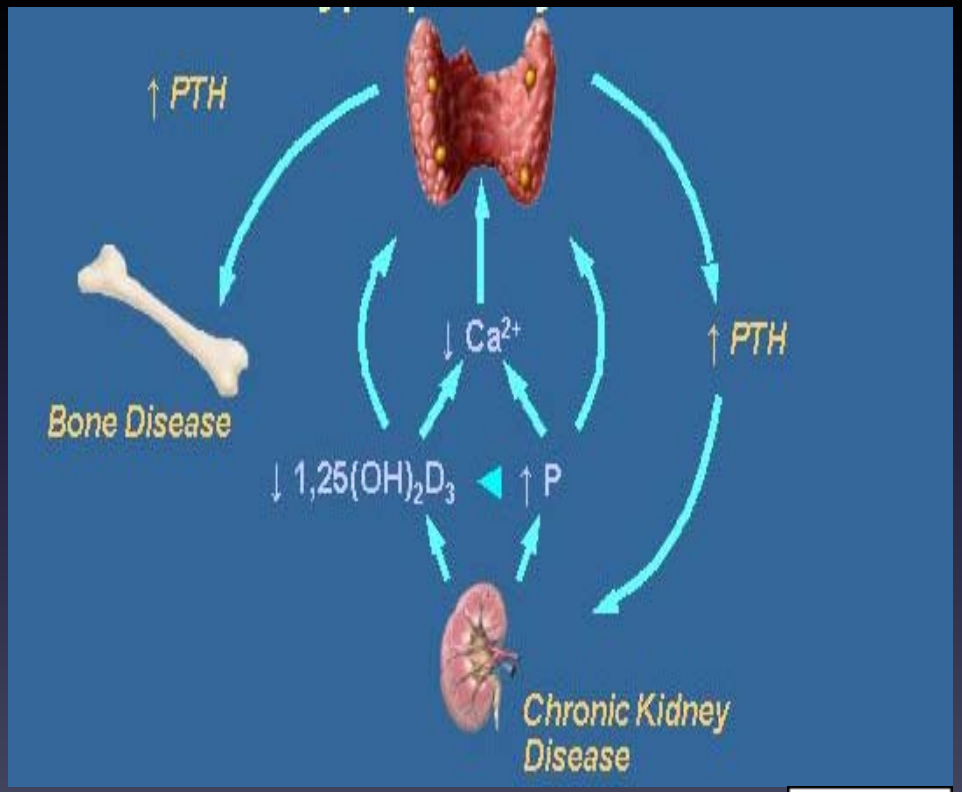
Hungry bone syndrome

Background

- In recent years, secondary hyperparathyroidism has been mainly managed by combination treatment with calcium salts and calcitriol
- Treatment is effective in early stages but as secondary PT progresses, hypercalcemia/hyperphosphatemia prevail.
- VitD metabolites, calcimimetics or Aluminium-and Ca-free phosphate-binding agents



Parathyroidectomy

Is the treatment of choice in patients with severe HPT which failed medical therapy:

--persistently high serum PTH levels (>800pg/ml) in the presence of hypercalcemia and/or hyperphosphatemia

--Bone pain, myopathy, metastatic calcifications, pruritis

Parathyroidectomy

- A relatively safe operation
- mortality of <0.7%
- morbidity in terms of laryngeal nerve palsy of <0.7%
- re-operative rate of 1.3% for control of local bleeding

Jofre et al. Kid Int. 2003; 63 (Suppl. 85): S97–S100.

Complications: Hypocalcemia

- Incidence: 20-70%
- hypoparathyroidism from removal of all parathyroid tissue
- transient vascular compromise of the remaining parathyroid tissue
- long-term hypercalcemic suppression of non-adenomatous parathyroid tissue.
- extensive remineralization of the skeleton

Hungry bone syndrome

In patients with hyperparathyroidism:

--bone formation and bone resorption are both increased, bone mass loss is due to acceleration of bone resorption that is greater than the increased mineral apposition rate.

--After correction of hyperparathyroidism, increased bone remodeling units will mineralize and balance will be towards synthesis of bone with subsequent hypocalcemia and hypophosphatemia.

Incidence

- 329 patients on HD, 30 patients on PD retrospectively examined.
- 148 pts (145 HD, 3 PD)underwent parathyroidectomy.

Table 1. Demographic data

	Patients with PTx $N = 148$	Control $N = 309$
Age *years*	49 ± 14	61.5 ± 14.9[a]
Gender *% male*	48.6%	59%[b]
Time on dialysis *years*	8.6 ± 5.8	5.5 ± 5.4[a]
Diabetic	0.7%	19.4%[a]
Nondiabetic	99.3%	80.6%

Data were performed using Student *t* test.
[a] $P < 0.001$
[b] $P < 0.05$

- 20% developed hungry bone syndrome despite high doses of oral or intravenous calcium and treatment with calcitriol

Jofre et al. Kid Int. 2003; 63 (Suppl. 85): S97–S100.

Risk factors

- Retrospective analyis of 218 patients admitted for parathyroidectomy for primary HPT
- Patients with secondary hyperparathyroidism due to ESRD were excluded.
- Variables studied: age, sex, duration of documented hypercalcemia, indication for surgery, complications attributable to hyperparathyroidism, and family history of primary hyperparathyroidism.
- Laboratory parameters analyzed: total serum Ca , inorganic Phos, albumin, Mag, Alk Phos, BUN, Cr, N-terminal PTH, serum 25hydroxyvitamin D, urine specific gravity, 24-hr urinary Ca, and cortical bone density .

