Chapter 9: Serum Phosphate, Calcium and Parathyroid Hormone

Summary

- Serum phosphate control in dialysis patients is poor, and the variation between units is wide and significant. Four units have median serum phosphates above the standard of 1.8 mmol/L. Overall, only 60% of dialysis patients have serum phosphate under 1.8mmol/L.

- Comparative audit of serum calcium is rendered difficult by the problems of serum albumin measurement and the differences between the BCG and BCP methods for this. The median corrected calcium is just under 2.5 mmol/L for all units and modalities.

- The median PTH for all patients lies well within the standard with little difference between modalities. The spread of PTH levels is remarkable: some units – York and Wrexham – achieve over 90% compliance with the standard, some only 50%.

- The Renal Association has no standard for the serum calcium phosphate product, but the DOQI guidelines recommend the product should be less than 4.4 $mmol^2/L^2$ (= 55 mg^2/dl^2). Control is better on PD; 71% of PD patients achieve the standard, and 62% on HD ($p < 0.01$), with a wide variation between units.

- Registry data show that both poor serum phosphate control and poor calcium phosphate product control correlate with poor survival.

Introduction

Traditionally, control of phosphate, calcium, and parathyroid hormone metabolism has been regarded as control of renal bone disease: while nephrologists have recognised its importance, previous audit data from the Renal Registry reports show that this has never been done well. The clinical focus on this area of metabolism has shifted in the last few years with the appreciation that serum calcium and phosphate control are important to prevent accelerated vascular disease. There is thus a shift of emphasis from what is important in controlling bone disease (when a relatively high serum calcium may be considered acceptable), to what is important in preventing vascular disease, for which control of the serum calcium/phosphate product may be critically important. For this reason, data on control of the serum calcium/phosphate product are included in this chapter.

Recommended target concentrations for all of these analytes are published in the Renal Association Standards document. No separate standards are set for differing dialysis modalities. Nevertheless, differing modalities offer different challenges in achieving metabolic control, so as well as the pooled dialysis data, data for haemodialysis and CAPD are also shown separately.

Serum phosphate

The Renal Association Standard states

> ***Serum phosphate (measured before a dialysis session in HD patients) should be below 1.8mmol/L.***

As ever, serum phosphate control is poor, but the variation between units is wide (Figures 9.1–9.6). Four units have median serum phosphate which lies outside the standard of 1.8 mmol/L. Overall, 60% of dialysis patients have serum phosphate under 1.8mmol/L. In general, the phosphate control is a little better on peritoneal dialysis. For patients on HD, the percentage of patients with a serum phosphate of <1.8 mmol/L differed significantly between centres (χ^2 = 221, d.f. = 39, p < 0.001). For patients on PD, the percentage of patients with a serum phosphate of <1.8 mmol/L differed significantly between centres (χ^2 = 102, d.f. = 38, p < 0.001).

Even the best units have poor phosphate control, but the variability does suggest that a clinical focus on phosphate control can bring biochemical benefits, which might be translated into future survival benefits.

Previous data from the Registry[1] have shown that patients with moderate elevation of serum phosphate have the best prognosis, as was suggested by earlier American studies.[2,3] These patients are thought to be fitter, relatively well dialysed, more active and eating well. The serum phosphate elevation reflects the limits of current dialysis techniques. It should not be assumed that a high phosphate is a good thing; if it could be lowered in these patients it would probably be beneficial to them.

Good phosphate control has not historically been a high clinical priority in many units. Control is largely achieved by a combination of dietary restriction and the use of phosphate binders, but the Registry

