Chapter 8: Serum Calcium, Phosphate and Parathyroid Hormone

Summary

Control of serum calcium varies widely among units. Non-compliance with the target range may be due to either hypo- or hypercalcaemia,

There are continuing problems with comparative audit of corrected serum calcium due to difficulties with albumin measurements. Reliance on the BCG method to measure serum albumin (which over-estimates serum albumin) to correct calcium, may be concealing hypercalcaemia. Use of uncorrected calcium concentrations may help comparative audit and should be further explored.

Many centres have difficulty achieving the target phosphate concentrations for the majority of patients. These targets may not be achievable with current phosphate binders and dialysis regimes.

There are significant differences in control of serum phosphate between centres.

There is significant variation in control of hyperparathyroidism among centres and between modalities within some centres. Much could be learned from detailed comparisons between the centres of the approaches to the prevention and treatment of hyperparathyroidism.

Introduction

The control of calcium, phosphate and parathyroid hormone activity in patients receiving renal replacement therapy is important in preventing progressive renal osteodystrophy and ectopic calcification. There is also evidence that poor control of calcium/phosphate metabolism may accelerate cardiac and vascular disease. Recommended target concentrations for all of these analytes are published in the Renal Association standards document.

Harmonisation of laboratory data between hospitals

Previous Registry reports have considered in detail the problems arising from inter-laboratory variation. The Registry continues to work with the Association of Clinical Biochemists and the UK NEQAS scheme to minimise the effect of analytical factors on comparative audit. Where NEQAS data was available, calcium and phosphate have been corrected by a 'harmonisation' factor. There are particular problem with calcium measurements when correcting for serum albumin. This relates to the different methodologies for measuring serum albumin and the different formulae applied to correct to a standard albumin concentration. This is considered in greater detail in chapter 9.

Serum calcium

Measurement of serum calcium

Centre	Method	Uncorrected range	Corrected range	Correction formula
A	Arsenazo	2.10-2.60	2.10-2.60	+0.02(40-Alb)
B	Arsenazo	2.10-2.60	Not reported	+0.02(40-Alb)
C	CPC	2.12-2.65	Not reported	Not Reported
D	CPC	2.05- 2.60	2.05- 2.60	+0.025(40-Alb)
E	CPC	2.12-2.55	2.12-2.55	+0.025(40-Alb)
F	Electrode	2.20-2.80	2.20-2.80	+0.025(40-Alb)
G	Arsenazo	2.10-2.60	2.10-2.60	+0.2(40-Alb)
H	Arsenazo	2.20-2.60	2.20-2.60	+0.017(43-Alb)
I	Arsenazo	2.20-2.60		-((0.0175xALb)+0.7)
J	Arsenazo	2.00-2.60	2.10-2.5	Not Reported
K	Arsenazo	2.20-2.60	Not reported	Not Reported
L	CPC	2.20-2.60		+0.02(40-Alb)
M	CPC	2.18-2.63		+(0.02(40-Alb)
N	CPC	2.10-2.65		+0.02(40-Alb)
O	Arsenazo	2.20-2.62	2.20-2.62	+0.02(40-Alb)
P	CPC	2.20-2.60	2.20-2.60	+0.02(40-Alb)
Q	Arsenazo	2.12-2.62	Not reported	Not Reported
R	Arsenazo	2.22-2.58	2.22-2.58	-((0.0116xAlb) +0.4652)
T	CPC	2.05-2.65	2.10-2.60	+ (40-Alb)0.02
U	Electrode	2.10-2.65	2.10-2.65	-((0.017xALb)+0.692)
V	CPC	2.20-2.60	2.20-2.60	+0.016(46-Alb)
W	Electrode	2.13-2.63		+0.02(40-Alb)
X	Electrode	2.20-2.60	2.20-2.60	+(-0.016 alb)+0.59

Conversion factor for calcium mg/dl = mmol/L x 4

Table 8.1 Laboratory methodologies for serum calcium

The different laboratory methodologies, normal ranges and correction formulae are given in table 8.1. The Registry calculated serum calcium concentrations corrected for serum albumin from uncorrected calcium data using a standard formula :-

Corrected calcium = uncorrected calcium + ((40 – albumin) x 0.02)

Where only corrected calcium was reported by the local laboratory, this was first uncorrected using the local formula then corrected using 'standard' registry formula. The target range for corrected calcium was set at 2.25-2.65 mmol/l.

Corrected serum calcium

The Renal Standards document recommends that ***total calcium should fall within the normal range quoted by the local pathology laboratory, corrected for serum albumin concentration.***

Haemodialysis

The percentage of haemodialysis patients within the target range (2.26-2.65mmol/l) varied widely among centres from >80% to <50% (figure8.1). Centre W with the lowest % of patients within target range had the highest median calcium concentration (figure8.2). However, the results for this centre are markedly affected by correction for albumin (see also chapter 9). Poor compliance with the standard may be due to either relative hypocalcaemia (centre B) or hypercalcaemia (centre R).