Brasier et al. Am J Med 1988; 84: 654–660.

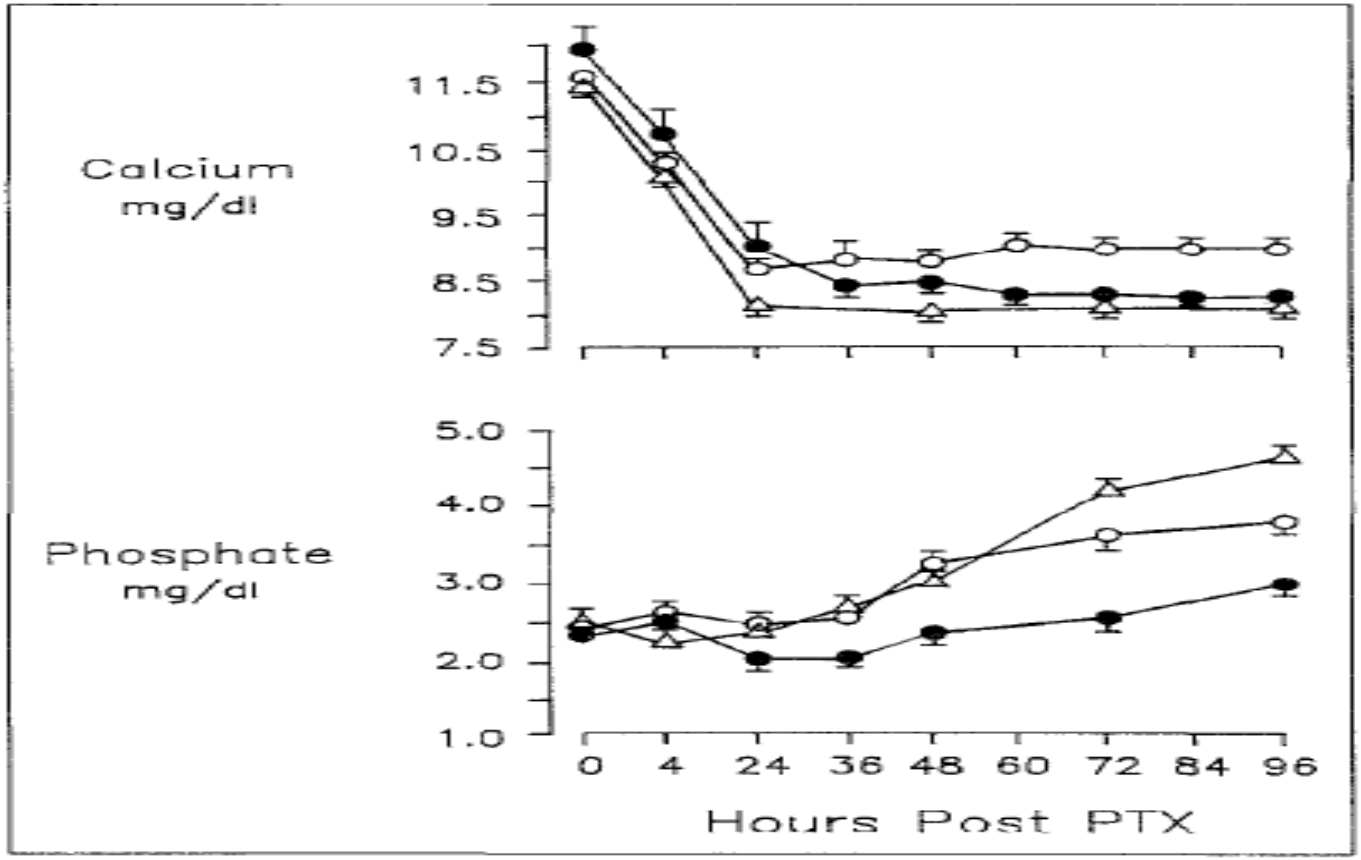


Figure 1. *Metabolic response to parathyroidectomy (PTX). Calcium and phosphate levels after parathyroidectomy for 151 patients with uncomplicated courses (○-○), 25 patients in whom hungry bone syndrome developed (●-●), and 22 patients with hypoparathyroidism (△-△). For the patients with hungry bone disease, all calcium and phosphate values after 48 hours are significantly less than the corresponding value for the group with an uncomplicated course ($p < 0.05$). For the patients with hypoparathyroidism, all calcium values after 48 hours are significantly less ($p < 0.05$), and all phosphate values after 72 hours are significantly greater ($p < 0.05$) than the corresponding value for the group with an uncomplicated course.*

Brasier et al. Am J Med 1988; 84: 654–660.

