

CHAPTER 10: RENAL BONE DISEASE

Summary

- The mean serum calcium level ranged from 2.3 to 2.4 mmol/l and mean serum phosphate level 1.8 to 1.9 mmol/l. The mean values of both parameters have remained stable from 1993 to 2002.
- The mean calcium-phosphate product ranged from 4.3 to 4.5 mmol²/L².
- The mean serum intact PTH ranged from 118 to 420 ng/L. There was a significant decrease in the levels of intact PTH from 1993 to 1998.
- There is a U-shape distribution in survival among dialysis patients in relation to serum calcium, phosphate, calcium x phosphate product and serum intact PTH.

Introduction

Over the past decade there has been an increasing number of patients receiving renal replacement therapy throughout Malaysia. Renal bone disease remains an important morbidity suffered by these patients. Bone disease begins early in the pre-dialysis phase when 50% of kidney function is lost and the ill effects can persist even following a successful renal transplant. In the absence of bone biopsy patients on dialysis should be monitored for disturbances in calcium phosphate metabolism and for secondary hyperparathyroidism using serum calcium, phosphate and intact parathyroid hormone (iPTH) levels. We reviewed data on the levels of serum calcium, phosphorous and serum iPTH collected over the past 10 years from 1993 to 2002, and evaluated their effect on patient survival.

Results

The mean values of uncorrected and corrected serum calcium were 2.3 to 2.4 mmol/l. (Corrected calcium was taken as the sum of uncorrected calcium plus the product of 40 minus albumin multiply by 0.2) The levels showed little fluctuation over the 10 years. (Fig 10.1, Table 10.1). In accordance to KDOQI guidelines, 2003[1], patients on dialysis should maintain serum levels of corrected total calcium within the normal range for the laboratory used, preferably at the lower end (2.1 to 2.37 mmol/l). The above results are within the desired limit set by KDOQI.

The mean serum phosphate in our patients was 1.8 to 1.9 mmol/l throughout 1993 to 2002 (Figure 10.2, Table 10.2). This is higher than the recommended range set by KDOQI 2003 and the British Renal Association[2]. Following the KDOQI guidelines, the serum levels of phosphate for patients on haemodialysis should be maintained between 1.13 to 1.78 per day. The levels for haemodialysis patients according to the British Renal Association is 1.2 to 1.7 mmol/l [2]. High phosphate levels above 2.08 mmol/l [6.5 mg/dl] are associated with an increased risk of mortality as shown by Levin et al [3]. The local Malaysian diet may contain higher phosphate content. In addition, the main phosphate binder used was and continues

to be calcium carbonate, a relatively ineffective phosphate binder. Aluminium hydroxide has fallen out of favour because of the risk of aluminium toxicity.

The mean calcium phosphate product varied between 4.3 to 4.5 mmol²/L² (Figure 10.3, Table 10.3). This is greater than the cut-off point of 4.2 mmol²/L² as defined by KDOQI. This is best achieved by controlling serum phosphate levels within target range. Raised calcium phosphate products are associated with increased risk of cardiovascular mortality. [4].

The mean serum iPTH ranged from 118 to 420 ng/L. (Figure 10.4) There was a decreasing trend of iPTH levels from 1993 to 1998 after which the levels plateaued. This trend had mainly been contributed by a reducing proportion of patients with iPTH greater than 250 ng/L and an increasing proportion with iPTH less than 100 ng/L. (Table 10.4) The falling levels of iPTH could be related to an increasing numbers of diabetic and elderly patients entering dialysis. Diabetic and elderly patients are associated with a higher incidence of adynamic bone disease and hence lower serum iPTH levels compared to non diabetic patients [5].

The survival of patients was analysed against variables such as serum calcium, phosphate, calcium x phosphate product and serum iPTH level [Figures 10.5, 10.6, 10.7, 10.8, Tables 10.5, 10.6, 10.7, 10.8]. In general the survival curves showed a U-shaped distribution for all four parameters i.e. the values at either extremes of each parameter were associated with poorer survival.

Each parameter carried an optimal range between which survival was the highest. For serum calcium the optimal range was 2.2 mmol/l to 2.6 mmol/l, levels for optimum serum phosphate were between 1.8 to 2.0 mmol/l, calcium x phosphate product 4.5-5.5 mmol²/L² and serum iPTH 100-250 ng/L. The survival outcomes were understandably poorer in the higher extremes of phosphate and calcium phosphate product as these are accepted as cardiovascular risk factors in the dialysis population. Besides hyperphosphataemia and elevated calcium x phosphate product, a high iPTH level is also recognized as independent risk factor

in the pathogenesis of cardiac disease. The reasons for the reduced survival in relation to the lower extremes of calcium, phosphate and calcium x phosphate product is unexplained. It is possible that the poorer survival related to a low serum phosphate and calcium x phosphate product is a reflection of malnutrition.

