamine aluminium, beta 2 microglobulin, ferritin and bone mineral density with bone histomorphometry from 80 patients on chronic dialysis. Of 80 transiliac bone biopsies, 14 were collected at autopsy. Peak values of predialysis blood samples taken the month before bone biopsy were used for correlations. Osteitis fibrosa was diagnosed in 36%, mixed osteodystrophy in 37.5%, aluminium-induced osteomalacia in 21% and adynamic bone disease in 8.7%. Aluminium staining was detected in 15 patients with a positive DFO test. A positive correlation was detected between levels of iPTH and woven osteoid, bone resorption, osteoclastic index, total labeled bone surface, bone formation and mineral apposition rates ($P < 0.001$), confirming the association of increasing levels of iPTH and histomorphometric indices of bone turnover. However, no iPTH 'cut points' are described for these associations and tetracycline labeling was used in only 66 of the patients (Level II evidence).

Coen et al (2002) reported a study in which 35 patients on haemodialysis underwent blood testing and bone biopsy. For hyperparathyroid bone disease, iPTH values (mean \pm SD) were 776 ± 660 pg/mL (82 ± 70 pmol/L), 263 ± 296 pg/mL (28 ± 31 pmol/L) for mixed osteodystrophy and 104 ± 83 pg/mL (11 ± 8.8 pmol/L) for low bone turnover ($P < 0.01$; ANOVA). The study is limited in having a single blood sample for PTH levels and bone histomorphometry was available for only 29/35 patients (Level II evidence).

For the non-invasive assessment of renal osteodystrophy, assays for intact-PTH and PTH(1–84) have similar diagnostic value. (Guideline b)

Monier-Faugere et al (2001) reported a study in which bone biopsies and blood samples for the determination of bone turnover indices, iPTH and PTH(1–84) were obtained in 51 adult patients on haemodialysis ($n = 32$) and continuous ambulatory peritoneal dialysis (CAPD) [$n = 19$] not treated with drugs affecting bone, such as vitamin D and corticosteroids. Blood levels of C-terminal PTH fragments were calculated by subtracting PTH(1–84) from iPTH values. Patients were classified according to their levels of bone turnover, determined as activation frequency. Levels of both iPTH and PTH(1–84) discriminated between high or normal and low bone turnover ($P < 0.01$). PTH(1–84) and the ratio PTH(1–84)/non-PTH(1–84) correlated with bone turnover ($r = 0.73$ and $r = 0.68$; $P < 0.01$, respectively). The values for PTH(1–84) and iPTH that best differentiate between low and normal or high bone turnover are not provided in the text (Level II evidence).

Salusky et al (2003) reported on 33 patients aged 12.8 ± 4.4 years who were treated with continuous cycling peritoneal dialysis (CCPD). These patients underwent blood testing and bone biopsy. PTH levels were measured as iPTH and PTH(1–84). The PTH levels determined by both assays were highly correlated ($r = 0.89$, $P < 0.001$). Correlations were similar for the association of iPTH to bone formation ($r = 0.67$, $P < 0.0001$) and PTH(1–84) to bone formation ($r = 0.64$, $P < 0.0001$). However, this was a paediatric study population and the associations may not be applicable to adults (Level II evidence).

In the study of Coen et al (2002), in which 35 patients on haemodialysis underwent blood testing and bone biopsy, the correlation coefficient for iPTH and PTH(1–84) assays was 0.9833. These PTH assays had similar accuracy for the diagnosis of low bone turnover versus mixed osteodystrophy and high bone turnover, with areas under the ROC curves of 0.859 and 0.842, respectively. The assays did not differ in discrimination of any bone histomorphometric parameter other than eroded surface ($P < 0.01$ for PTH(1–84) vs $P < 0.001$ for iPTH).