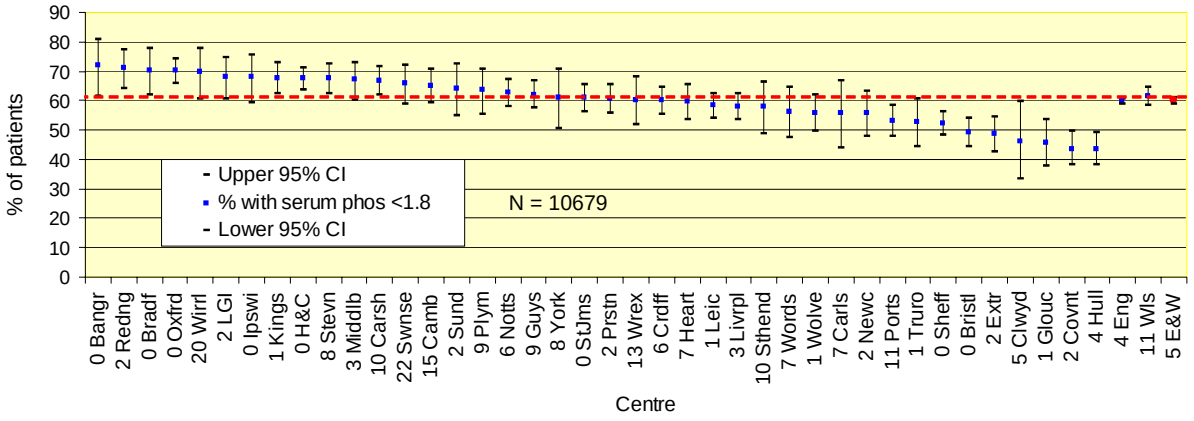

Figure 9.1. Percentage of dialysis patients in RA range for serum phosphate

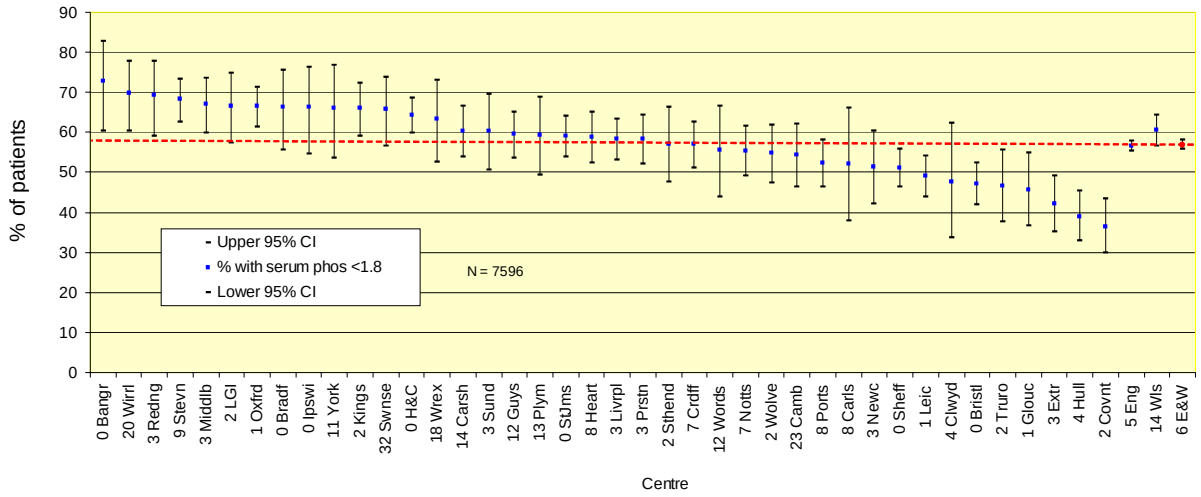

Figure 9.2. Percentage of HD patients in RA range for serum phosphate

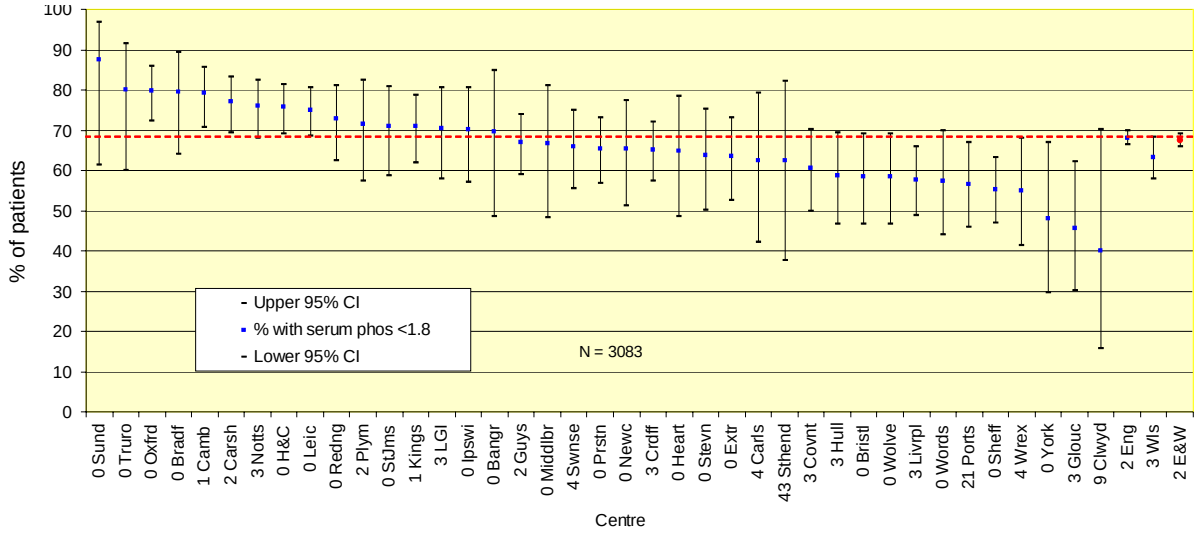

Figure 9.3. Percentage of PD patients in RA range for serum phosphate

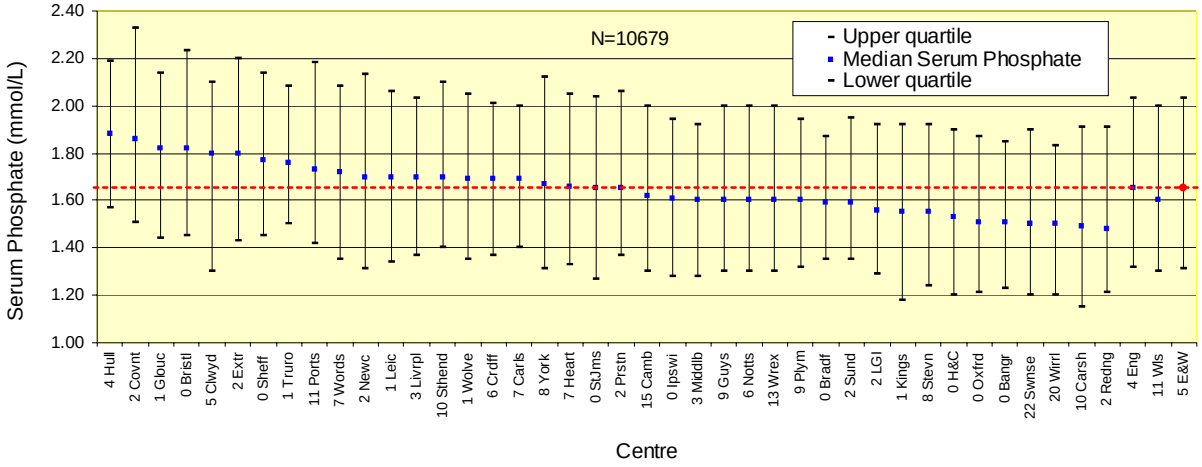

Figure 9.4. Median serum phosphate mmol/L: dialysis patients

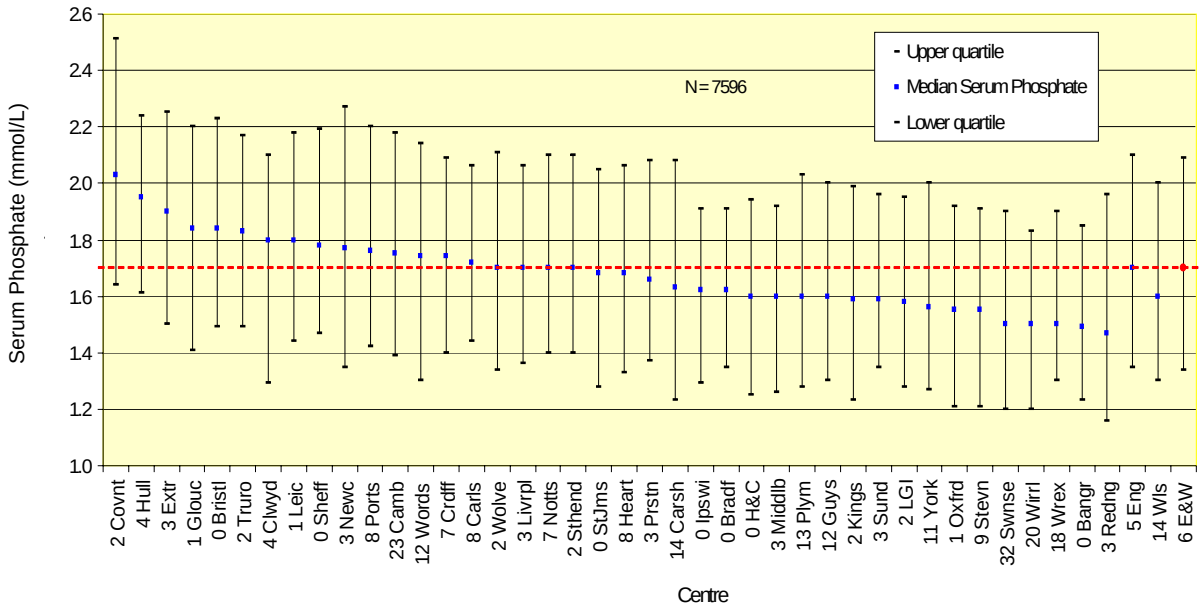

Figure 9.5. Median serum phosphate mmol/L: HD patients

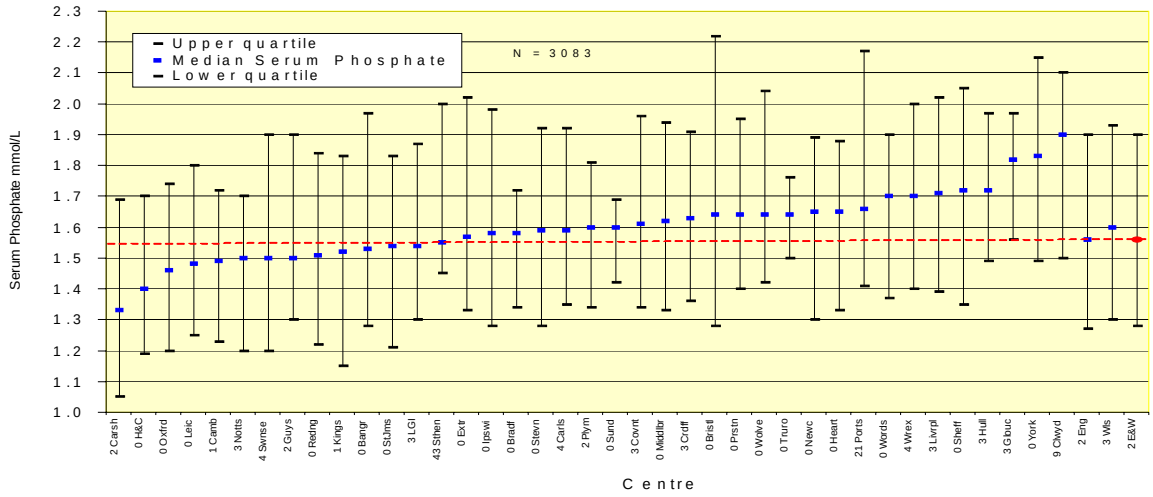

Figure 9.6. Median serum phosphate mmol/L: PD patients

does not have detailed data on the means used to attempt serum phosphate control in individual patients or renal units. A significant number of patients use Alucaps as a phosphate binder, especially if there is a tendency towards hypercalcaemia. This drug will shortly cease to be available in the UK, which will reduce the therapeutic armamentarium, and will have enormous cost implications in patients who cannot take calcium containing phosphate binders. This will put further pressure on the ability of renal units to effect good serum phosphate control.

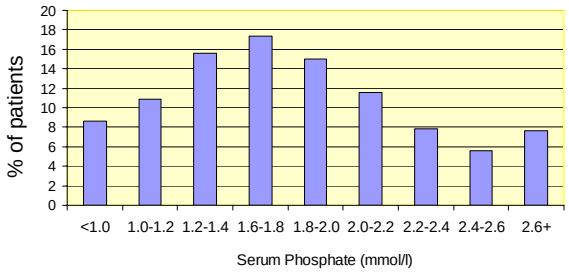

Figure 9.7. Distribution of serum phosphate: all dialysis

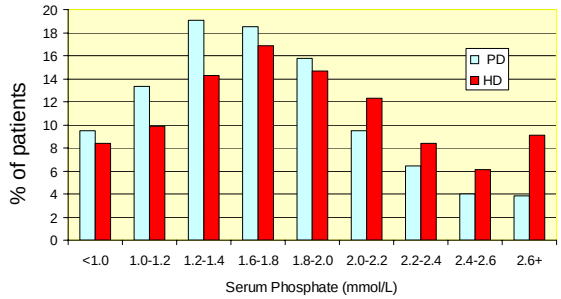

Figure 9.8. Distribution of serum phosphate by PD and HD

The distribution of serum phosphate values for all dialysis patients is shown in Figure 9.7. The differences between HD and PD patients are illustrated in Figure 9. 8.