Hence, further studies on the factors affecting the U-shaped distribution of mortality among

patients with low serum calcium, phosphate and iPTH levels are needed in order to plan strategies to reduce the proportion of patients in these extremes of ranges.

There was insufficient data in the Renal Registry on the type of bone disease in the dialysis population. This area too needs further studies.

Table 10.1 Distribution of corrected serum Calcium, all dialysis patients 1993-2002.

Year	Number of Subjects	Mean	SD	Median	LQ	UQ	% of patients ≥ 2.2 & ≤ 2.6 mmol/L
1993	782	2.3	.3	2.3	2.2	2.5	57
1994	1044	2.3	.3	2.3	2.2	2.5	55
1995	1232	2.4	.3	2.4	2.2	2.5	59
1996	1477	2.4	.3	2.4	2.2	2.6	57
1997	2104	2.4	.3	2.4	2.2	2.5	58
1998	2566	2.3	.3	2.3	2.2	2.5	59
1999	3251	2.4	.3	2.4	2.2	2.5	60
2000	4336	2.4	.3	2.4	2.2	2.5	61
2001	5363	2.4	.3	2.4	2.2	2.5	63
2002	5975	2.3	.3	2.3	2.2	2.5	60

Table 10.2 Distribution of serum Phosphate, all patients 1993-2002

Year	Number of Subjects	Mean	SD	Median	LQ	UQ	% of patients ≥ 1.6 & < 1.8 mmol/L	% of patients ≥ 1.8 & < 2.2 mmol/L	% of patients ≥ 2.2 & ≤ 2.6 mmol/L
1993	774	1.9	.5	1.9	1.5	2.2	16	27	16
1994	1042	1.9	.5	1.8	1.5	2.2	18	29	14
1995	1261	1.8	.5	1.8	1.5	2.2	18	29	15
1996	1532	1.9	.5	1.8	1.5	2.2	16	28	14
1997	2122	1.9	.5	1.8	1.5	2.2	16	26	16
1998	2589	1.9	.5	1.9	1.5	2.2	16	30	16
1999	3446	1.8	.5	1.8	1.5	2.2	15	27	16
2000	4716	1.8	.6	1.8	1.5	2.2	16	28	14
2001	5499	1.8	.5	1.8	1.4	2.1	17	26	15
2002	6155	1.8	.5	1.8	1.5	2.2	16	25	16