Reichel et al (2003) conducted a study of 141 unselected patients on haemodialysis, who were tested using the Nichols, Elecsys and Scantibodies assays for iPTH and PTH(1–84), together with indirect biochemical markers of bone turnover using assays for TRAP 5b (Suomen Bioanalytikka, Oulo, Finland) and bone specific alkaline phosphatase (Beckman-Coulter Inc, Fullerton, CA, USA). The three intact PTH assays used yielded results that were comparable. Correlation coefficients of assays for iPTH and PTH(1–84) and of the three intact PTH assays were 0.97–0.98. The capacity of all PTH assays to predict serum concentrations of biochemical bone markers was comparable. However, the value of this study is limited because indirect biochemical markers of bone turnover were assessed rather than bone histomorphometry (Level III evidence).

Suggestions for clinical care

1. For patients on dialysis, normal bone turnover is generally associated with levels of iPTH that are 1–3 times the upper normal range of the assay. For bone, the suggested target iPTH is from 1–3 times the upper normal range of the assay, with most opinion favouring 2–3 times.

Prospective studies to assess the impact of maintaining target levels of PTH on bone histomorphometry are not available but association studies included in the K/DOQI guidelines (National Kidney Foundation 2003) and those of Couttenye et al (1996), Canavese et al (1998) and Coen et al (2002) support this suggestion for clinical care.

2. Markedly elevated levels of iPTH are associated with an increased risk of cardiovascular mortality and sudden death. Values that are > 7 times the upper normal range of the iPTH assay should generally be avoided.

Ganesh et al (2001) described two national samples of US haemodialysis patients ($n = 12833$) dating from 1990 and 1993, who were studied to test the hypothesis that elevated phosphate increases the risk of cardiac death. Laboratory data was from hospital records at the start of or 1 month after commencement of treatment. Data on cause of death were obtained from the Health Care Financing Administration. PTH levels were available on only 6634 patients. Over a 2-year follow up, 4120 deaths occurred among the 12833 patients.

A higher mortality was associated with higher levels of serum phosphate and an increased incidence of sudden death and death from coronary artery disease was associated with an increased calcium x phosphate product. Log PTH was associated with cerebrovascular and sudden death, and death from other cardiac and unknown

causes. Sudden death was related to log PTH in a non-linear fashion and was assessed by iPTH quintiles. In this analysis, and after adjustment for phosphate and the calcium x phosphate product, a significant association of iPTH and sudden death was found for patients in the iPTH quintile > 495 pg/mL (52 pmol/L) vs 91–197 pg/mL (9.6–21 pmol/L; RR 1.25, P < 0.05).

Limitations of this study include the means of obtaining data and categorising causes of death, which were open to error. Only single biochemical values were available on most patients and the assay for PTH was not uniform. The quintile of iPTH associated with an increased incidence of sudden death included patients with iPTH levels up to 9476 pg/mL (1004 pmol/L), so patients with extreme levels of iPTH may have driven this association. Due to the racial, social demographic mix, and high incidence of diabetes in the US population, these results may not be applicable to other populations. Lastly, prevalent patients in cohort studies such as this are at different stages of their illness and association studies do not prove causality (Level III evidence).

Marco et al (2003) reported on 143 Caucasian, Spanish haemodialysis patients, who were followed for 6 years. The end-point was death or censored due to transplantation. Intact-PTH results were categorised as < 12 pmol/L, 12–50 pmol/L and > 50 pmol/L and analysed using multiple Cox models. Biochemical data was the mean of 3 (4-monthly) measures taken the year prior to the study.

At 6 years, 27.2% of patients were alive on haemodialysis. A total of 24.4% had died of cardiovascular causes, 34.9% of non-cardiovascular causes and 13.2% had been transplanted. Univariate analysis of iPTH groups did not distinguish between cardiovascular and non-cardiovascular death but after adjusting for co-variables (age, gender, diabetes, smoking and serum phosphate), the relative risk (RR) of death was 3.9 (CI: 1.2–12.9; P = 0.02) for iPTH levels of 12–50 pmol/L vs > 50 pmol/L. This compared to a RR of death of 2.8 (CI: 1.1–7.1) for a calcium x phosphate product > 4.3 mmol²/L² (Level III evidence).