TABLE III Outcome after Parathyroidectomy

	All Patients	Uncomplicated Course	Hungry Bone Syndrome	Hypoparathyroidism
Length of hospital stay (days)	7.1 ± 0.35 (189)	6.5 ± 0.33 (143)	9.6 ± 1.4* (24)	8.2 ± 0.6* (22)
Follow-up				
Duration (months)	4.0 ± 0.45 (100)	3.5 ± 0.5 (70)	4.5 ± 1.6 (17)	5.7 ± 1.2 (13)
Calcium (mg/dl)	9.4 ± 0.05 (93)	9.4 ± 0.06 (66)	9.3 ± 0.16 (15)	9.4 ± 0.12 (12)
Phosphate (mg/dl)	3.5 ± 0.06 (88)	3.5 ± 0.07 (61)	3.1 ± 0.14* (15)	3.9 ± 0.18* (12)
Albumin (g/dl)	4.2 ± 0.06 (44)	4.3 ± 0.06 (31)	4.0 ± 0.22 (7)	4.2 ± 0.13 (6)
Alkaline phosphatase (IU/liter)	37.2 ± 3.9 (31)	32.5 ± 2.1 (20)	62 ± 14.0* (5)	32 ± 4.9 (6)
N-terminal parathyroid hormone (pg/ml)	14.2 ± 1.3 (32)	14.2 ± 1.6 (23)	16.6 ± 3.4 (5)	11 ± 4.2 (4)

* $p < 0.05$ when compared with the corresponding values for group with uncomplicated course. Values are mean ± SEM. Numbers in parentheses refer to number of patients for whom follow-up data were recorded.

Brasier et al. Am J Med 1988; 84: 654–660.

TABLE IV **Multivariate Analysis of Predictive Factors for the Development of the Hungry Bone Syndrome**

Factor	Correlation Coefficient	F Ratio	p Value
Adenoma volume	0.297	14.586	0.0002
Blood urea nitrogen	0.361	13.414	0.0003
Alkaline phosphatase	0.0541	10.489	0.0014
Age	0.239	5.194	0.0239
Constant	−16.2932		

The discriminant sum can be calculated by multiplying the multivariate coefficient with the corresponding value of adenoma volume (cm^3), blood urea nitrogen (mg/dl), alkaline phosphatase (IU/liter), and age (years). The sum of these values plus the constant yields the discriminant score.

TABLE V **Probability of Hungry Bone Syndrome as Function of the Discriminant Sum for All Patients Undergoing Initial Neck Exploration**

Discriminant Sum	Probability of Hungry Bone Syndrome
<8	2.6%
8–10	21%
10–12	39%
>12	67%

For each patient, the discriminant sum is calculated as described in Table IV. Probability is calculated as the number of true positives divided by the number of all patients undergoing initial neck exploration.

Brasier et al. Am J Med 1988; 84: 654–660.

Prevention:

1) Calcitriol
2) Bisphosphonates

Nephron *46:* 18–22 (1987)

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Effect of Calcitriol in the Control of Plasma Calcium after Parathyroidectomy

A Placebo-Controlled, Double-Blind Study in Chronic Hemodialysis Patients

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- Randomized, placebo controlled, double blinded study
- Investigate whether the administration of calcitriol was of significant benefit in the treatment of hypocalcemia after PTx
- 14 ESRD on HD with severe secondary HPT underwent PTx
- Patients in each group were supplemented with calcium as well as calcitriol, or placebo 24 hrs after surgery
- Starting dose: calcium carbonate 8g and calcitriol 2mcg/day

Table II. Plasma biochemistry before (T0) as well as 7 days (T7) and 14 days (T14) after parathyroidectomy (mean ± SEM)

		Group 1 (calcitriol)	n	Group 2 (placebo)	n
Toal Ca, m*M*	T0	2.43 ± 0.03	7	2.31 ± 0.03	7
	T7	2.24 ± 0.10	7	1.90 ± 0.09[a]	7
	T14	2.29 ± 0.3	7	1.92 ± 0.10[b]	7
Ionized Ca, m*M*	T0	1.18 ± 0.03	6	1.11 ± 0.03	6
	T7	1.09 ± 0.08	5	0.87 ± 0.05[a]	5
	T14	1.17 ± 0.10	4	1.00 ± 0.05[b]	6
Phosphorus, m*M*	T0	2.05 ± 0.10	7	1.97 ± 0.11	7
	T7	0.99 ± 0.13[a]	7	0.87 ± 0.09[a]	7
	T14	1.16 ± 0.20[b]	7	0.92 ± 0.05[b]	7
Magnesium, m*M*	T0	1.10 ± 0.09	7	1.27 ± 0.11	5
	T7	1.12 ± 0.06	6	1.11 ± 0.12	4
	T14	1.20 ± 0.03	5	1.21 ± 0.07	5
Total proteins, g/l	T0	68.3 ± 1.3	7	70.8 ± 1.0	7
	T7	71.2 ± 2.0	7	69.6 ± 1.4	7
	T14	68.1. ± 1.3	7	71.8 ± 2.2	7

Statistically significant differences ($p = 0.05$ or less): [a]T7 versus T0; [b]T14 versus T0. n = Number of patients.