Figure 10.1 Distribution of corrected serum Calcium, all patients

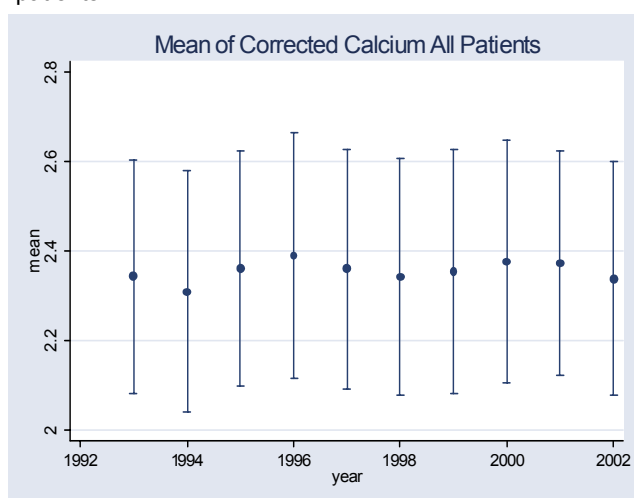


Figure 10.2 Distribution of serum Phosphate, all patients

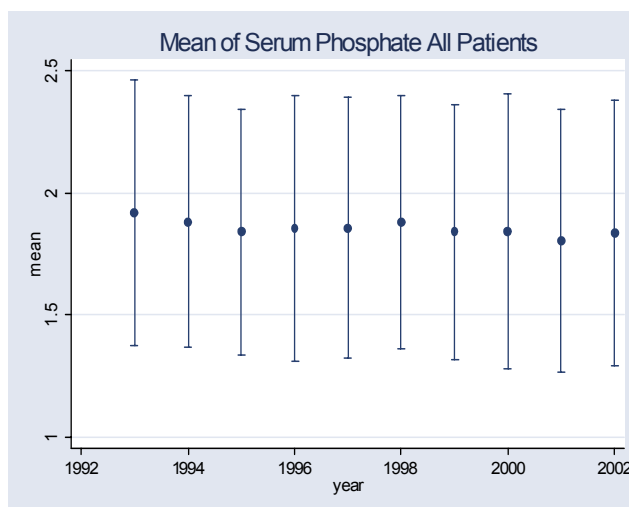


Table 10.3 Distribution of calcium x phosphate product, all patients 1993-2002

Year	Number of Subjects	Mean	SD	Median	LQ	UQ	% of patients <3.5 mmol ² /L ²	% of patients ≥3.5&<4 mmol ² /L ²	% of patients ≥4&<4.5 mmol ² /L ²	% of patients ≥4.5&<5 mmol ² /L ²	% of patients ≥5&<5.5 mmol ² /L ²	% of patients ≥5.5 mmol ² /L ²
1993	766	4.5	1.3	4.4	3.6	5.3	23	15	16	16	10	20
1994	1033	4.3	1.2	4.2	3.5	5	24	18	17	14	11	15
1995	1225	4.3	1.2	4.2	3.5	5	26	16	16	17	11	15
1996	1455	4.4	1.3	4.4	3.5	5.1	24	15	15	16	12	17
1997	2085	4.4	1.3	4.2	3.4	5.1	27	15	15	15	11	17
1998	2524	4.4	1.2	4.3	3.5	5.1	25	15	18	14	12	17
1999	3204	4.3	1.3	4.2	3.4	5.1	29	15	15	14	11	17
2000	4269	4.3	1.3	4.2	3.4	5.1	28	15	16	14	10	17
2001	5279	4.3	1.3	4.1	3.3	5.1	30	16	15	13	10	16
2002	5894	4.3	1.3	4.2	3.3	5.1	30	16	15	13	10	17

Figure 10.3 Distribution of calcium x phosphate product, all patients

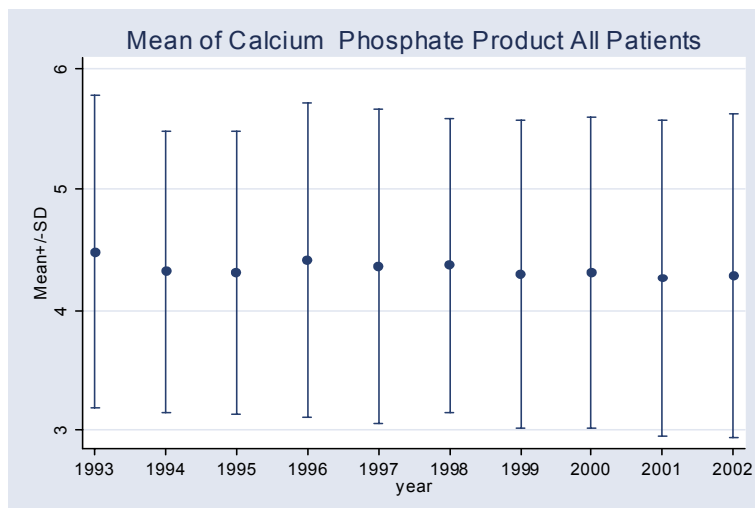


Table 10.4 Distribution of serum iPTH, all patients 1993-2002

Year	Number of Subjects	Mean	SD	Median	LQ	UQ	% of patients <100 ng/L	% of patients ≥100&<250 ng/L	% of patients ≥250 ng/L
1993	0								
1994	17	420.5	391	253	65	771.5	29	18	53
1995	266	307.6	385.2	169.5	50	408	40	19	41
1996	454	224.9	315.3	84	30	282	53	19	28
1997	1382	177.7	262.7	71	25	208	58	20	22
1998	1219	118.6	186.4	45	15.5	133	69	17	14
1999	1900	175.4	247.5	75.3	23	229.5	57	21	23
2000	2653	143.1	225	55	17	166	65	18	17
2001	3293	135.8	210.8	56	17	160	64	20	16
2002	3868	162.8	244.4	69	20.5	195	59	21	20