Block et al (2004) described mortality and morbidity data collected on 40,538 haemodialysis patients with at least one determination of serum phosphate and calcium during the last 3 months of 1997. Intact-PTH values, available for 5995 patients, were stratified into 4 categories of < 150 pg/mL (16 pmol/L), 150–300 pg/mL (16–32 pmol/L), 300–600 pg/mL (32–64 pmol/L) and > 600 pg/mL (64 pmol/L). Follow up was for 12–18 months.

The annual mortality rate was 19.5%. After adjustment for case mix and laboratory variables, serum phosphate concentrations > 5.0 mg/dL (1.6 mmol/L) and higher adjusted serum calcium concentrations were associated with an increased risk of death. PTH values unadjusted for age, sex, race and diabetes showed an increased RR of death in patients with low vs high levels of PTH, of borderline significance. However, adjusted levels of iPTH ≥ 600 pg/mL (64 pmol/L) were associated with an increase in the relative risk of death, most of which was attributable to patients with iPTH levels > 900 pg/mL (95 pmol/L). Severe hyperparathyroidism (PTH > 1200 pg/mL [127 pmol/L]) was associated with increased all-cause hospitalisation. Hyperphosphataemia and hyperparathyroidism (PTH > 900 pg/mL [95 pmol/L]) were significantly associated with cardiovascular hospitalisation and PTH was weakly

associated with fracture-related hospitalisation. Limitations of this US association study are similar to those of the study by Ganesh et al (2001) described above. Single PTH levels (that may not reflect PTH trends) were available for only 14.8% of patients. Diagnostic codes were used to assess outcomes and may have missed significant events (Level III evidence).

Young et al (2005) reported on the Dialysis Outcomes and Practice Patterns Study (DOPPS), which described all-cause and cardiovascular mortality for 17,236 randomly selected patients from 307 representative dialysis facilities in the US, Europe, and Japan between 1996 and 2001. Intact-PTH assays were used.

All-cause mortality was significantly and independently associated with serum concentrations of phosphate, calcium and the calcium x phosphate product, dialysate calcium and iPTH (RR 1.01 per 100 pg/dL [10.6 pmol/L], $P = 0.04$). Cardiovascular mortality was significantly associated with serum phosphate, calcium, the calcium x phosphate product and PTH (RR 1.02, $P = 0.03$). High levels of PTH were, among other factors, directly associated with black race, and were inversely related to treatment and the presence of diabetes in Japan. These findings may not apply to populations of different racial mix (Level III evidence).

3. When iPTH levels are below 7 times the assay upper range, therapies to achieve bone targets for PTH that compromise target levels of serum calcium, phosphate or the calcium x phosphate product should be used with caution.

Unlike associations of mortality and levels of phosphate, calcium or the calcium x phosphate product, elevated PTH levels are associated with mortality only when markedly raised. In the study of Ganesh et al (2001), for each 1 mg/dL increase in the level of multivariate-adjusted serum phosphate, the risk of coronary artery disease (CAD) increased by 9% and sudden death by 6%. A linear relationship was found for sudden death or CAD and the calcium x phosphate product. Log iPTH was associated with cerebrovascular and sudden death, plus death from unknown or other cardiovascular causes. However, when iPTH was assessed by quintiles (0–32, 33–90, 91–197, 198–495 and 496–9478 pg/mL), compared to patients with an iPTH level in the range 91–197 pg/mL (9.6–21 pmol/L), a significant association with sudden death was only present for patients with iPTH levels > 495 pg/mL (> 52 pmol/L; RR 1.25, $P < 0.05$) [Level III evidence].

In the association study of Block et al (2004), an increased relative risk of mortality was associated with elevated iPTH levels adjusted for case mix and other laboratory variables, largely driven by values of iPTH over 95 pmol/L. On the other hand, the RR of mortality increased across the range of serum calcium levels adjusted for albumin and of multivariate-adjusted serum phosphate. Unadjusted levels of iPTH below 150 pg/mL (15.9 pmol/L) were associated with increased mortality but this association was not present when adjusted for case-mix and other co-variables (Level III evidence).