Figure 9.9 shows the change over 5 years in the mean serum phosphate in all patients from the 19 units who have contributed to the Registry throughout that time. Change has been very small with a fall from 1.74 mmol/L to 1.70 mmol/L for patients on HD and 1.67 mmol/L to 1.56 mmol/L for patients on PD.

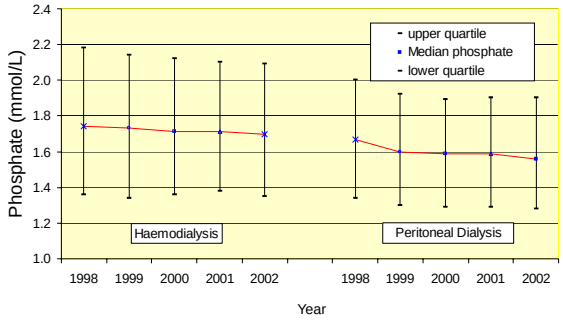

Figure 9.9. Change in median phosphate 1998–2002

Serum calcium

The Renal Association Standard states:

> ***Serum calcium, adjusted for albumin concentration, should be between 2.2 and 2.6 mmol/L, in HD (pre-dialysis sample) and in PD patients.***

As ever, comparative audit in this area is difficult if not impossible. This is largely because of differences in analytical methods between units, and even between satellite units managed by one clinical team. The main problems are:

1. Different methods in analysing serum albumin, particularly the changing use of the BCG and BCP methods, which are not directly comparable in patients with renal failure (see the Registry reports 1999–2002).
2. Different mathematical methods being applied to correct serum calcium for serum albumin concentration.

Consequently, there have been suggestions that the uncorrected calcium should be used for comparative audit. Although all units measure this and hence the data are complete, the Renal Association Standard is for the corrected serum calcium (2.2–2.6 mmol/L).

In previous years, the Registry has uncorrected each unit's corrected calcium using the renal unit's correction formula, and then recorrected the calcium with a single correction formula. This use of a single correction formula allowed a degree of standardisation, but was still susceptible to the problems of serum albumin measurement. Unfortunately, not all units have reported their formula, so