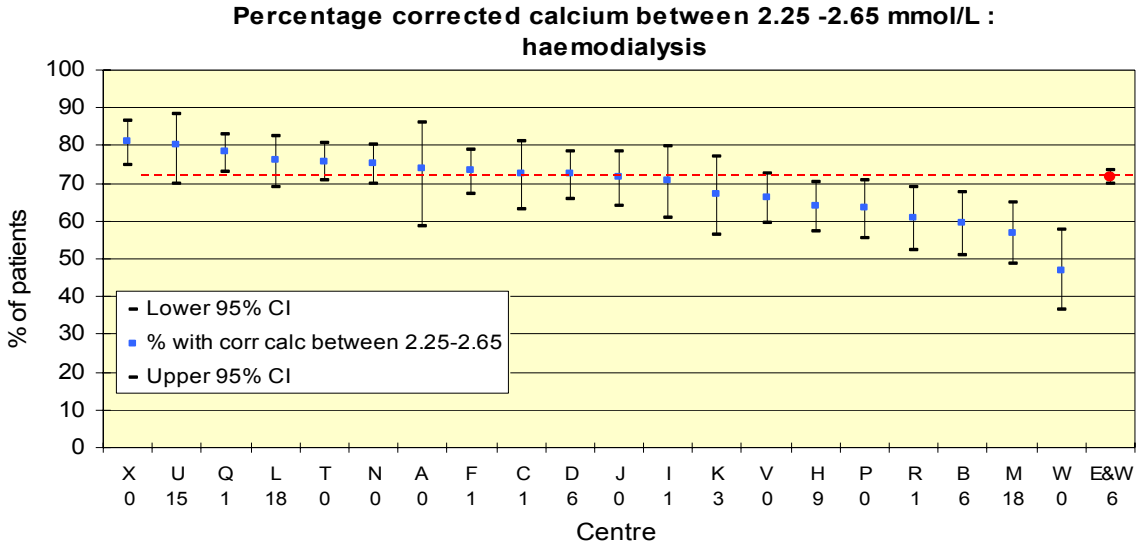

Figure 8.1 Percentage corrected serum calcium within 2.25-2.65 mmol/L on HD

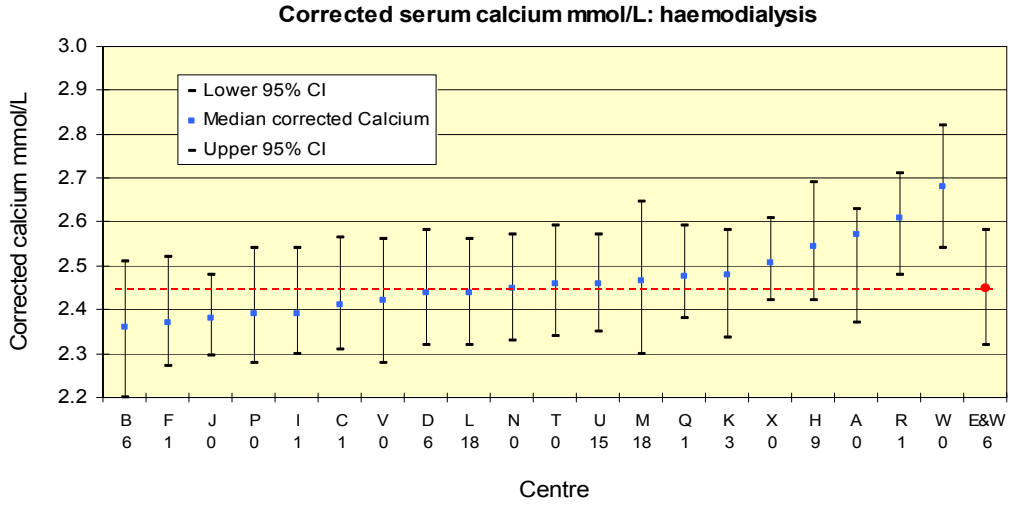

Figure 8.2 Median corrected serum calcium on haemodialysis

Peritoneal dialysis

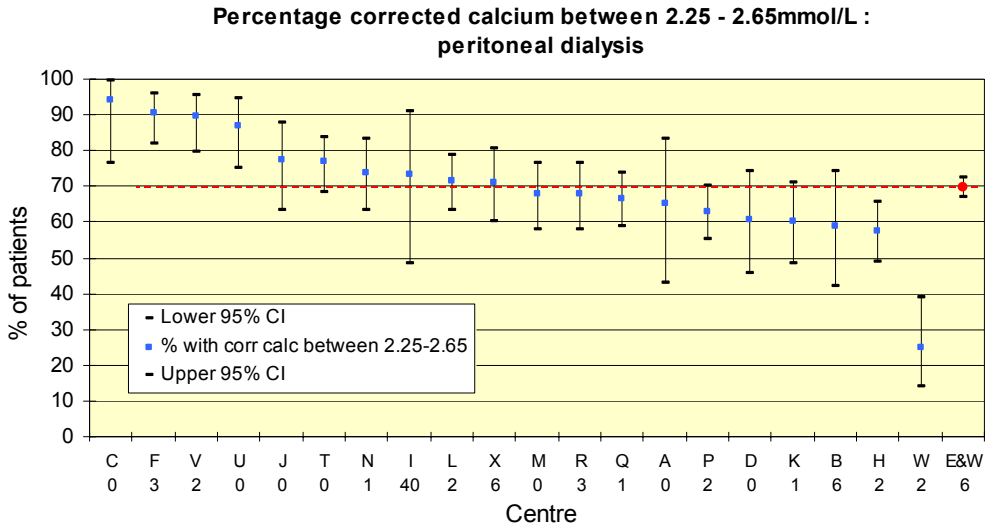

Figure 8.3 Percentage corrected serum calcium in range 2.25-2.65 mmol/L:on PD

Results for peritoneal dialysis patients were very similar to those for haemodialysis patients (figures 8.3, 8.4). Excluding centre W, whose results seem to be outlying, largely through problems with correction for albumin, the compliance with target calcium varied from 95% to <60% (figure 8.3). Again either low or high median calcium could be associated with poor achievement of target (figure 8.4). For both haemodialysis and peritoneal dialysis, approximately 70% of patients in England and Wales had calcium concentrations within the suggested range.