Clair et al. Nephron 1987 46: 18-22

Table III. Plasma biochemistry before (T0) as well as 7 days (T7) and 14 days (T14) after parathyroidectomy (mean ± SEM)

		Group 1 (calcitriol)	n	Group 2 (placebo)	n
Alkaline phosphatase activity, nkat/l (normal <1,500)	T0	7,131 ± 1,723	7	8,893 ± 1,594	7
	T7	5,618 ± 751	7	11,418 ± 3,293	5
	T14	5,398 ± 966	3	15,774 ± 2,707[b,c]	5
iPTH, ng/ml (normal <0.5)	T0	2.79 ± 0.40	6	3.12 ± 0.43	7
	T7	0.67 ± 0.10[a]	5	0.79 ± 0.16[a]	7
	T14	0.50 ± 0.12[b]	4	0.74 ± 0.22[b]	7
25-OH-D, ng/ml (normal 5–25)	T0	15.5 ± 4.8	7	19.1 ± 5.4	6
	T7	11.2 ± 2.0	6	13.5 ± 4.0	5
	T14	9.7 ± 1.6	7	12.5 ± 2.6	7
Aluminum, μ*M*	T0	2.0 ± 0.3	6	2.1 ± 0.4	7
	T7	1.5 ± 0.2	6	2.1 ± 0.6	6
	T14	1.4 ± 0.5	5	1.5 ± 0.3	5

Statistically significant differences ($p = 0.05$ or less): [a]T7 versus T0; [b]T14 versus T0; [c]T14 of group 1 versus T14 of group 2.

Clair et al. Nephron 1987 46: 18-22

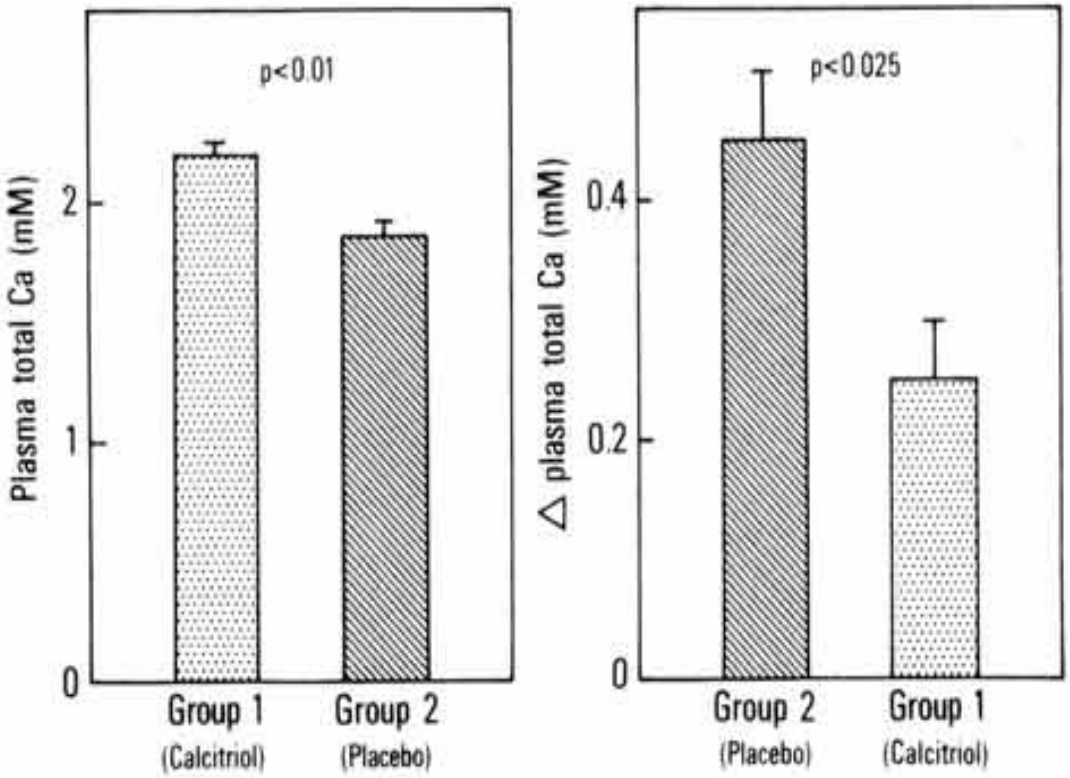

Fig. 2. a Mean plasma total calcium concentration of group-1 (calcitriol) patients during days 3–9 following parathyroidectomy (2.20 ± 0.06 m*M*) as compared to that of group-2 (placebo) patients (1.86 ± 0.05 m*M*). **b** Decrease in mean plasma total calcium concentration during days 3–9 as compared to the mean value of three determinations before parathyroidectomy in group-2 (placebo) patients (0.45 ± 0.05 m*M*) and group-1 (calcitriol) patients (0.25 ± 0.06 m*M*).