Stevens et al (2004) reported on 515 prevalent dialysis patients in British Columbia, Canada, in 2000. Data was available for serum calcium, phosphate and iPTH. Over 3 years, 185 deaths occurred and the relative risk of mortality was higher for those patients with higher levels of serum phosphate (> 2.26 mmol/L) and higher levels of

the calcium x phosphate product ($> 5.64 \text{ mmol}^2/\text{L}^2$). Mortality did not differ for patients with levels of iPTH above or below 27.3 pmol/L (iPTH assay normal upper range 7.6 pmol/L). When combinations of calcium, phosphate and iPTH were assessed, the relative risk of mortality was greater for patients with a combination of adjusted serum calcium $> 2.5 \text{ mmol/L}$, phosphate $> 1.78 \text{ mmol/L}$ and iPTH $< 27.3 \text{ pmol/L}$ than for similar calcium and phosphate levels but with an iPTH $> 27.3 \text{ pmol/L}$. In this association study, a single blood sample was drawn for iPTH, calcium and phosphate. While elevated levels of phosphate but not iPTH were independently associated with mortality, no conclusions can be drawn regarding the possible effect of therapeutic interventions (Level III evidence).

4. PTH levels determined using assays for iPTH and PTH(1–84) correlate closely. However, iPTH assays vary in their detection of C-terminal PTH fragments and values may differ between assays. PTH(1–84) assays that measure the full length polypeptide, are reported to be more directly comparable. For comparison of PTH values in multicentre clinical trials, the use of a PTH(1–84) assay may be preferable.

Lepage et al (1998) conducted a study that compared the ability of three commercial kits (Nichols [NL], Incstar [IT], and Diagnostic System Laboratories [DSL]) to measure PTH in sera from 112 patients with CKD and to detect PTH(1–84) and non-(1–84)PTH on HPLC profiles of pooled serum from patients with uraemia and iPTH concentrations ranging from 10–100 pmol/L. Intact-PTH concentrations measured with the three assays in the 112 uraemic samples were highly correlated ($r^2 \geq 0.89$, $P < 0.0001$). However, actual values measured with NL were on average, 23% higher than IT and values measured with DSL were 23%–56% higher than IT. The NL assay detected significantly more non-PTH(1–84) than did the DSL or IT assays. Limitations of the study are that indirect biochemical markers of bone turnover were assessed, but the study did not aim to assess the relationship of these to bone histomorphometry. The CKD stage of patients was not defined (Level III evidence).

The study of Reichel et al (2003) has been referred to above. The correlation coefficient of assays for iPTH and PTH(1–84) and of the 3 intact assays with each other was 0.97–0.98 and the iPTH assays used in this study (Elecsys, Scantibodies and Nichols) yielded results that were comparable (Level III evidence).

Martin et al (2004) reported a study in which sera were collected from 23 haemodialysis patients for the measurement of PTH(1–84) using the cyclase activating PTH (CAP) assay (Scantibodies Laboratory Inc., Santee, CA, US) and Bio-Intact PTH (Nichols Institute Diagnostics, San Clemente, CA, US) assay. Values were highly correlated with the results being virtually identical, and the report concluded that assays for PTH(1–84) should provide the means to obtain meaningful target therapeutic ranges that are reproducible across different laboratories for the management of hyperparathyroidism (Level III evidence).

In the brief communication of Terry et al (2003), 10 sera from healthy volunteers and 10 from haemodialysis patients were assayed using both the Scantibodies and Nichols PTH(1–84) assays. Deming regression analysis comparing the 2 assays yielded a slope of 0.904, which was different from 1. Nevertheless, results of the

assays correlated closely ($r^2 = 0.987$). For values of PTH(1–84) > 120 pg/mL (12.7 pmol/L), the Scantibodies assay may give a value approximately 10% greater than the Nichols assay (Level III evidence).

