The diagnosis of secondary hyperparathyroidism

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Introduction

To most physicians, the diagnosis of hyperparathyroidism (HPT) means an elevated parathyroid hormone (PTH) level as measured by a radioimmunoassay for PTH. However, to the nephrologist, the presence of HPT is generally accepted, but the major concern is how to evaluate the magnitude of HPT. Furthermore, to the nephrologist, the diagnosis of HPT often means more than a measured PTH level, but rather knowing that the PTH level reflects the effects of PTH on an end-organ such as bone. Further complicating the situation is that during the past 25 years at least four different PTH assays, which recognize different amino acid sequences of PTH, have been developed to evaluate the magnitude of HPT. Two additional factors also affect the interpretation of the PTH assay. These are the ambient serum calcium concentration and the presence of renal failure. Since PTH secretion is stimulated by hypocalcemia and inhibited by hypercalcemia, an interpretation of a PTH value must take into consideration the serum calcium concentration. Since certain PTH assays, such as the carboxy-terminal (C) and mid-region (MM), measure fragments of PTH known to accumulate in renal failure, PTH values as measured by these assays will be different in renal failure; furthermore, the information provided by these PTH assays may be different in the steady state as opposed to dynamic testing where PTH levels are changing rapidly in response to changes in the serum calcium concentration. Finally, in addition to the PTH assay, other biochemical tests have been used to evaluate the effects of PTH on bone. My objective is to evaluate how biochemical tests correlate with the extent and type of bone disease in the azotemic and dialysis patient. However, my primary focus will be the PTH assay in the diagnosis of secondary hyperparathyroidism.

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The PTH assay in renal failure

Since HPT is known to develop in early renal failure, several studies have measured PTH levels to determine if the magnitude of HPT correlates with the progression of renal failure[1-3]. Three such studies are presented in Table I; in each of these studies, a different PTH assay was used A C-PTH assay was used in the study in children by Hodson et al.[1], an amino (N) terminal PTH assay in the study by Pitts et al.[2], and an immunoradiometric (IRMA) assay for intact PTH in the study by Reichel et al.[3]. In each study, PTH levels were stratified for the degree of renal failure and increased as renal failure progressed. However, only

Table I. A comparison of different PTH assays and serum alkaline phosphatase stratified for the magnitude of renal failure

Hodson et al. (1) [a, b]		
GFR (ml/min/m²)	**C-PTH (ng/ml)**	**Alkaline phosphatase (U/L)**
Normal	0.30 ± 0.15	150 ± 75
50 to 80	0.52 ± 0.54	236 ± 70
30 to 49	0.52 ± 0.37	248 ± 67
20 to 29	1.14 ± 0.96	225 ± 66
5 to 19	2.52 ± 1.20	406 ± 241

Pitts et al. (2)	
GFR (ml/min)	**N-PTH (ng/ml)**
107 ± 36 (Normal)	11 ± 8
64 ± 14	22 ± 11
28 ± 5	46 ± 31 *
10 ± 4	145 ± 136 *

Reichel et al. (3)			
GFR (ml/min)	**PTH (pmol/L)**	**Above normal**	**Alkaline phosphatase (U/L)**
Normal	3.5 (2.3-4.9)	0/22	
60-90	5.6 (2.2-13) *	6/19	115
40-60	8.1 (2.9-24) **	12/22	103
20-40	13 (5.4-59) **	20/22	125

Mean ± SD
[a] Reference number in parenthesis.
[b] Statistical analysis not provided for study.
* $P < 0.05$ vs Normal.
** $P < 0.05$ vs Normal and previous value.

Table II. A correlation of different PTH assays with parameters of bone histology

First author	Year	Reference	Osteoblast surface	Osteoclast surface	Bone formation rate
Correlation of C-PTH with Bone Histology					
Hruska	1978	4	r = 0.62	r = 0.51	–
Evans	1982	5	r = 0.74	r = 0.74	r = 0.89
Hodson	1982	1	–	r = 0.66	NS
Felsenfeld	1982	6	–	r = 0.93	–
Voigts	1984	7	r = 0.40	r = 0.31	–
Chan	1985	8	r = 0.66	r = 0.54	–
Charhon	1986	9	r = 0.78	r = 0.73	r = 0.74
Salusky	1988	10	–	r = 0.61	r = 0.55
Solal	1991	11	r = 0.39	r = 0.44	r = 0.56
Correlation of N-PTH with Bone Histology					
Voigts	1984	7	r = 0.73	r = 0.66	–
Malluche	1984	12	r = 0.72	r = 0.56	–
Piraino	1988	13	r = 0.54	r = 0.58	r = 0.55
Andress	1989	14	r = 0.76	r = 0.67	r = 0.53
Correlation of intact PTH with Bone Histology					
Solal	1991	11	r = 0.42	r = 0.51	r = 0.63
Quarles	1992	16	r = 0.81	r = 0.66	r = 0.84

in the study by Reichel et al. which measured intact PTH, was there a significant difference between normals an patients with early renal failure. Serum alkaline levels were provided in two studies[1,3] and were much less discriminating than PTH at separating the stages of renal failure.