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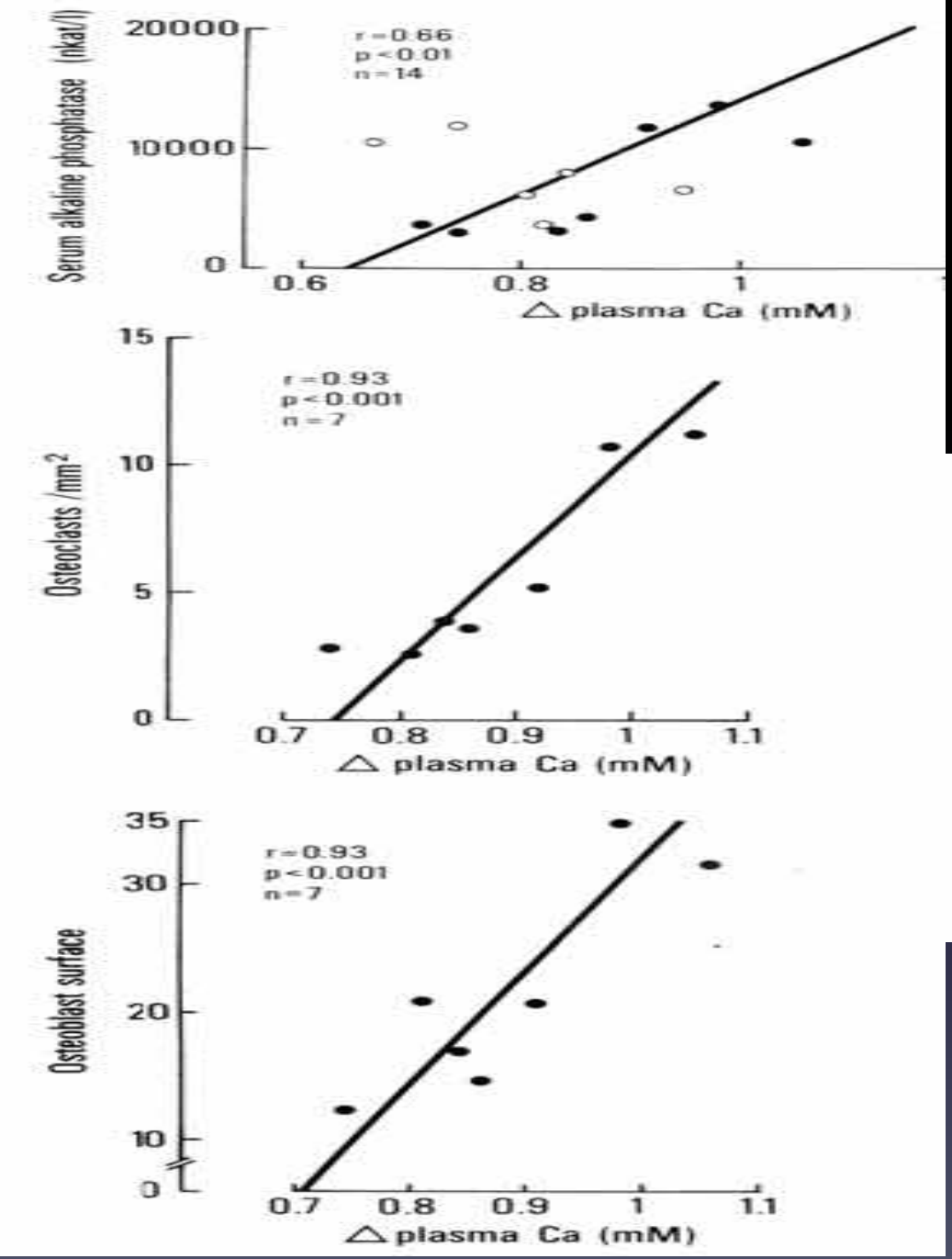


Fig. 1. a Decrease in plasma total calcium 24 h after parathyroidectomy as a function of serum alkaline phosphatases before surgery. **b** Decrease in plasma total calcium 24 h after parathyroidectomy as a function of osteoclast number in those patients in whom bone histomorphometry was available. **c** Decrease in plasma total calcium 24 h after parathyroidectomy as a function of osteoblast surface in those patients in whom bone histomorphometry was available.

Clair et al. Nephron 1987 46: 18-22

Calcitriol

- 20 patients on HD with severe HPT underwent PTx
- Patients assigned to either a tx group(A) or control group(B)
- (A) group: received Ca supplements +calcitriol PO
- (B): received Ca supplements and placebo
- Aim of the study is to rule out acute effects of calcitriol administration on bone cells in HD pts undergoing PTx because of severe secondary HPT
- Acute changes in serum levels of bone markers of synthesis and resorption evaluated in pts with or without calcitriol tx.

Mazafarro et al. Nephrol Dial Transplant. 2000 Jun;15(6):877-82.

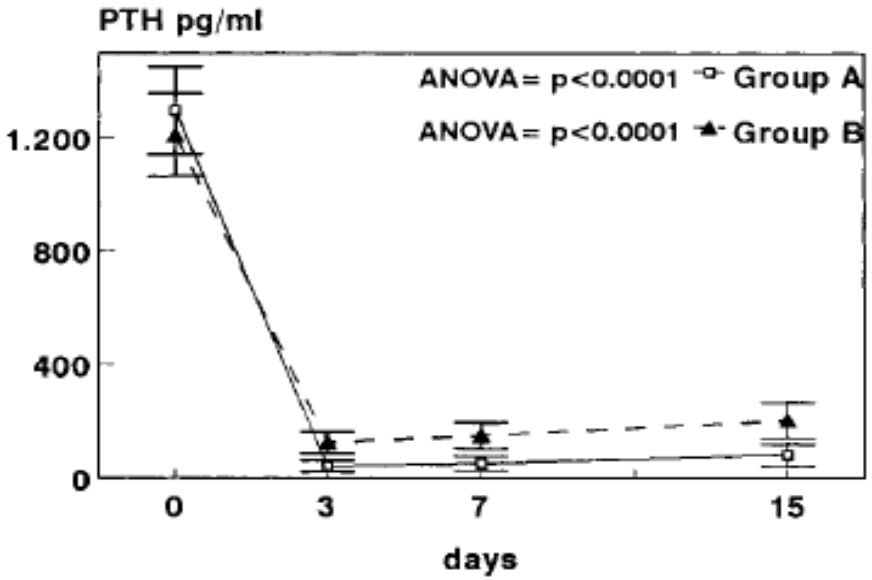
Table 1. Basal clinical, biochemical and bone histological data (M ± SD) in the two groups of patients