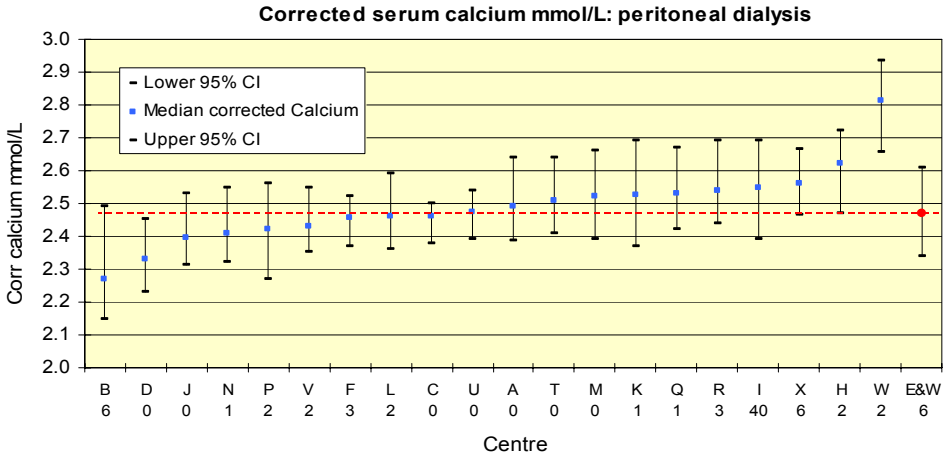

Figure 8.4 Median corrected serum calcium on peritoneal dialysis

Uncorrected serum calcium

Using uncorrected calcium concentration would remove some of the complications related to serum albumin assay techniques and correction formula. The data for both haemodialysis and

peritoneal dialysis patients are shown in figures 8.5 and 8.6. These show less variation between units. Centre W, which has low serum albumin as measured by the BCP method, and therefore high corrected serum calcium, still has relatively high serum calcium but is no longer an outlier. If widespread reliable direct serum ionised calcium measurement is not possible, uncorrected serum calcium may be more meaningful for comparative audit in future years. This is being discussed with the Association of Clinical Biochemists and is the subject of further work.

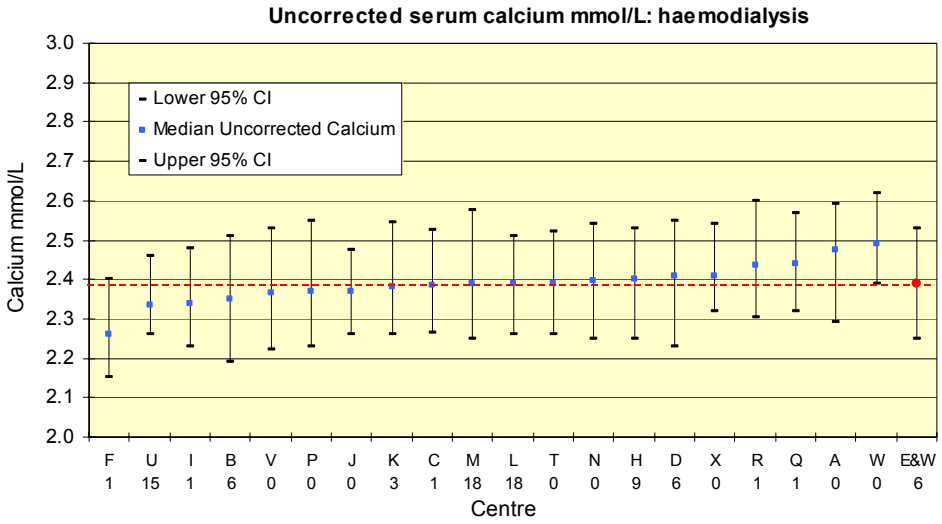

Figure 8.5 Median uncorrected serum calcium on haemodialysis

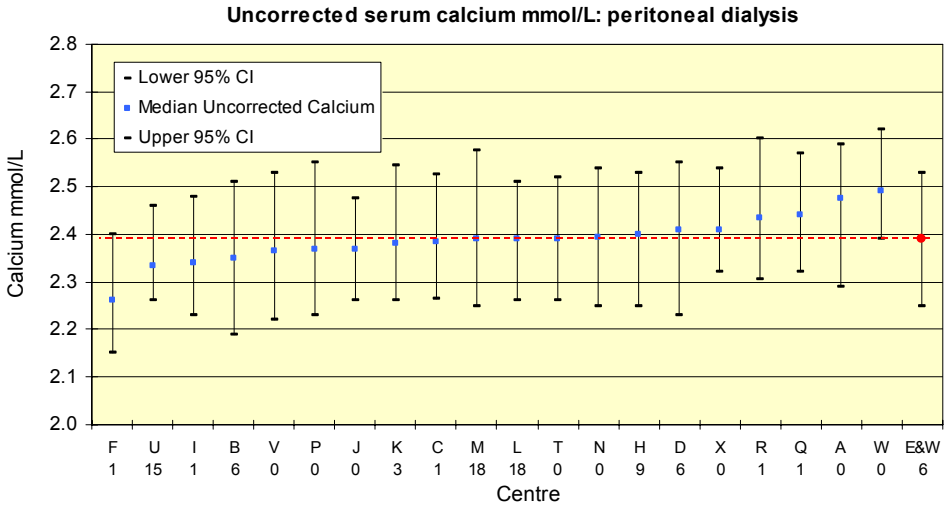

Figure 8.6 Median uncorrected serum calcium on peritoneal dialysis

Serum phosphate

The methodologies for measuring serum phosphate are listed in table 8.2. Note the variation in quoted normal range for laboratories using the same method of measurement.