Figure 10.4 Distribution of serum iPTH, all patients

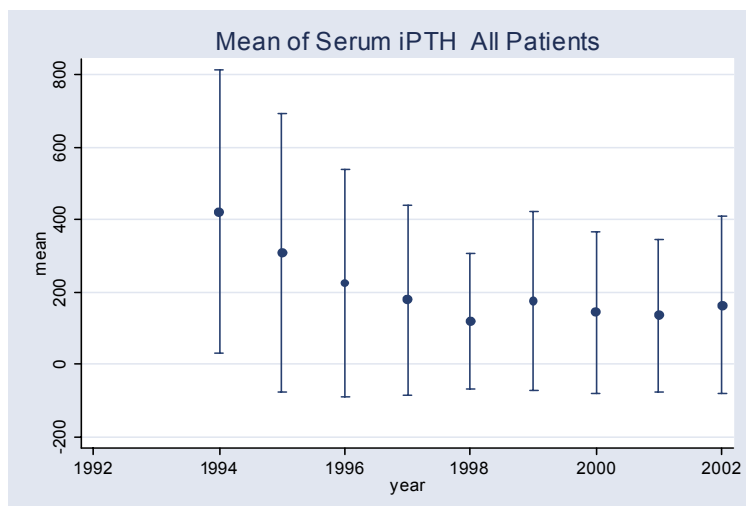


Table 10.5 Adjusted patient survival by serum Calcium, all dialysis patients 1997-2003
(Adjusted for age, gender, diagnosis, time on RRT and modality)

	N	Hazard Ratio	95% CI	P-value
< 2.2	1693	1.56	(1.38,1.78)	0.000
≥ 2.2-<2.6*	5059	1		
≥ 2.6	273	1.76	(1.39,2.22)	0.000

* Reference Group

Figure 10.5 Adjusted patient survival in relation to serum Calcium, all patients 1997-2002
(Adjusted for age, gender, diagnosis, time on RRT and modality)

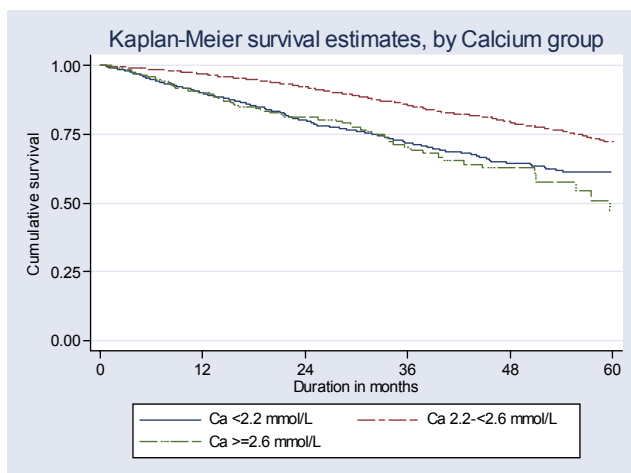


Table 10.6 Adjusted patient survival by serum Phosphate all dialysis patients 1997-2003
(Adjusted for age, gender, diagnosis, time on RRT and modality)

Serum phosphate (mmol/L)	N	Hazard Ratio	95% CI	P-value
< 1.6	2385	1.43	(1.24,1.65)	0.000
1.6-<1.8*	1721	1		
1.8-<2.0	524	0.89	(0.70,1.14)	0.356
2.0-<2.2	857	0.94	(0.77,1.16)	0.577
2.2-<2.4	627	0.93	(0.73,1.17)	0.526
2.4-<2.6	493	1.20	(,0.94,1.52)	0.139
≥ 2.6	366	1.81	(1.41,2.33)	0.000

* Reference Group

Figure 10.6 Adjusted patient survival in relation to serum Phosphate, all dialysis patients 1997-2002
(Adjusted for age, gender, diagnosis, time on RRT and modality)

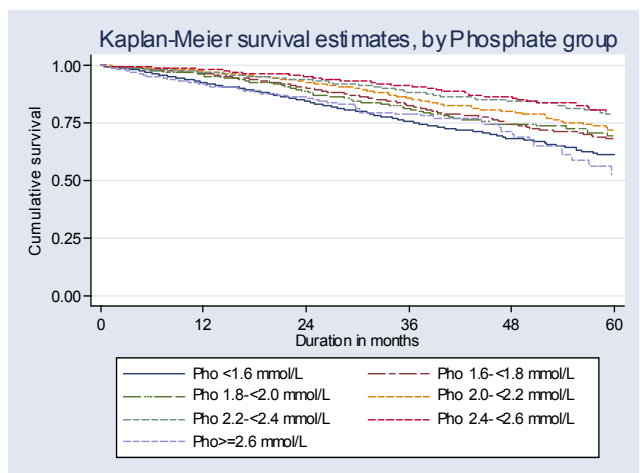


Table 10.7 Adjusted patient survival by calcium x phosphate product, all dialysis patients 1997-2003
(Adjusted for age, gender, diagnosis, time on RRT and modality)