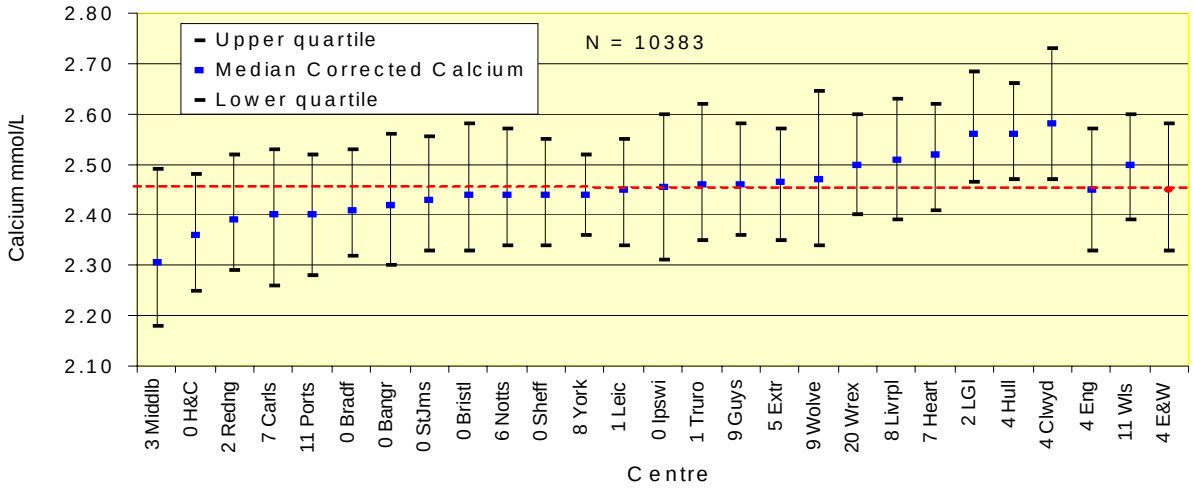

Figure 9.10. Median corrected calcium by centre: dialysis

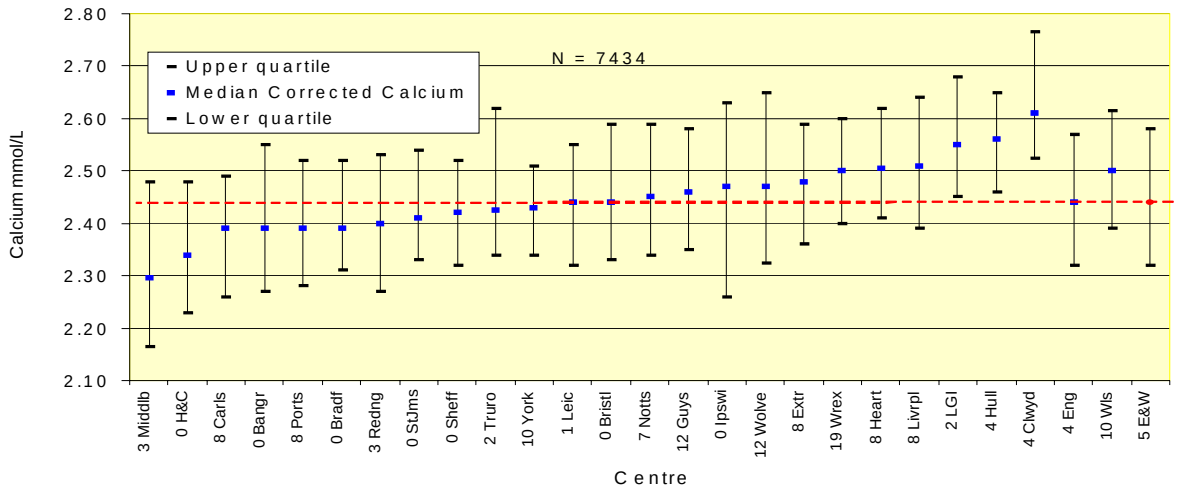

Figure 9.11. Median corrected calcium by centre: HD

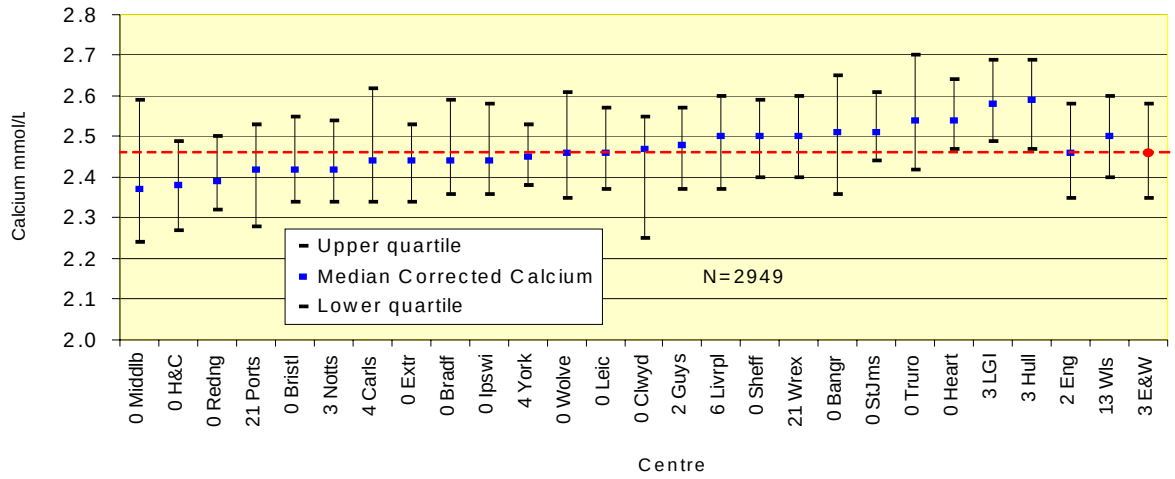

Figure 9.12. Median corrected calcium by centre: PD

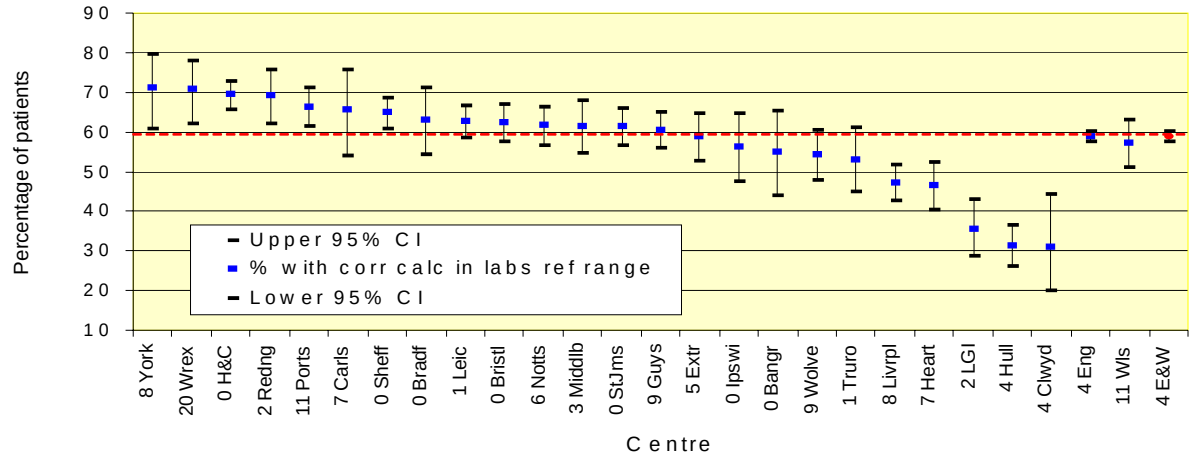

Figure 9.13. Percentage of patients with corrected calcium within 2.2 to 2.6 mmol/L: dialysis

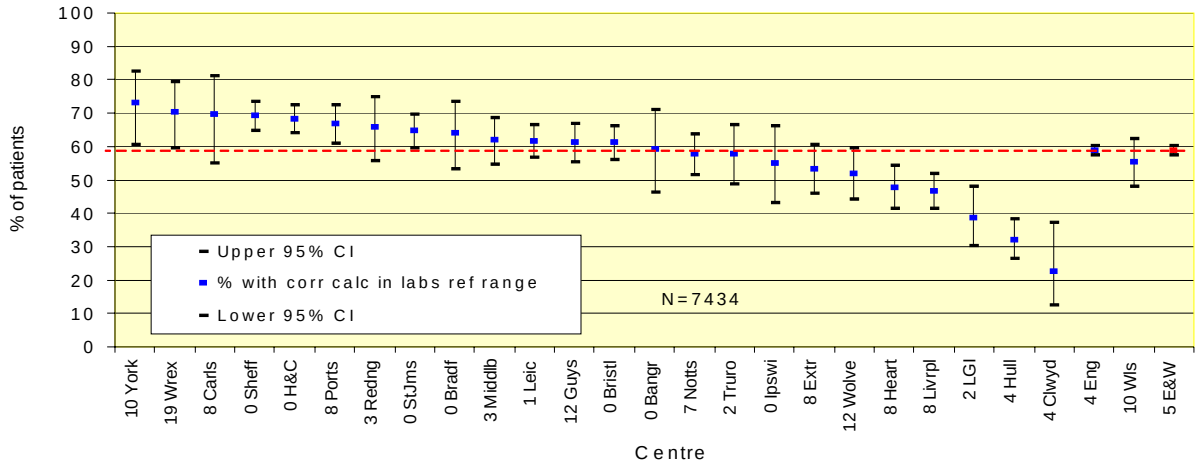

Figure 9.14. Percentage of patients with corrected calcium within 2.2 to 2.6 mmol/L: HD