Measurement of phosphate

Centre	*Methodology*	Lab reference Range mmol/L
A	PMb	0.90-1.50
B	PMb	0.74-1.40
C	PMb	0.80-1.40
D	PMb	0.80-1.45
E	PMb	0.80-1.40
F	PMb	1.40-2.20
G	PMb	0.80-1.40
H	PMb	0.80-1.40
I	Fish/Sub	0.80-1.40
J	PMb	0.80-1.40
K	PMb	0.80-1.40
L	PMb	0.80-1.45
M	PMb	0.80-1.45
N	PMb	0.75-1.35
O	PMb	0.80-1.45
P	PMb	0.80-1.40
Q	PMb	0.80-1.45
R	PMb	0.75-1.40
T	PMb	0.80-1.45
U	PMb	0.80-1.40
V	PMb	0.80-1.30
W	PMb	0.82-1.55
X	PMb	0.70-1.40

Conversion factor mg/dl = mmol/L x 3.1

Table 8.2 Methodologies for measurement of serum phosphate

Haemodialysis

The Renal Standards document recommends ***a target range for predialysis serum phosphate of 1.2 –1.7 mmol/L.***

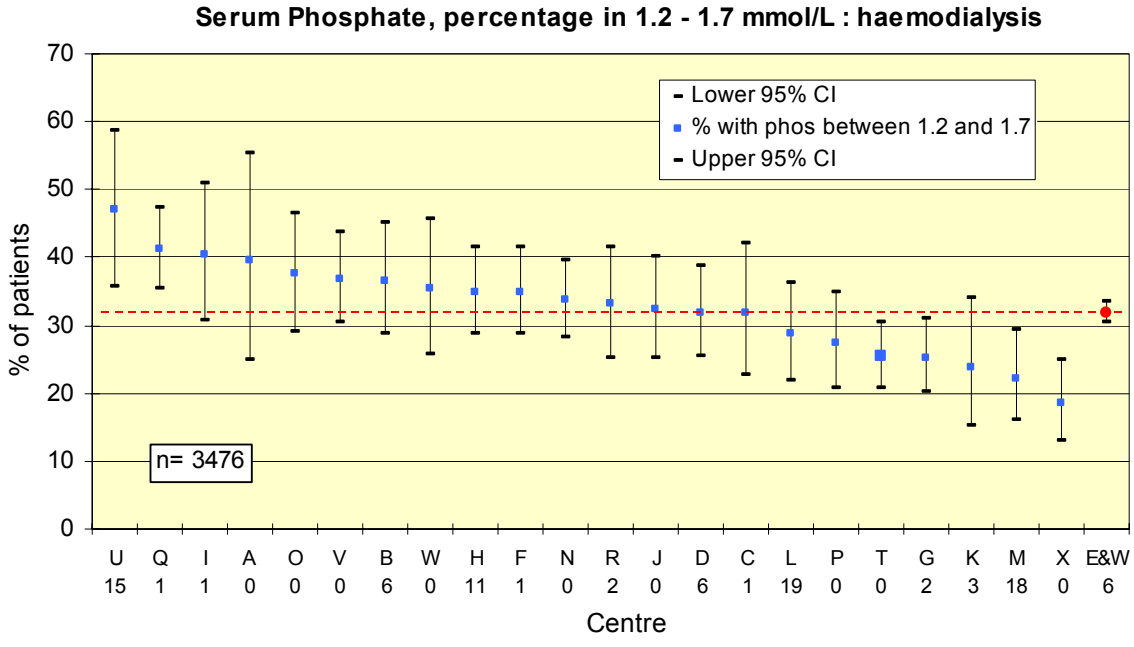

Figure 8.7 Percentage patients with phosphate between 1.2 and 1.7 mmol/L: - HD

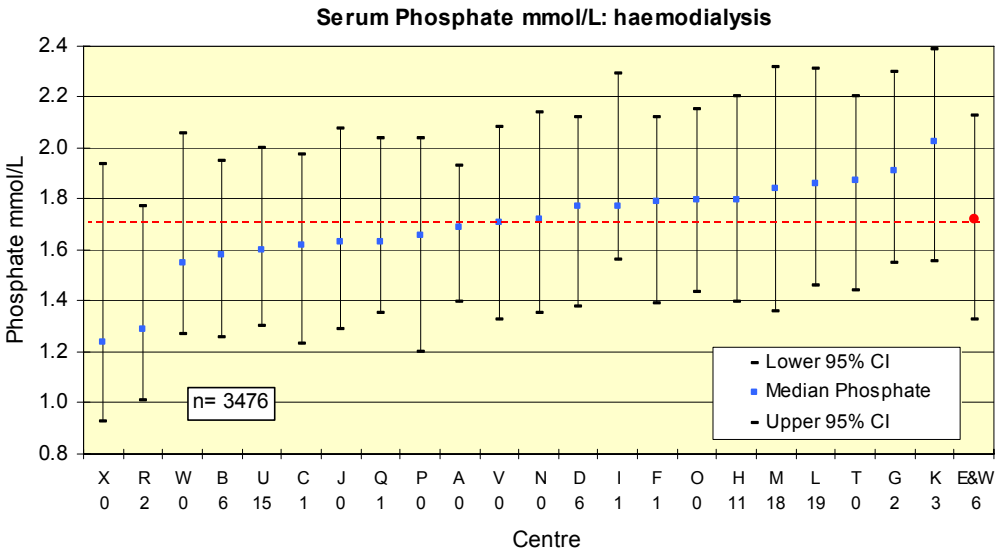

Figure 8.8 Median serum phosphate on haemodialysis

Most centres have difficulty in achieving the suggested standards for phosphate for both haemodialysis (1.1-1.7mmol/l) (figures 8.7, 8.8) and peritoneal dialysis (1.1-1.6mmol/l) (figures 8.9,8.10). Even the best performing centre had <50% of haemodialysis patients within the target range. Overall, for England and Wales only on third of haemodialysis patients had control of serum phosphate within the suggested standard range (figure8.7). Haemodialysis results from centre X should be ignored as on investigation they were post-dialysis samples. Centre X has now instituted a laboratory flag to indicate a post dialysis sample and this is stored on the renal system.