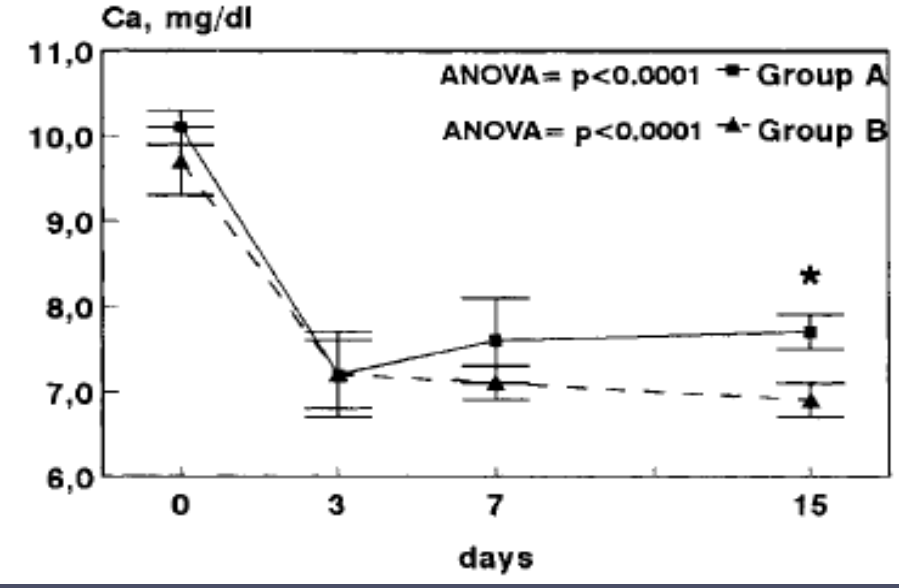
	Group A	Group B	Normal range
Number	10	10	
Age (years)	40.8 ± 9.7	49.6 ± 9.9	–
Male/female	5/5	3/7	–
HD (years)	9.3 ± 5.1	8.5 ± 3.4	–
Ca (mg/dl)	10.1 ± 0.7	9.7 ± 1.3	8.8–10.5
P (mg/dl)	6.4 ± 1.5	5.6 ± 1.5	3.0–4.5
iPTH (pg/ml)	1297 ± 464	1210 ± 442	10–55
ICTP (ng/ml)	481 ± 152	277 ± 126 (*)	1.8–5.0
PICP (ng/ml)	307 ± 139	309 ± 200	66–173
AP (mU/ml)	1115 ± 734	1419 ± 1225	35–125
BGP (ng/ml)	362 ± 182	244 ± 96	2–12.5
Bone aluminium	0	0	0
OV/BV (%)	19.3 ± 10.7	13.0 ± 7.4	1.39 ± 1.08
ES/BS (%)	12.0 ± 4.4	12.0 ± 4.5	1.52 ± 1.28
OcS/BS (%)	5.5 ± 2.2	4.9 ± 1.2	0.18 ± 0.19
OS/BS (%)	59.9 ± 17.2	53.8 ± 21.3	9.58 ± 6.88
ObS/BS (%)	34.2 ± 18.1	33.3 ± 22.3	0.20 ± 0.49
dLS/BS (%)	33.5 ± 20.0	35.1 ± 11.9	6.74 ± 4.26
Mlt (days)	20 ± 5.8	15 ± 4.6	33.8 ± 10.2
BFR/BS ($\mu m^3/\mu m^2$/day)	0.70 ± 0.49	1.00 ± 0.83	0.066 ± 0.037
AjAR (μm/day)	1.19 ± 0.57	1.61 ± 0.84	0.441 ± 0.126

*$P < 0.009$ as compared to group A.

OV/BV, osteoid volume; ES/BS, eroded surface; OcS/BS, osteoclastic surface; OS/BS, osteoid surface; ObS/BS, osteoblastic surface; dLS/BS, double-labelled surface; Mlt, mineralization lag time; BFR/BS, bone formation rate; AjAR, adjusted apposition rate.

Mazafarro et al. Nephrol Dial Transplant. 2000 Jun;15(6):877-82.