Shigematsu et al (2004) describe their study in which serum was obtained from 80 haemodialysis patients and assayed using the Scantibodies Total PTH (iPTH) and Whole PTH(1–84) assays and the Nichols Institute Intact PTH and Bio-Intact PTH(1–84) assays. Pooled serum was spiked with synthetic PTH(7–84). Samples were sent monthly for 3 months, to a reference laboratory for PTH measurement. The PTH(1–84) assays provided almost identical values ($r = 0.99$; $P < 0.0001$). For the intact assays, identical samples measured by the Scantibodies Total PTH assay gave lower values than the same sample measured by the Nichols Intact-PTH assay, although the 2 assays correlated ($r = 1$). Total and iPTH assays differed in their recognition of synthetic PTH(7–84), measuring 57% and 93%, respectively.

5. In assessing bone turnover, the value of the PTH(1–84)/non-PTH(1–84) ratio remains uncertain.

Monier-Faugere et al (2001) reported a study in which bone biopsies and a single blood sample were collected from 51 adult patients on dialysis. The patients were not on treatment with drugs likely to affect bone, such as vitamin D or corticosteroids. Blood levels of long C-terminal PTH fragments were calculated by subtracting levels of PTH(1–84) from iPTH. Patients were classified according to their levels of bone turnover (assessed as activation frequency), based on bone histomorphometry. The PTH(1–84)/non-PTH(1–84) fragment ratio was the best predictor of bone turnover. A ratio > 1 predicted high or normal bone turnover (sensitivity 100%), whereas a ratio < 1 indicated a high probability of low bone turnover (sensitivity 87.5%) (Level II evidence).

However, these results were not confirmed in the study of Coen et al (2002) assessing 35 patients on haemodialysis who underwent blood testing and bone biopsy. No association was detected between the ratio of PTH(1–84)/non-PTH(1–84) and bone histomorphometry (which was available for 29/35 patients) (Level II evidence).

In the paediatric study of Salusky et al (2003) described above, patients were grouped according to the presence or absence of secondary hyperparathyroidism on bone biopsy. The ratio of PTH(1–84)/non-PTH(1–84) did not differentiate between these groups (Level II evidence).

A review of the 3 previous studies conducted by Goodman (2003), concluded that due to conflicting data, the value of the PTH(1–84)/non-PTH(1–84) ratio was yet to be confirmed.

The PTH(1–84)/non-PTH(1–84) ratio was also assessed in the study of Reichel et al (2003), described above. No significant correlation was detected between the PTH(1–84)/non-PTH(1–84) ratio and any PTH assay or biochemical bone turnover marker tested. For 8 patients with a ratio < 1, PTH levels were lower but the mean non-PTH(1–84) concentration was similar in the two groups. In the group with a PTH(1–84)/non-PTH(1–84) ratio > 1, mean bone specific alkaline phosphatase, TRAP 5b, and osteocalcin concentrations were higher. The major limitation of this

study is that bone histomorphometry was not assessed and the lack of association of the PTH ratio and tested bone turnover markers may not reflect the potential of the ratio to predict bone histomorphometry (Level III evidence).

Nakanishi et al (2001) assessed levels of iPTH, PTH(1–84) and the calculated non-PTH(1–84) in 99 patients without diabetes who had been on haemodialysis > 10 years (16 ± 5.2 years). PTH(1–84) correlated with bone specific alkaline phosphatase but the calculated PTH(1–84)/non-PTH(1–84) ratio did not. This study did not assess the ratio in relation to bone histomorphometry (Level III evidence).

Negri et al (2003) conducted a study that assessed iPTH levels in 24 patients on CAPD. Of these, 15 had levels of iPTH < 100 pg/mL (10.6 pmol/L) and were classified as having low bone turnover. PTH(1–84) and serum Cross Laps (CTX) were measured and PTH(1–84)/non-PTH(1–84) ratios were calculated. There was a close correlation between PTH(1–84), iPTH and serum Cross Laps (CTX), but ratios of PTH(1–84)/non-PTH(1–84) did not differ significantly for patients with iPTH levels above or below 100 pg/mL. This study did not assess the ratio in relation to bone histomorphometry (Level III evidence).