Peritoneal dialysis

The Renal Standards document recommends ***a target range for serum phosphate of 1.1 –1.6 mmol/L.***

The results for peritoneal dialysis patients are shown in figures 8.9 and 8.10

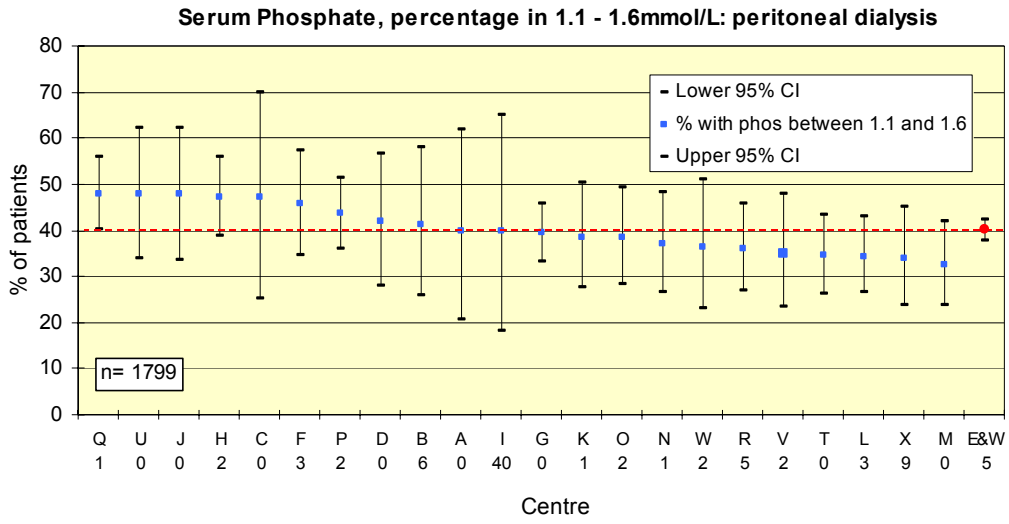

Figure 8.9 Percentage patients with serum phosphate between 1.1 and 1.6 mmol/L: PD

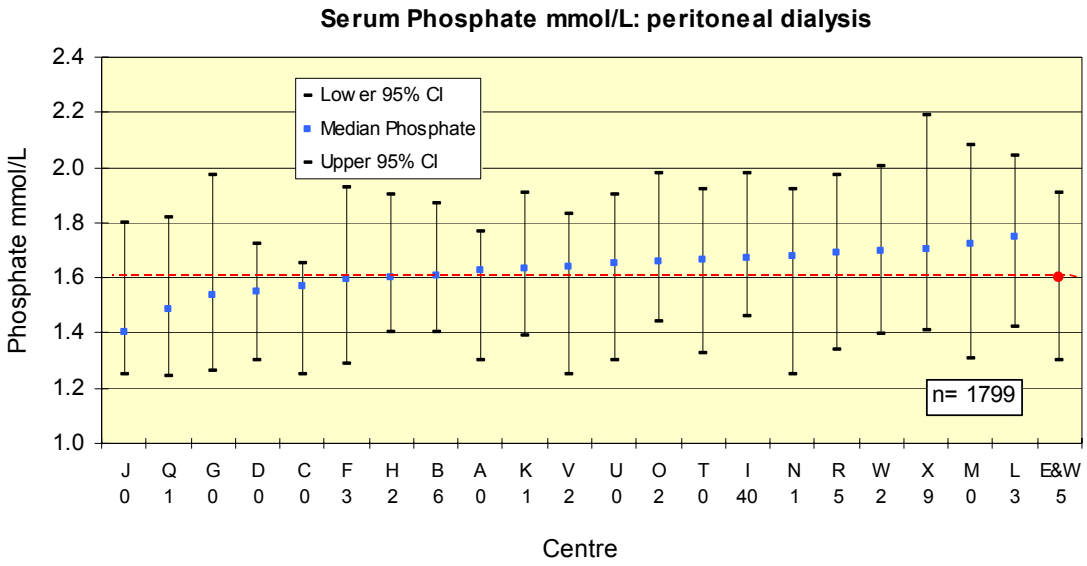

Figure 8.10 Median serum phosphate on peritoneal dialysis

Significance of differences in serum phosphate between centres.

For patients on HD, a chi-squared test was used to determine whether the percentage of patients with phosphate ≤ 1.70 mmol/L differed between centres. For patients on PD, a chi-squared test was used to determine whether the percentage of patients with phosphate ≤ 1.60 mmol/L differed between centres. Note that the analysis used lab-harmonised phosphate.

For patients on HD, the percentage of patients with phosphate ≤ 1.70 mmol/L differed significantly between centres ($X^2 = 129.8$, d.f. = 21, $p<0.001$).

For patients on PD, the percentage of patients with phosphate ≤ 1.60 mmol/L differed significantly between centres ($X^2 = 46.3$, d.f. = 21, $p<0.001$).