- Total dose of IV Ca administered was not different between the 2 groups
- Total dose of PO Ca administered was statistically lower in group A.
- Group A had significantly higher Serum Ca levels at day 15 than group B

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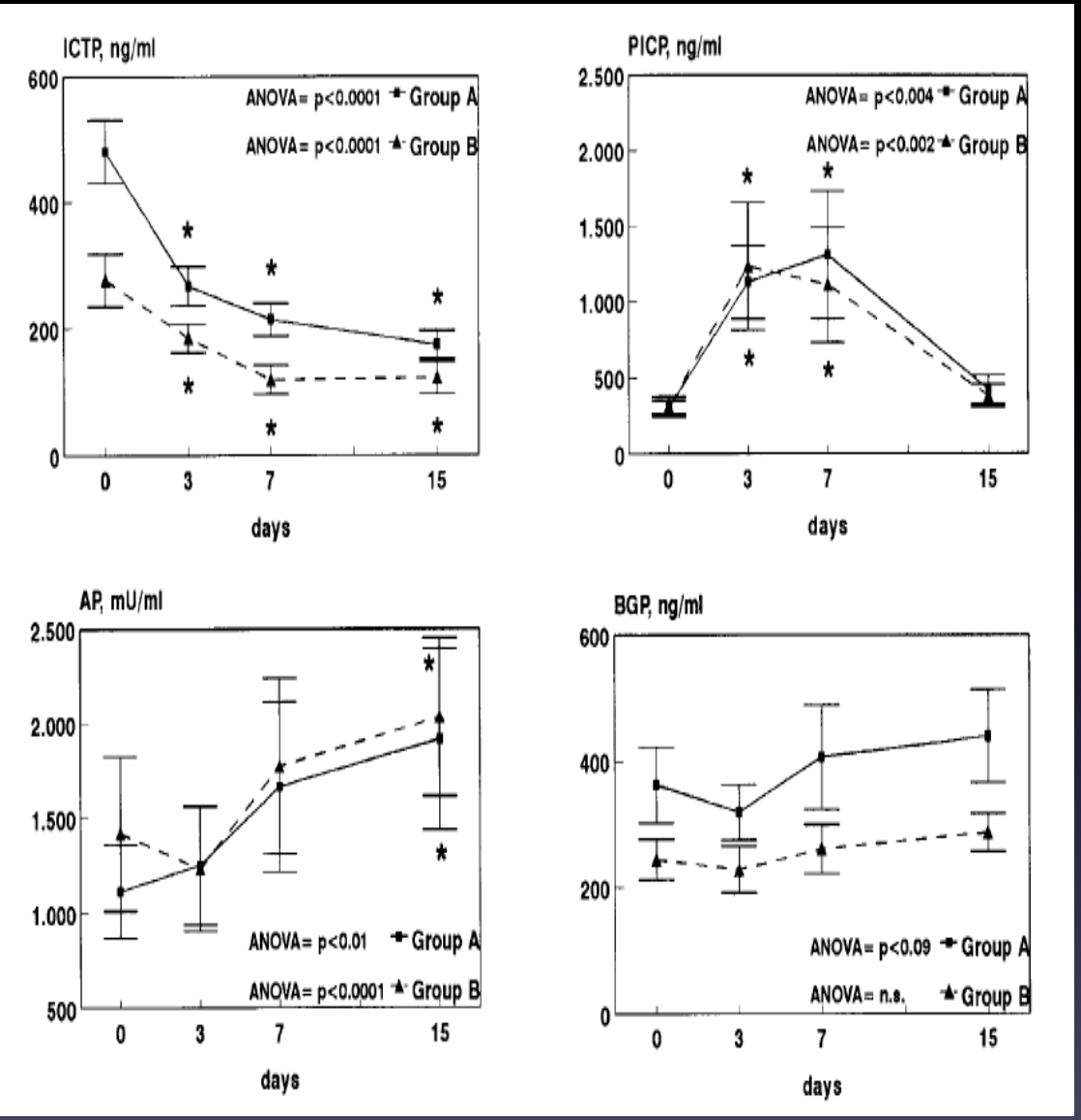

- AP, BGP, PICP are markers of bone synthesis
- ICTP is a marker of bone resorption
- The fall in ICTP serum levels and increment of PICP could explain hypocalcemia after PTx
- This phenomenon is not affected by Vit D administration
- Vit D after PTx improves hypocalcemia mainly through increased intestinal absorption of calcium and enhances calcium efflux across the quiescent layer of bone cells from the rapidly exchangeable pool

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Bisphosphonates

- Retrospective study, 23 patients.
- The patients were classified into two groups: HBS group and the non-HBS group
- Study the effect of preoperative administration of bisphosphonates on postoperative hypocalcemia in patients with primary hyperparathyroidism.

Table 2. Clinical and laboratory analyses of patients before parathyroidectomy (grouped by occurrence of hungry bone syndrome)

	HBS	Non-HBS	*P*
No.	9	14	
Sex (M/F)	0/9	3/11	0.253
Age (years)	56 ± 6	58 ± 4	0.900
Serum calcium before operation (mg/dl)	11.8 ± 0.4	12.0 ± 0.3	0.658
I-PTH (pg/ml)	289 ± 93	309 ± 58	0.186
Alkaline phosphatase (U/l)	248 ± 48	169 ± 31	0.123
Blood urea nitrogen (mg/dl)	20 ± 2	21 ± 3	0.831
Bisphosphonate pretreatment (no. of persons)	0	6	0.048*

* $P < 0.05$

Lee et al. J. Bone Miner Metab 2006; 24: 255–8.