Calcium phosphate product	N	Hazard Ratio	95% CI	P-value
<3.5	2008	1.41	(1.23,1.61)	0.000
3.5-<4.5*	2358	1		
4.5-<5.5	1488	0.84	(0.71,0.98)	0.032
≥ 5.5	855	1.23	(1.03,1.48)	0.023

* Reference Group

Figure 10.7 Adjusted patient survival in relation to calcium x phosphate product, all dialysis patients 1997-2002
(Adjusted for age, gender, diagnosis, time on RRT and modality)

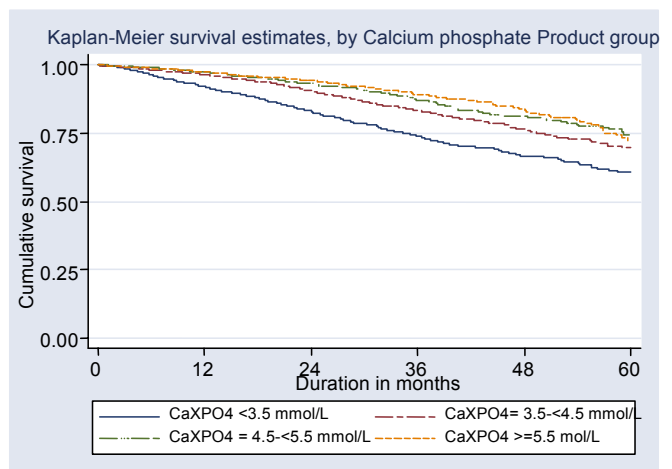
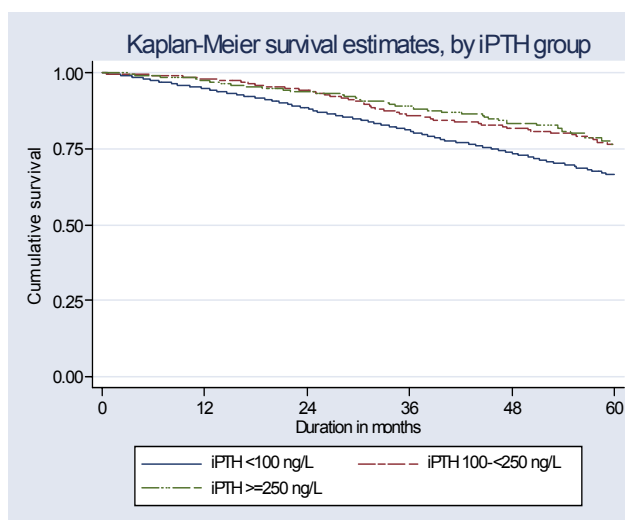


Table 10.8 Adjusted patient survival by serum iPTH , all patients 1997-2003
(Adjusted for age, gender, diagnosis, time on RRT and modality)

iPTH	N	Hazard Ratio	95% CI	P-value
<100	5582	1.59	(1.32, 1.92)	0.000
≥ 100 -<250*	878	1		
≥ 250	518	1.19	(0.89, 1.59)	0.244

* reference group

Figure 10.8 Adjusted patient survival in relation to serum iPTH , all patients 1997-2002
(Adjusted for age, gender, diagnosis, time on RRT and modality)



References

1. Eknoyan G, Levin A, Levin N. Bone metabolism and disease in chronic kidney disease. *Am J Kidney Dis* 2003, Suppl Vol 42,(4): 1-220.
2. Ansell D, Feest T. UK Renal Registry Report 2002. UK Renal Registry, Bristol, UK.
3. Ganesh SK, Stack AG, Levin NW, Hulbert-Shearon T, Port FK. Association of elevated serum PO(4) product, and parathyroid hormone with cardiac mortality risk in chronic haemodialysis patients. *J Am Soc Nephrol*. 2001; 12(10):2131-8.
4. Block GA, Hulbert-Shearon TE, Levin NW, Port FK, USRDS, Ann Arbor, MI, USA. Association of serum phosphorus and calcium x phosphate product with mortality risk in chronic haemodialysis patients: a national study. *Am J Kidney Dis*. 1998; 31(4): 607-17.
5. United States Renal Data System, USRDS 2003 Annual Data Report: Atlas of End Stage Renal Disease in the United States, National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases, Bethesda, MD, 2003