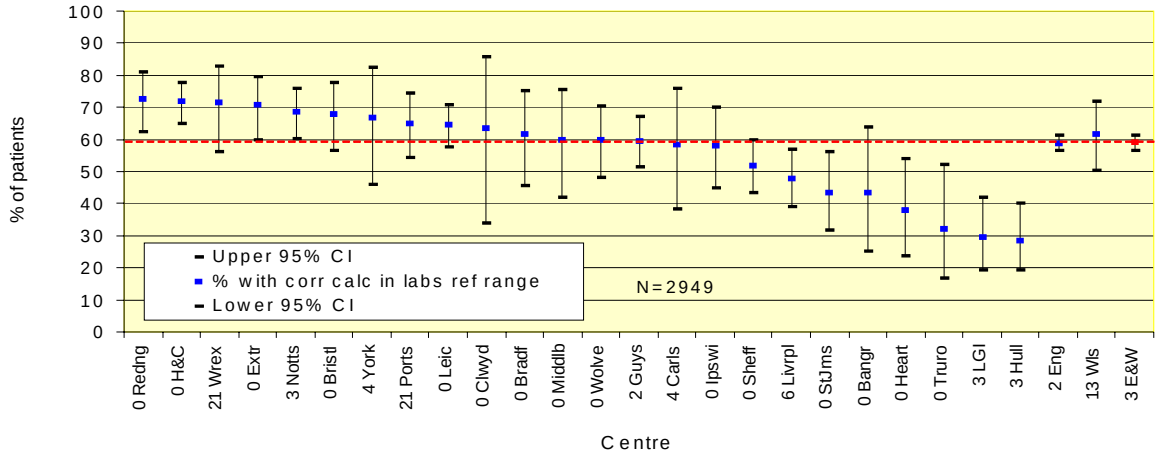

Figure 9.15. Percentage of patients with corrected calcium within 2.2 to 2.6 mmol/L: PD

even standardisation in this way has not been possible this year.

Since nephrologists in each unit will be making clinical decisions based on their local corrected calcium results, these data are in some sense the most valid. Such data allow audit of how well a unit is achieving what it sets out to achieve. Whether a corrected serum calcium of, say, 2.4 mmol/L in Cardiff is the same as a corrected serum calcium of 2.4 mmol/L in Bristol is unknown.

Only 24 units have reported adequate percentages of their own corrected calciums so the data are incomplete. These data are illustrated in Figures 9.10 to 9.15.

The median corrected calcium lies just under 2.5 mmol/L for all units and all modalities: it appears a little higher in PD patients than in those on haemodialysis, but this is not statistically significant. Hypocalcaemia is much less of a clinical problem than hypercalcaemia, perhaps related to the prevalence of calcium based phosphate binders in current use.

Serum parathyroid hormone

The Renal Association Standard states:

> ***Parathyroid hormone (PTH) concentration 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.***

Comparison of serum PTH values from different units is difficult. Analysis from previous years has shown that most laboratories have either taken their upper limit of normal from textbooks, or the assay manufacturer's leaflet (usually derived from USA population). This leads to variations in the quoted normal range. In addition several different assays are in use. The assays used and variations in quoted normal range are listed at the end of this chapter in Table 9.2. To enable some form of comparative audit, the Registry has converted all results to the pmols/L range, and chosen an upper limit of 4 times the median upper lab value.

The Renal Association Standard for serum PTH in dialysis patients gives an upper limit only – four times the upper limit of normal for a laboratory, and does not suggest that there is a clinical risk associated with over suppression of PTH. The median PTH for all patients lies well within the standard although the distribution is wide (Figures 9.16 to 9.21). There seems little difference in absolute PTH between PD and haemodialysis patients. The spread of PTH levels is remarkable however, with some