Table 3. Clinical and laboratory analyses of patients before parathyroidectomy (grouped by bisphosphonate pretreatment and preoperative calcium concentrations)

	Bisphosphonate pretreatment	No bisphosphonate pretreatment		
		Severe hypercalcemia	Mild hypercalcemia	*P*
No.	6	6	11	
Sex (M/F)	1/5	1/5	1/10	0.902
Age (years)	58 ± 7	51 ± 10	61 ± 3	0.726
Calcium before operation (mg/dl)[a]	12.2 ± 0.6	12.9 ± 0.1	11.2 ± 0.2	0.002*
I-PTH (pg/ml)	327 ± 103	390 ± 124	238 ± 58	0.155
Alkaline phosphatase (U/l)	224 ± 50	156 ± 88	191 ± 31	0.662
Blood urea nitrogen (mg/dl)	26 ± 5	21 ± 2	18 ± 2	0.125
Occurrence of HBS (no. of persons)	0	4	5	0.051
Nadir calcium (mg/dl)	9.3 ± 0.2	8.3 ± 0.4	8.3 ± 0.3	0.058
No. of days to Ca nadir[b]	4 ± 1	3 ± 1	2 ± 0	0.038*

* $P < 0.05$

HBS, hungry bone syndrome; Nadir calcium, minimal plasma concentration of calcium after operation

[a] Severe hypercalcemia group $P = 0.001$, compared with mild hypercalcemia group

[b] Bisphosphonate group $P = 0.025$, compared with mild hypercalcemia group

Dosage of bisphosphonates was not controlled

Varying dosages of calcium (and vitamin D) were administered to the subjects after the hypocalcemia occurred.

Lee et al. J. Bone Miner Metab 2006; 24: 255–8.

Original Article

Administration of pamidronate helps prevent immediate postparathyroidectomy hungry bone syndrome

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- 37 ESRD patients on HD have undergone total (4 gland) surgical parathyroidectomy
- Aim: to determine whether bisphosphonates administration would reduce the incidence of postoperative HBS, and reduce the necessity for intravenous Ca supplementation
- Tx group: administered 30 mg disodium pamidronate(if wt >80kg) and 45mg (if wt>80 kg), 1–2 days before surgery
- Both groups: oral vit D analogue started preoperatively, with PO Ca, and dialysates were switched from low-Ca to higher-Ca solutions

Table 1 Demographics of pamidronate and standard therapy groups

	Pamidronate group	Standard therapy group
Number of patients	27	10
Age (year)	53.6 ± 15	48.2 ± 18.6
Sex (% male)	55.6	70
% haemodialysis	88.5	70
Duration of dialysis (month)	78 (42–91)	68 (50–106)
PTH preoperative (pmol/L)	109 ± 67	155 ± 84
ALP preoperative (IU/L)	217 ± 167	196 ± 133
Phosphate preoperative (mmol/L)	1.84 ± 0.56	2.01 ± 0.40

Data are expressed as mean ± SD or median (25–75%). Normal parathyroid hormone (PTH) < 7 pmol/mL, and alkaline phosphatase (ALP) < 120 IU/L.

Table 2 Corrected serum calcium concentrations

	Pamidronate group	Standard therapy group
Preoperative	2.36 ± 0.18	2.58 ± 0.21
Postoperative	2.39 ± 0.25	2.50 ± 0.32
Day 1 post operation	2.33 ± 0.15	2.10 ± 0.47*
Day 2 post operation	2.32 ± 0.23	2.07 ± 0.30*
Day 3 post operation	2.35 ± 0.29	2.06 ± 0.30*
Day 4 post operation	2.28 ± 0.22	2.25 ± 0.40
Day 7 post operation	2.26 ± 0.24	2.18 ± 0.37

Data are expressed as mean ± SD or median (25–75%). *$P < 0.05$ vs preoperative value.

- For standard tx group, iCa was measured according to the protocol 36 times, and all patients (10/10) required more than one intravenous calcium bolus.
- for the pamidronate group, ionized calcium was measured according to the protocol 12 times, and only two patients (2/27) in the pamidronate group required intravenous calcium ($P < 0.001$).
- The mean length of hospital stay for the pamidronate group following PTX was 5.4 +/- 2.3 days, whereas that for the standard treatment group was 9.2 +/- 1.9 days ($P < 0.05$).

Table 3 DEXA scan results of the lumbar spine (L1–L4) and the femoral neck before PTX, and then the percentage annual change post PTX, adjusted for time

	Pamidronate group	Standard therapy group	
pre-PTX L1–L4 (g/cm^2)	1.01 ± 0.19	1.23 ± 0.33	$P = 0.12$
pre-PTX hip (g/cm^2)	0.95 ± 0.21	0.87 ± 0.19	$P = 0.27$
post-PTX L1–L4 (% change)	0.041 ± 0.04	0.058 ± 0.41	$P = 0.23$
post-PTX hip (% change)	0.03 ± 0.03	0.107 ± 0.10	$P = 0.15$

Data are expressed as mean ± SD. PTX, parathyroidectomy.

In a subset of patients, six controls and 10 of the pamidronate group, DEXA scans were available for review both before parathyroidectomy, and post surgery, median 20 months (range 6–26).

After PTx, the increase in bone mineral density at both the lumbar spine (L1–L4) and the femoral neck were less in the pamidronate group (not statistically significant)

Treatment

- Oral calcium supplementation: 2-4 g of elemental calcium/day
- IV calcium if rapid or progressive reduction in serum Ca or symptoms related to hypocalcemia or Serum Ca<7.5 mg/dl
- Vit D supplementation
- Magnesium supplementation
- Correction of hypophosphatemia only if severe (<1mg/dl)