Changes in serum phosphate 1998 – 1999

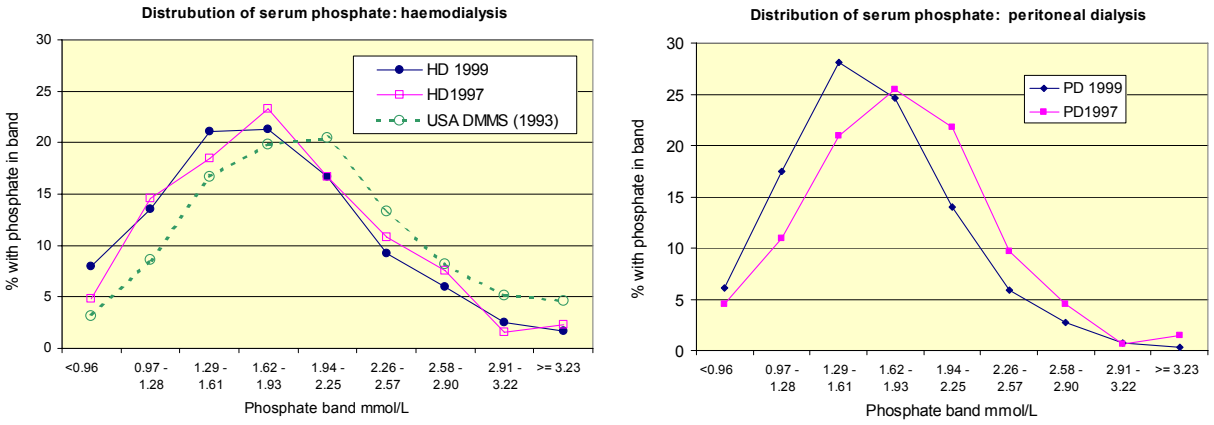

Figure 8.11 Serum phosphate distribution by year
Formula to convert from mmol/L to mg/dl is: - mg/dl = mmol/L x 3.1

The Registry now has serial data on phosphate control. This is compared with data from USRDS in figure 8.11. There is an improvement with time for peritoneal dialysis patients but not for haemodialysis patients

However, there is considerable variation among units with some appearing to improve and others with deteriorating results (figs 8.12 and 8.13). There was no overall change in the proportion of patients with a high serum phosphate.

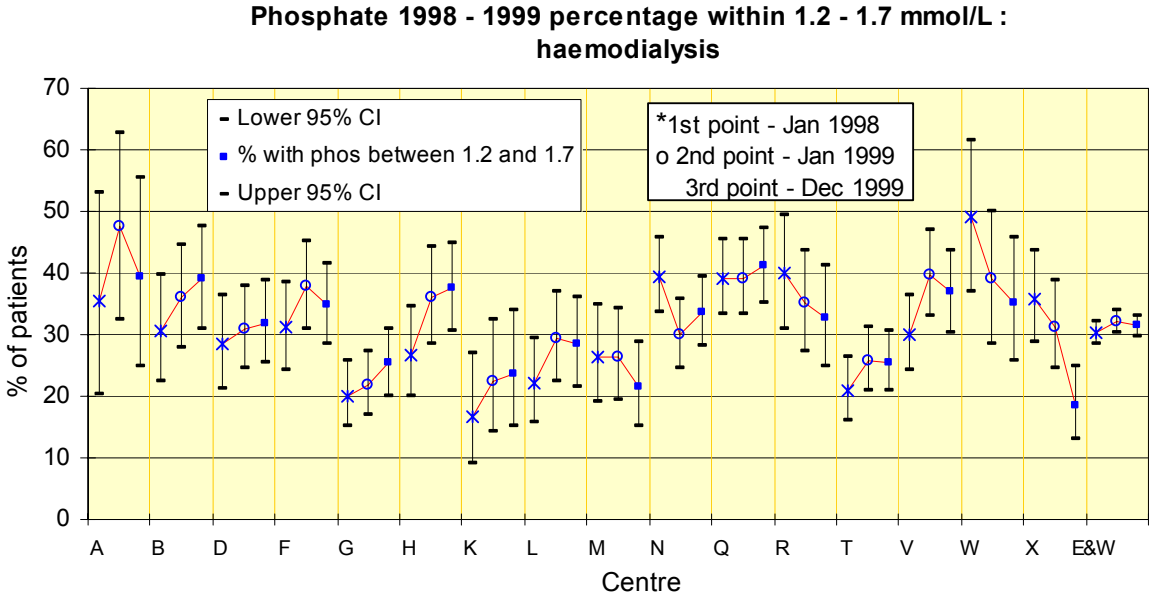

Figure 8.12 Change in % phosphate 1998 – 1999 in range 1.2-1.7 mmol/L: haemodialysis

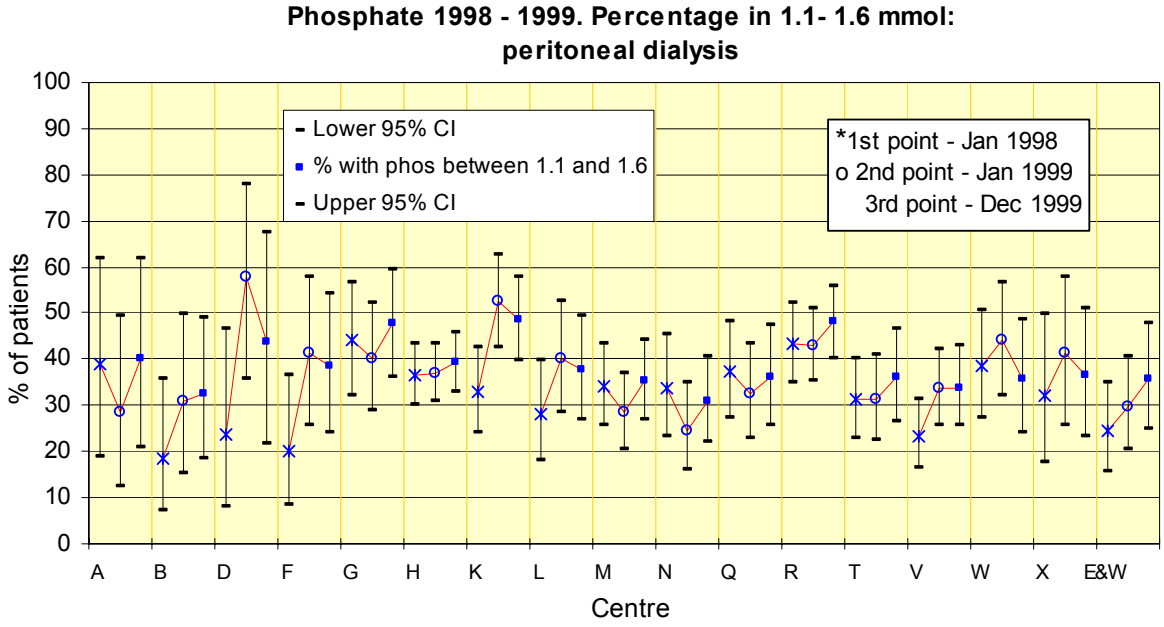

Figure 8.13 Change in phosphate 1998-1999 between 1.1 and 1.6 mmol/L: peritoneal dialysis