Suggestions for clinical care: 6 and 7.

The opinion-based suggestion for frequency of checking levels of iPTH reflects standard practice in many Australian and New Zealand dialysis units and regulatory requirements for the use of cinacalcet. The suggestion that bone and cardiovascular outcomes may correlate more closely with PTH trends or averaged values is based on parathyroid cellular proliferation occurring over weeks to months and cardiovascular changes and bone remodelling over months to years. On the other hand, calcium regulates secretion of PTH within seconds to minutes and transcriptional regulation of PTH by calcitriol and calcium occurs over hours. Therefore, single PTH levels may reflect recent therapeutic interventions but may not be indicative of longer-term outcomes.

WHAT DO THE OTHER GUIDELINES SAY?

Kidney Disease Outcomes Quality Initiative: Guideline 1.1 (p. S52-S53): Serum levels of intact plasma parathyroid hormone should be measured in all patients with CKD and GFR < 60 mL/min/1.73 m² (evidence). The target range of iPTH in patients with GFR < 15 mL/min/1.73 m² is 150–300 pg/mL (16.5–33.0 pmol/L) (National Kidney Foundation 2003).

UK Renal Association: Parathyroid hormone: (p.59): Intact-PTH concentrations should be less than four times the upper limit of normal of the assay used in patients being managed for chronic renal failure or after transplantation and in patients who have been on HD or PD for longer than three months. (B) (The Renal Association 2002).

Canadian Society of Nephrology: No recommendations.

European Best Practice Guidelines: Guideline VII.3 addresses hyperphosphataemia and calcium-phosphorus ion product, but does not address levels of PTH (ERA 2002).

International Guidelines: KD: IGO: Recommendations are based on the K/DOQI Bone and Mineral Clinical Practice Guidelines.

IMPLEMENTATION AND AUDIT

Most renal units assess iPTH levels at 2–3 month intervals. Units should undertake audits to determine which patients are attaining targets for calcium, phosphate, the calcium x phosphate product and iPTH. In some cases, patients will attain targets with minor improvements in compliance or alterations of therapy. In others, targets will prove difficult to achieve without resorting to non-calcium-, non-aluminium-containing phosphate binders, calcimimetic drugs or parathyroidectomy. However, target levels for iPTH should not be achieved at the expense of worsening levels of calcium, phosphate or the calcium x phosphate product.

SUGGESTIONS FOR FUTURE RESEARCH

The ANZDATA registry should consider collecting data prospectively, updated each survey, to include serum iPTH, calcium, phosphate, causes of hospitalisation, cardiovascular events, fracture and all-cause mortality. This would provide valuable information on the proportion of patients attaining biochemical targets and prospective data on attaining biochemical targets and subsequent morbidity and mortality. If data on therapy were collected, the impact of changes to therapy, such as the use of calcimimetics or newer phosphate binders could be assessed. There is currently little data available on the impact of these expensive therapies on important patient-based outcomes.

Much cross-sectional data correlating levels of PTH and bone histomorphometry predates current dialysis practices and therapy for hyperparathyroidism. Prospective studies to assess the influence of current therapies on levels of iPTH, biochemical bone turnover markers, and bone histomorphology would be most valuable. Cross-sectional studies of patients currently receiving dialysis, with correlation of bone histomorphometry to levels of PTH(1–84), iPTH and bone turnover markers not influenced by renal function, such as bone specific alkaline phosphatase and tartrate-resistant acid phosphatase 5b, may also be useful. Combinations of PTH and newer bone turnover markers may provide an improved means of non-invasively assessing bone histomorphometry.