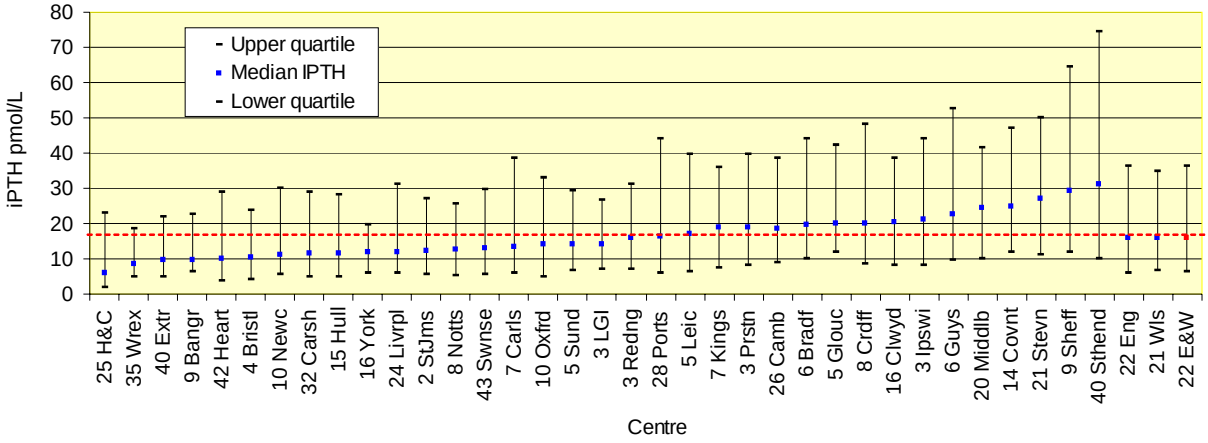

Figure 9.16. Median iPTH by centre: dialysis

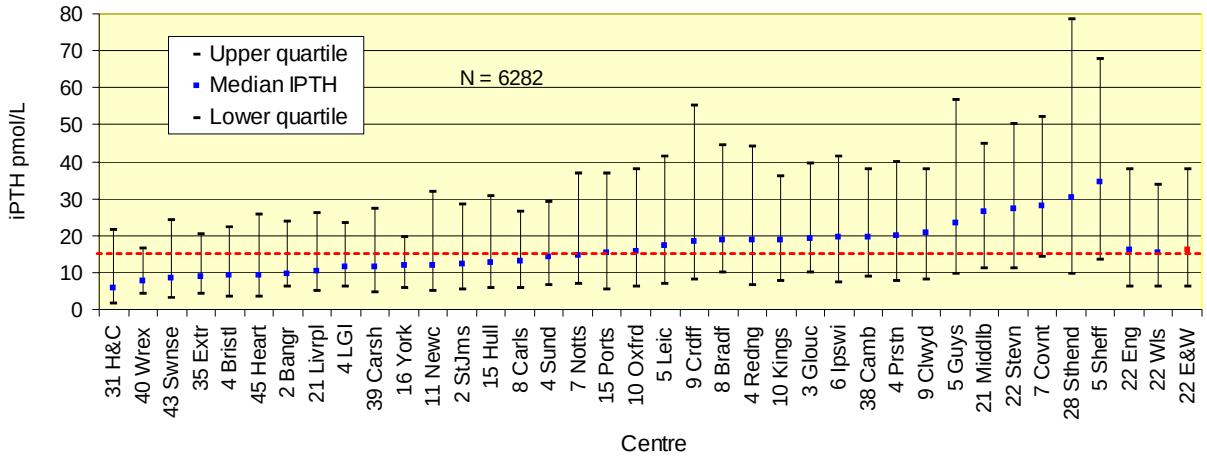

Figure 9.17. Median iPTH by centre: HD

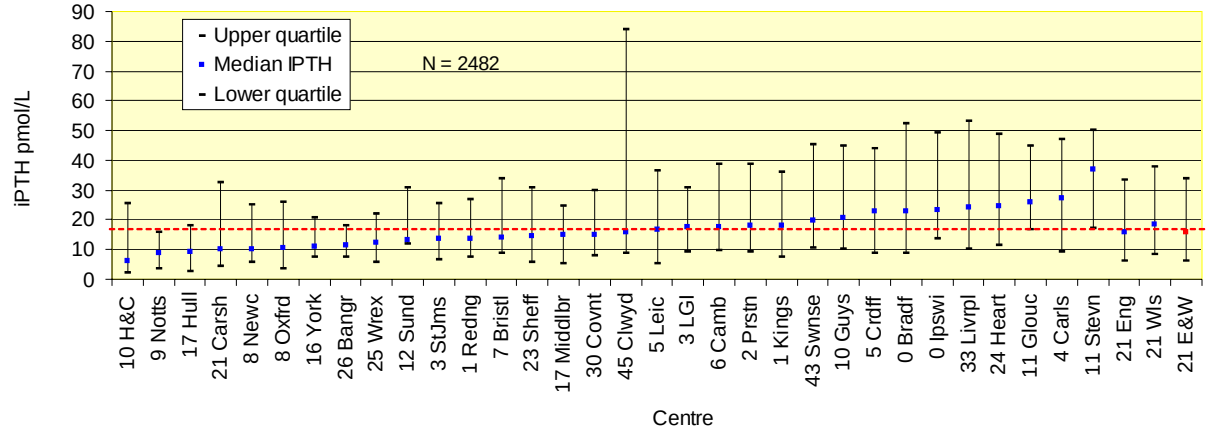

Figure 9.18. Median iPTH by centre: PD

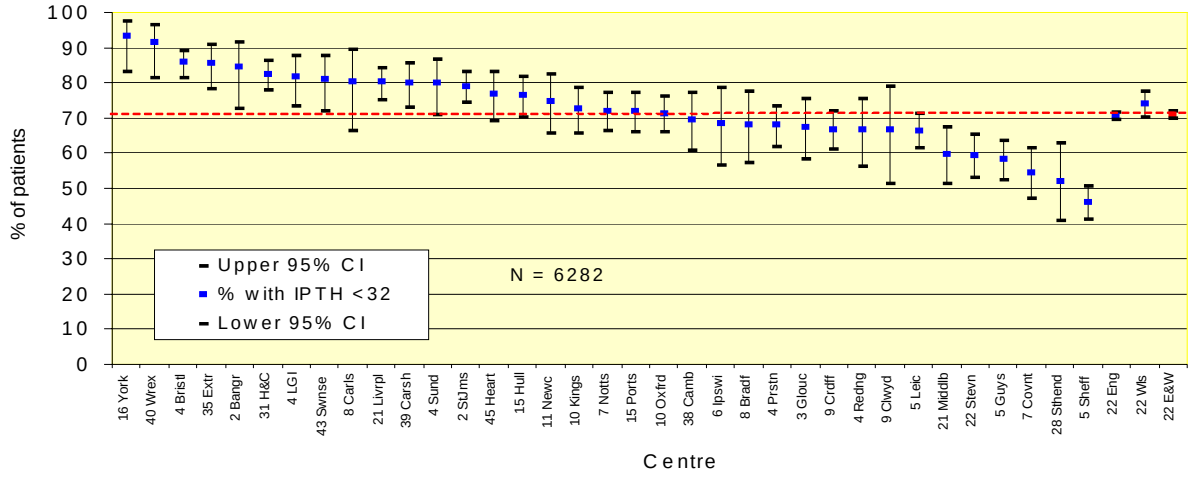

Figure 9.19. Percentage of patients with iPTH < 32 pmol/L: dialysis

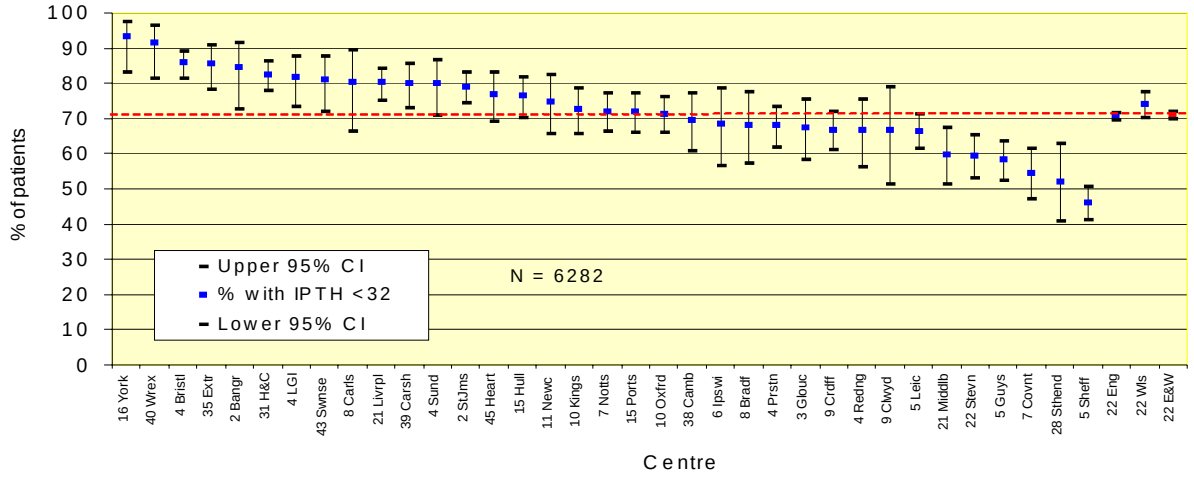

Figure 9.20. Percentage of patients with iPTH < 32 pmol/L: HD

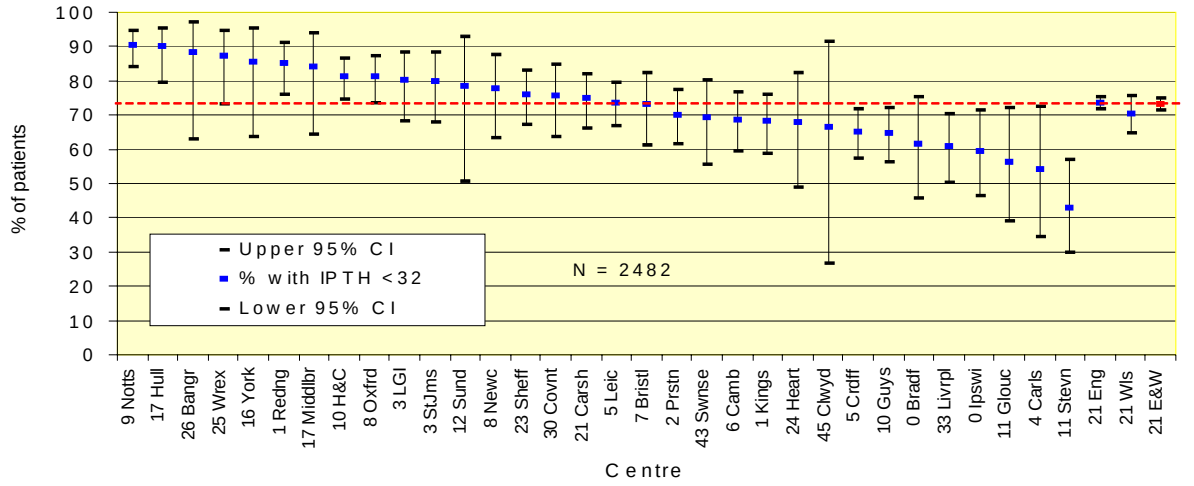

Figure 9.21. Percentage of patients with iPTH < 32 pmol/L: PD

units – York and Wrexham – achieving over 90% compliance with the standard, while at the other end of the scale, only 50% compliance is achieved.

Calcium/phosphate product

The Renal Association has no standard for the serum calcium phosphate product.

The Renal Association has no standard for the serum calcium phosphate product, but the DOQI guidelines recommend the product should be less than 4.4 $mmol^2/L^2$ (= 55 mg^2/dl^2). A little over half of our reporting units achieve this as a median but the range is wide. Control is better on PD, with 71% of patients achieving the standard, than HD (62%) ($p < 0.01$) (Figures 9.22 and 9.23).

Serum phosphate and survival