Serum parathyroid hormone

Different laboratories use different methodologies for PTH. Even where laboratories use the same assay method local normal ranges vary as shown in table 8.3. For consistency a value of 23pmmol/l has been taken as the upper limit of the standard suggested by the Renal Association, as this is 3x the most commonly quoted upper limit of normal.

Centre	Methodology	Lab ref Range	3 x upper ref. Range
A	Elecsys	15-65 ng/L	20
B	DPC	12-72 ng/L	23
C	DPC	1.3-7.6 pmol/L	23
D	Birmingham S.O	12-72 ng/L	23
E	DPC	12-72 ng/L	23
F	INCSTAR/DPC	10-55/11-62 ng/L	18./20
G	DPC	1.3-7.6 pmol/L	23
H	DPC	12-72 ng/L	23
I	Chiron	10-65 ng/L	16
J	DPC	12-72 ng/L	23
K	DPC	1.3-7.6 pmol/L	23
L	Nichols	0.9-5.4 pmol/L	16
M	DPC	10-70 ng/L	22
N	Chiron	<4.0 pmol/L	23
O	DPC	1.3-7.6 pmol/L	23
P	DPC	10-65 ng/L	20
Q	Nichols	1.0-6.1 pmol/L	18
R	IDS	1.1-4.2 pmol/l	13
T	Nichols	Oct-50	20
U	Nichols	0.9-5.4 pmol/L	16
V	Nichols	10-65 ng/L	20
W	Nichols	0.9-5.4 pmol/L	16
X	DPC	12-72 ng/L	23

Conversion factor: ng/L = pmol/L x 9.5

Table 8.3 Laboratory methodology for serum iPTH

The Renal Standards document recommends ***that iPTH (intact hormone assay) should be maintained at between 2 and 3 times the local normal range***

As in the 1999 Registry report perhaps the most notable fact was the percentage of patients with no PTH data (defined as no value in the previous 9 months). This ranged from 0-28% for haemodialysis, 0-46% for peritoneal dialysis and overall approximately 25% of patients had missing data.

Haemodialysis

The percentage of haemodialysis patients with iPTH <23pmol/l varied from over 80% to <50% (figure 8.14). There was also considerable variation in median serum iPTH concentrations (figure 8.15). This probably reflects differences in approaches to the prevention and management of hyperparathyroidism.