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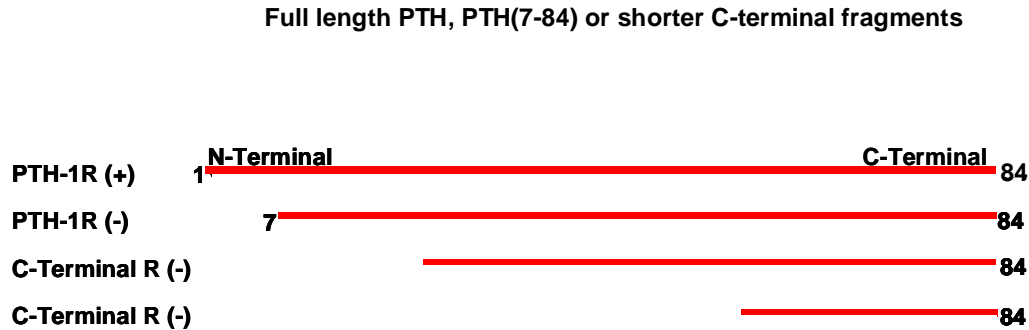
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APPENDICES

Fig. 1

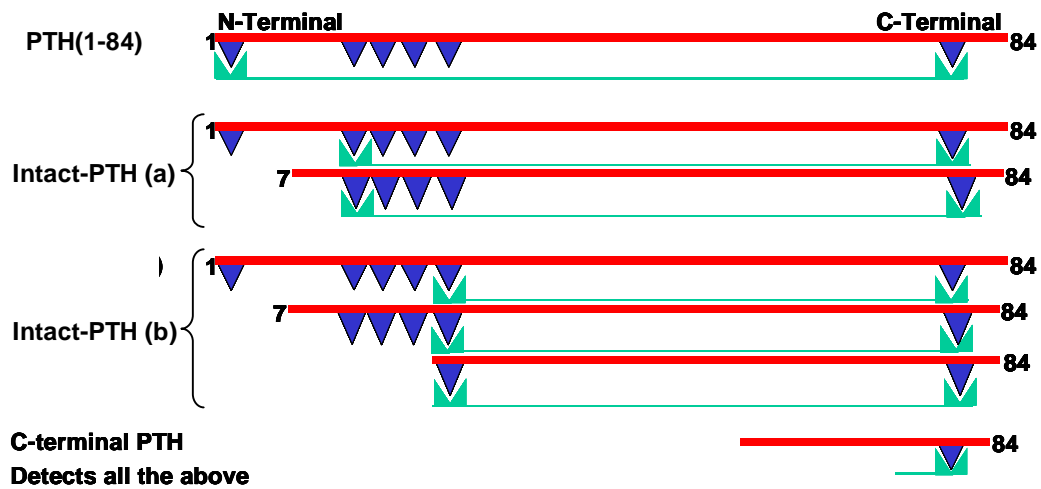
PTH receptors and their calcaemic / anti-calcaemic actions



PTH(1–84) binds to the PTH–1 receptor (PTH–1R) and is calcaemic (+). PTH(7–84) may antagonise the actions of PTH receptor agonists by downregulating the receptor and inducing receptor endocytosis, thus having an anti-calcaemic effect (-) (Sneddon et al 2004, Friedman 2004). Short C-terminal fragments (particularly those fragments shorter than 55–84) account for most of the PTH resistance seen in CKD, through binding to a C-terminal receptor (C-terminal R). Activation of this receptor, expressed on osteoclast precursors and possibly on marrow stromal cells that support osteoclast formation and activity, can inhibit bone resorption, at least in part by reducing the rate of formation of new osteoclasts (Murray et al 2005).

Fig. 2

Specificity of PTH assays



PTH assays are shown as green bars with antibodies directed to PTH binding sites. Assays for PTH(1–84) bind determinants in the N-terminal 1–4 and C-terminal region. These assays detect PTH(1–84) and may detect short, C-terminally truncated fragments.

Two intact-PTH assays (a) and (b) are shown, binding full length PTH, PTH(7–84) and due to different antigenic determinants in the 15–34 region, differing amounts of shorter fragments. Assays specific for C-terminal PTH recognise determinants in the PTH 69–84 region and depending on affinity, can bind all of the above.