Registry data show that poor phosphate control and poor calcium phosphate product control correlate with poor survival, although they are clearly not entirely independent variables. However, differing calcium methodology confuses this somewhat. This emphasises the importance of this area of metabolism with the links to cardiovascular disease being potentially more important than damage to the skeleton.

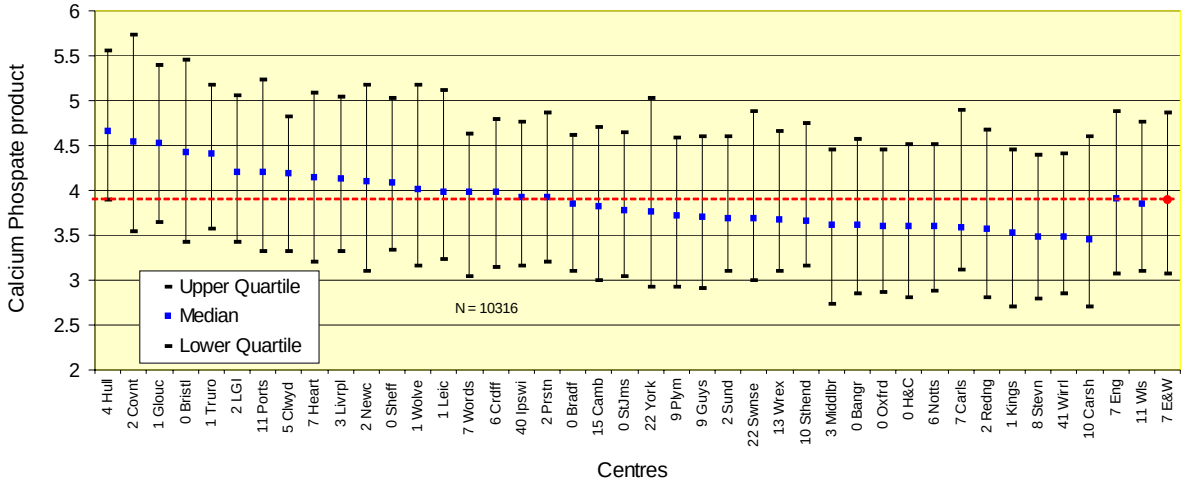

Figure 9.22. Calcium phosphate product in dialysis patients

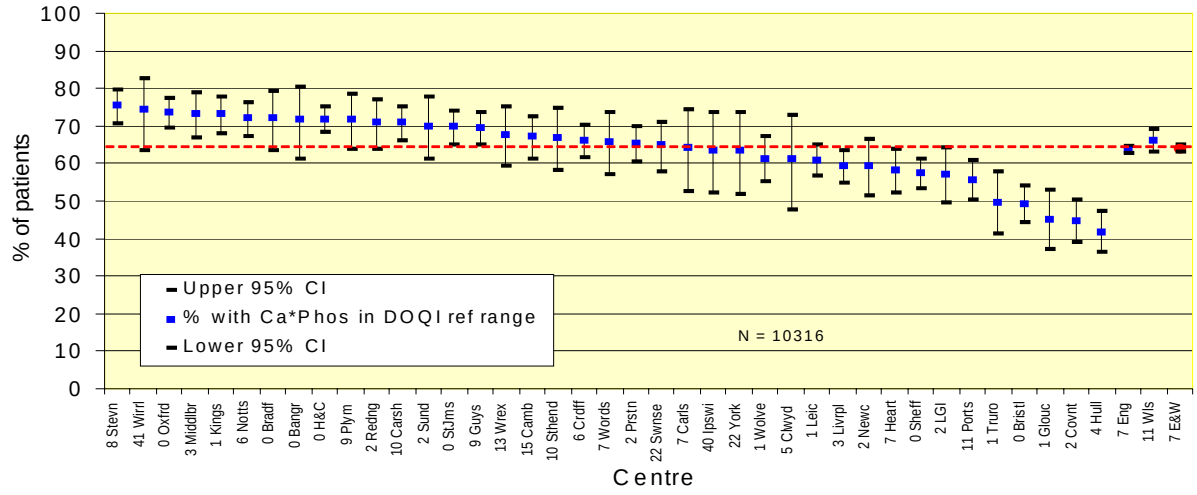

Figure 9.23. Compliance with the calcium phosphate DOQI guidelines in dialysis patients

Figure 9.24 shows the increased hazard of death with increasing serum phosphate. This has not been previously analysed by modality, but the risk of death with increasing phosphate is the same for both HD and PD. The non-linear association with survival was significant for both HD and PD ($p = 0.003$ and $p = 0.016$ respectively).

As serum albumin is an inverse inflammatory marker it has been shown in many studies to be closely linked with patient survival. Analysis of uncorrected calcium and survival shows a strong inverse correlation with survival as low uncorrected calcium is linked to low serum albumin levels ($p \leq 0.009$ HD, $p \leq 0.004$ PD). Using an albumin correction factor for calcium (BCG methodology only) this correlation with survival disappears ($p = 0.95$ HD and PD). Although the suggested correction formulae for BCP and BCG albumin methodologies are identical, the albumin values are very different so results have been analysed separately.