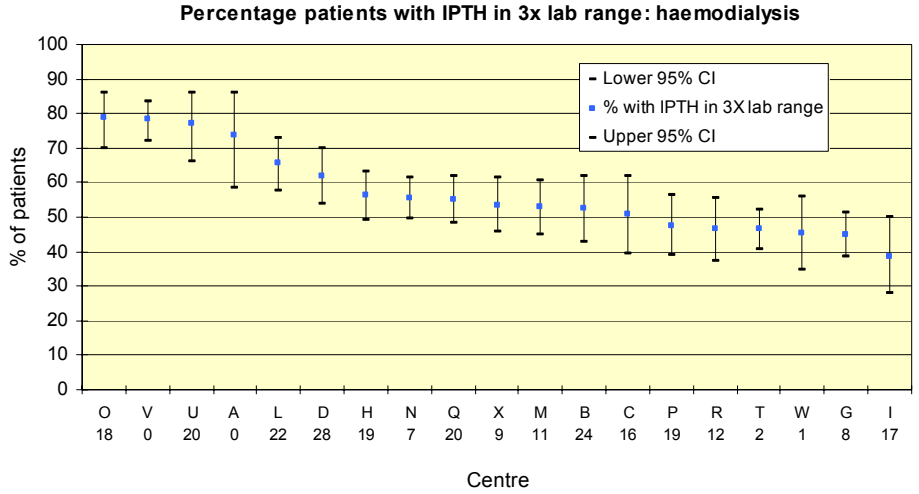

Figure 8.14 Percentage patients with serum iPTH in 3x lab range on HD

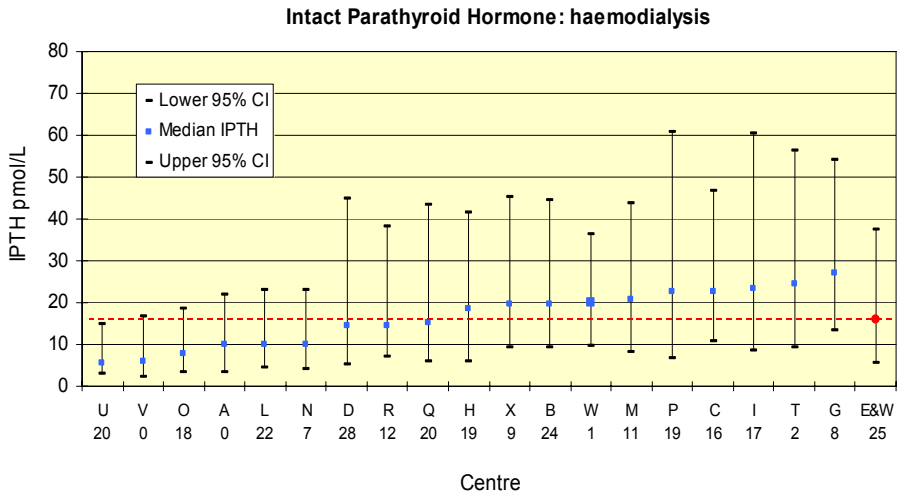

Figure 8.15 Median intact serum parathyroid hormone on HD

Peritoneal dialysis

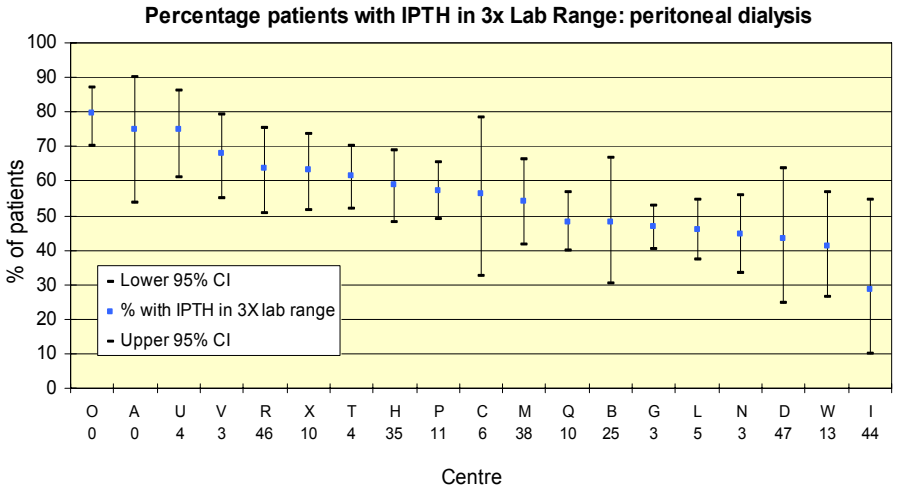

Figure 8.16 Percentage patients with serum iPTH in 3x lab range on PD

There is an even wider variation between units for achievement of the serum iPTH standard in peritoneal dialysis patients than in haemodialysis patients (figure 8.16).

The variation in median iPTH achieved is shown in figure 8.17. As in haemodialysis patients this appears to reflect differing attitudes to control of hyperparathyroidism. Some of the units with relatively low achievement of the standard in haemodialysis patients have much higher relative achievement in peritoneal dialysis patients. This suggests that practices and attitudes may differ within units for the two modalities of dialysis.

The median serum iPTH achieved in peritoneal dialysis patients in each unit are shown in figure 8.17.

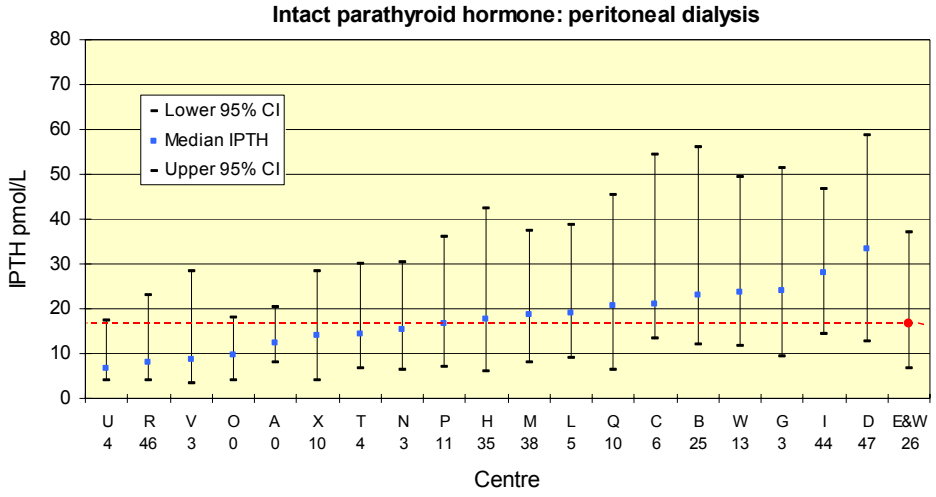

Figure 8.17 Median serum intact parathyroid hormone on peritoneal dialysis

Significance of differences in serum iPTH between centres.

A chi-squared test was used to determine whether the percentage of patients with iPTH ≤ 22.8 pmol/L differed between centres.

For patients on HD, the percentage of patients with PTH ≤ 22.8 pmol/L differed significantly between centres ($X^2 = 239.5$, d.f. = 18, $p<0.001$).

For patients on PD, the percentage of patients with PTH ≤ 22.8 pmol/L differed significantly between centres ($X^2 = 88.8$, d.f. = 18, $p<0.001$).

Conclusions

1. Control of serum calcium varies widely among units and compliance with the target range may be due to either hypo- or hyper-calcaemia
2. There are continuing problems with comparative audit of corrected serum calcium due to the difficulties with albumin measurements. Use of uncorrected calcium concentrations may solve this and should be further explored.

3. Many centres have difficulty achieving the target phosphate concentrations for the majority of patients. These targets may not be achievable with current phosphate binders and dialysis regimes.
4. The variation in control of hyperparathyroidism among centres and between modalities within each centre may reflect different policies. Much could be learned from detailed comparisons of the approaches to the prevention and treatment of hyperparathyroidism between the centres at each end of range.

The Renal Association Standards Committee is currently preparing a new standards document, and is considering several changes. The difficulties regarding different methods for measurement of albumin and the effect on corrected serum calcium will be taken into account. A higher upper limit for the serum phosphate standard is being considered. The recommendations for serum iPTH may also be more liberal.