Correlation of parameters of bone histology with the PTH assay

Since the C-PTH assay was the most widely available PTH assay 10 to 15 years ago, the largest number of studies correlating PTH levels with bone histology was performed with this assay. As can be observed in Table II, in the nine studies listed, the correlation between C-PTH and the osteoblast surface, bone formation rate, and osteoclast surface were, for the most part, significant with r values that ranged from 0.31 to 0.93. However, it should also be added that even though all these studies used a PTH assay which primarily recognized the carboxy-terminal fragment of PTH, these assays may not have been entirely comparable; this comment also applies to the N-PTH and MM-PTH assays.

Table II also includes four studies in which a N-PTH assay was used and two more recent studies in which an IRMA assay for intact PTH was used. All the studies using the N-PTH assay noted a significant correlation between PTH and the osteoblast surface, the bone formation rate, and the osteoclast surface; r values ranged from 0.53 to 0.76. In the two studies in which intact PTH was measured, the r values for the three histologic parameters ranged from 0.43 to 0.84. In one study, three PTH assays were used simultaneously[11]. Respective r values for the C-PTH, MM-PTH, and intact PTH levels and the osteoblast surface were 0.39, 0.38, and 0.42; for the bone formation rate, 0.56, 0.45, and 0.63; and for the osteoclast surface, 0.44, 0.38, and 0.51. Thus, while none of the correlations were quite as good as in some other studies, these data do suggest these assays are comparable when applied toward bone histology.

The data presented in Table II, would suggest that none of the three different PTH assays offers a clear advantage when PTH is correlated with bone histology in the dialysis patient. It may be that in the steady state condition, a sensitive PTH assay of any type, provides a reasonable evaluation of the effect of PTH on bone.

Correlation of parameters of bone histology with other biochemical tests

Besides PTH, several other biochemical tests have been used to evaluate the degree of bone activity. These have included serum alkaline phosphatase, osteocalcin, and insulin-like growth factor I (IGF-1). In two studies, serum osteocalcin, alkaline phophatase, and PTH were measured in dialysis patients at the same time that the bone biopsy was obtained[9,12]. When the osteoblast surface, the bone formation rate, and the osteoclast surface were correlated with serum osteocalcin, alkalina phosphatase, and PTH, the correlations for each, except for some minor variations, were comparable. Similarly, in another study when serum IGF-1 and N-PTH were measured, the correlations with the bone formation rate and osteoclast number were similar[14]; however, the correlation with osteoblast surface was better with N-PTH.

Table III. Types of renal osteodystrophy

	Osteoblasts and osteoclasts	Bone formation rate	Endosteal fibrosis	PTH
Osteitis fibrosa	↑↑↑	↑↑↑	↑↑↑	↑↑↑
Mixed disease	↑↑	↑↑	↑↑	↑↑
Mild disease	↑	↑	↑	↑
Osteomalacia	↓↓	↓↓	absent or ↑	normal or ↑
Aplastic bone disease	↓↓	↓↓	absent or ↑	normal or ↑

Types of renal osteodystrophy and the PTH assay

Another means of attempting to judge whether a PTH assay is more discriminating than another is to subdivide renal osteodystrophy into different types. As listed in Table III, these types of renal osteodystrophy are characterized by different degrees of HPT and cellular activity (osteoblasts and osteoclasts), and other characteristics such as endosteal fibrosis and bone formation rate. Thus, as shown in Table III, osteitis fibrosa and mixed disease, which actually may be a spectrum of the same process, are characterized by a marked increase in cellular activity, the bone formation rate, endosteal fibrosis, and markedly elevated PTH levels. Mild disease is characterized by a minimal increase in cellular activity, the bone formation rate, endosteal fibrosis, and a moderate elevation of PTH. Conversely, both osteomalacia and aplastic bone disease are characterized by a decrease in cellular activity, low bone formation rates, minimal if any endosteal fibrosis, and a relative deficiency of PTH. Aluminum toxicity is frequently associated with osteomalacia, and sometimes associated with aplastic bone disease.

In an attempt to determine whether the different PTH assays differentiate between the types of renal osteodystrophy, seven studies were evaluated[8, 11, 16, 17]; a C-PTH assay was used in four, an intact assay in two, and a MM-PTH assay in one. Since the PTH values between assays were widely divergent, it was decided to evaluate the ratio of increase. Thus, in each study the lowest PTH level was assigned a value of 1 and each other group a multiple of 1. For instance, if the lowest mean PTH level for a group in a study was 100 pg/ml and the mean PTH level in another group in the same study was 450 pg/ml, the second group would be assigned a value of 4.5 (450 divided by 100 pg/ml). Thus, as can be observed in Figure 1, the intact PTH assay appears to better discriminate between the two groups with low bone turnover, low-turnover aluminium bone disease and aplastic bone disease and the two groups with high bone turnover, mixed disease and osteitis fibrosa.