The uncorrected calcium phosphate product and hazard of death show a similar relationship for both HD and PD. Treated non-linearly, there is a significant effect of calcium/phosphate product on survival in HD patients and to a lesser extent PD (HD $p=0.007$, PD $p=0.009$). After adjusting for albumin, the risk increases for PD patients (Figures 9.25 and 9.26).

Laboratory methodologies

The methodologies used in each laboratory are listed in Tables 9.1 and 9.2.

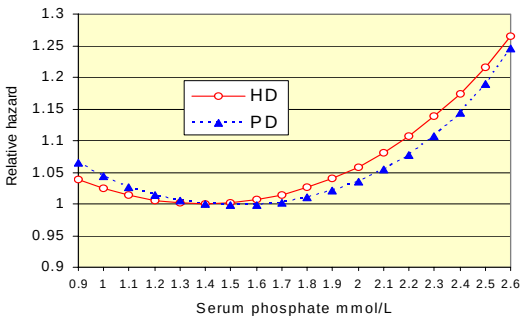

Figure 9.24. Serum phosphate and relative hazard of death by modality

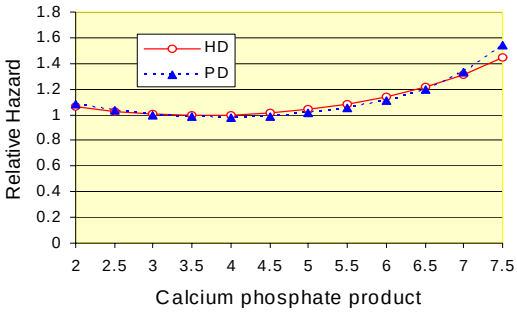

Figure 9.25. Uncorrected calcium phosphate product and relative hazard of death

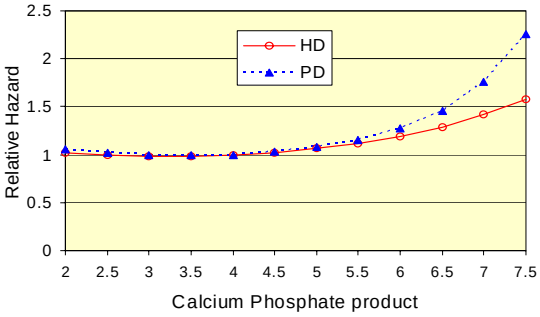

Figure 9.26. Corrected calcium (BCG albumin) phosphate product and relative hazard of death

Table 9.1. Serum calcium methodology

Laboratory	Method	Uncorrected Ref Range	Corrected Ref Range	Formula
Birmingham Heartlands	CPC	2.05–2.60	N/A	+0.025(40 –Alb)
Bradford	CPC	Not Reported	2.15–2.55	+(40 – Alb/40)
Cardiff (UHW) New analyser	Arsenazo	2.20–2.60	2.20–2.60	+0.02(40 – Alb)
Carlisle/Cumberland	Arsenazo	2.10–2.60	2.10–2.60	+0.02(40 – Alb)
Carshalton, St Helier	CPC	2.20–2.60	2.20–2.60	+0.02(40 – Alb)
Gloucester	Electrode	2.13–2.63	2.13–2.63	+0.02(40 – Alb)
Hull	Electrode	2.20–2.60	2.20–2.60	+(–0.016 × Alb) + 0.59
Leicester (LRI)	Arsenazo	2.10–2.60	2.10–2.60	+0.02(40 – Alb)
Leeds St James	CPC	2.20–2.60	2.20–2.60	+0.016(46 – Alb)
Liverpool (Royal)	CPC	2.20–2.60	2.20–2.60	+0.003(40.4 – Alb)
Nottingham	Arsenazo	2.40–2.80	N/A	+0.017(43 – Alb)
Plymouth Derriford	CPC	2.12–2.55	2.12–2.55	+0.025(40 – Alb)
Portsmouth (Queen Alex)	CPC	2.15–2.60	2.15–2.60	–(Alb × 0.017) + 0.70
Reading (Royal Berkshire)	Arsenazo	2.10–2.55	2.10–2.55	+1 – (albumin/41)
Southend*2 instruments in use Beckman& Dax	CPC	2.05–2.65	2.10–2.60	+(40 – Alb)0.02
Stourbridge/Wordsley (analysed at Dudley)	Arsenazo	2.20–2.60	2.20–2.60	+0.02(40 – Alb)
Sunderland	CPC	2.12–2.65	N/A	N/A
York	CPC	2.10–2.60	2.10–2.60	–(Alb × 0.25) +1
Wolverhampton	Arsenazo	2.17–2.66	2.17–2.66	+1 – (alb/40)
Wrexham	Electrode	2.10–2.65	2.10–2.65	–((0.071 × A3b) + 0.692)

* Conversion factor for calcium: mg/dl = mmol/L × 4s

Table 9.2. Serum phosphate and PTH methodologies

	Phosphate (mmol/L)		PTH	
Laboratory	**Method**	**Ref Range**	**Method**	**Ref Range**
Birmingham Heartlands	PMb	0.80–1.45	Elecsys (P Clark)	30–400ng/ml
Bradford	PMb	0.80–1.31	Nichols (LGI)	<65 ng/ml
Cardiff (UHW) New analyser	PMb	0.80–1.45	Nichols	0.9–5.4 pmol/L
Carlisle/Cumberland	PMb	0.90–1.50	Elecsys	15 – 65 ng/L
Carshalton, St Helier	PMb	0.80–1.40	DPC	3–48 ng/L
Gloucester	PMb	0.82–1.55	Nichols	0.9–5.4 pmol/L
Hull	PMb	0.70–1.50	DPC	7–53 ng/ml
Leicester (LRI)	PMb	0.80–1.40	DPC	1.3–7.6 pmol/L
Leeds St James	PMb	0.80–1.30	Nichols	11–55 ng/ml
Liverpool (Royal)	PMb	0.70–1.40	Nichols	1.1–6.9 pmol/L
Nottingham	PMb	0.80–1.40	DPC	8–78 ng/ml
Plymouth Derriford	PMb	0.80–1.40	DPC	12–72 ng/L
Portsmouth (Queen Alex)	PMb	0.80–1.50	DPC Immulite	<4.7 pmol/L
Reading (Royal Berkshire)	PMb	0.81–1.45	DPC	0.7–5.6 pmol/L
Southend*2 instruments in use Beckman& Dax	PMb	0.80–1.45	Roche elecys	1.05–6.9 pmol/L
Stourbridge/Wordsley (analysed at Dudley)	PMb	0.80–1.40	DPC	0.45–5.0 pmol/L
Sunderland	PMb	0.80–1.40	DPC	1.3–7.6 pmol/L
York	PMb	0.80–1.40	Nichols	10–60 ng/L
Wolverhampton	PMb	0.80–1.40	DPC	0.76–7.42 ng/L
Wrexham	PMb	0.80–1.40	Nichols	0.9–5.4 pmol/L

* Conversion factor for phosphate: mg/dl = mmol/L × 3.1
PMb = Phospho-molybdate method

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