A comparison of PTH assays

In two studies in dialysis patients, a comparison was performed between intact PTH and both C-PTH and MM-PTH[11, 18]. In a study in hemodialysis patients, Solal et al. reported a significant correlation between intact PTH

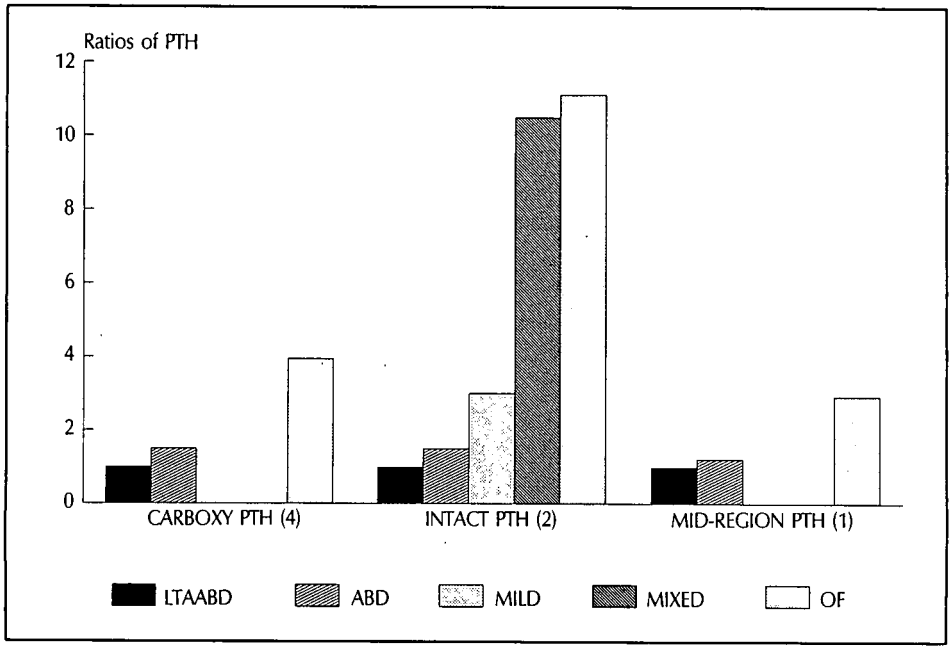

Fig. 1.—Shown are seven separate studies in which the types of renal osteodystrophy were subdivided. LTAABD is low turnover aluminium bone disease, ABD is aplastic bone disease, mild is mild hyperparathyroidism, mixed is mixed osteitis fibrosa-osteomalacia, and OF is osteitis fibrosa. Four studies used a carboxy-terminal PTH assay, two studies used an IRMA assay for intact PTH, and one study used a mid-region PTH assay. In each study, the group with the lowest PTH value was assigned a value of 1. The other groups were asigned a value which was a multiple of the lowest value. For example, if the LTAABD group had a mean value of 100 pg/ml, that group would be asigned a value of 1; if in the same study, the osteitis fibrosa group had a mean value of 1,150 pg/ml, that groups would be assigned a value of 11.5.

and C-PTH (r = 0.93) and between intact PTH and MM-PTH (r = 0.79)[11]. Martínez et al. studied both hemodialysis and CAPD patients[18]. The correlation between intact PTH and C-PTH was r = 0.89 in hemodialysis patients and r = 0.86 in CAPD patients; between intact PTH and MM-PTH, the respective correlations were r = 0.84 in hemodialysis patients and r = 0.75 in CAPD patients.

Perhaps of even greated interest in the same study by Martínez et al. was the report of differences between hemodalysis and CAPD patients in the ratios of MM-PTH and C-PTH to intact PTH[18]. The ratio of MM-PTH to intact PTH was greater in hemodialysis (55 ± 29) than in CAPD (39 ± 20) patiens ($p < 0.01$). Similarly, the ratio of C-PTH to intact PTH was greater in hemodialysis (105 ± 40) than in CAPD (59 ± 32) patients ($P < 0.001$). These findings would suggest that both MM-PTH and C-PTH are partially removed by peritoneal dialysis.

Acute changes in PTH and the PTH assay

A primary advantage of the IRMA assay for intact PTH would appear to be that it is 1) responsive to rapid changes in PTH levels, 2) not as influenced in renal failure by accumulation of PTH fragments that are dependent on renal excretion, and 3) not affected by preferential secretion of PTH fragments by the parathyroid glands during hypocalcemia and hypercalcemia. One study has compared the effect of hemodialysis on suppression of PTH as determined by an IRMA assay for intact PTH and an assay for MM-PTH[19]. The mean predialysis serum calcium was 2.23 ± 0.18 mmol/l and this increased to 2.68 ± 0.25 mmol/l at the end of hemodialysis. Intact PTH decreased by 45 % from 15.2 to 8.3 pmol/l wihile the change in MM-PTH was minimal 252 to 234 pmol/l. Thus, this study indicated that the measurement of intact PTH is better than the measurement of MM-PTH during acute changes in the serum calcium.

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