Chapter 10: Serum Calcium, Phosphate and Parathyroid Hormone

Summary

- Results for corrected calcium are highly dependent on serum albumin measurement. Units using the BCP method of albumin measurement have higher levels of corrected calcium and fewer patients within the standard range.

- Of all dialysis patients, 71% had a corrected serum calcium within the standard range. There was no significant difference between haemodialysis and peritoneal dialysis patients.

- Only 50% of dialysis patients had a serum phosphate within the standard range. The phosphate level was significantly lower in peritoneal dialysis patients.

- Serum intact parathyroid hormone fell within the standard range in 58% of dialysis patients.

- For corrected calcium, serum phosphate and intact parathyroid hormone, the range of difference between units was significant.

- There has been no improvement in control of these variables in the 5 years for which the Registry has data.

- With current dialysis techniques and drugs available, renal units find compliance with the recommended standards extremely difficult.

Introduction

The control of calcium, phosphate and parathyroid hormone (PTH) activity in patients receiving renal replacement therapy (RRT) is important in preventing progressive renal osteodystrophy and ectopic calcification. There is increasing evidence that a poor control of calcium/phosphate metabolism accelerates cardiac and vascular disease. Recommended target concentrations for all of these analytes are published in the Renal Association Standards document.

Considering that the measurement of 'routine' biochemical parameters is bread and butter medicine for nephrologists, and that it is easy to establish consensus that a low albumin and poorly controlled calcium metabolism are to be avoided, comparative audit in this area is very hard.

The problem stems first from the well–rehearsed differences in measurement of serum albumin from centre to centre, both in terms of the assay and in terms of defining normality. This is compounded by differing mathematical approaches to 'correcting' the calcium. This means that a corrected calcium that is apparently the same from two centres may not actually *be* the same.

These problems lead to more than semantic arguments. Small differences can make a centre compliant or non-compliant with Renal Association Standards. Renal units with several satellites may use different laboratories and make even internal comparison difficult. It has been suggested that using uncorrected calcium might facilitate comparative audit, but this probably brings an equally difficult set of unquantifiable confounding variables. Measuring ionised calcium would be the ideal approach.

The latest Renal Association Standards document sets the same standards for calcium, phosphate and PTH whatever the modality of treatment. The concept of a 'renal failure career' is gaining currency, so although we continue to report haemodialysis (HD) and peritoneal dialysis (PD) data separately, the different treatment modality data are also combined for each unit, unlike in previous reports.

When comparing the percentage achievement of standards by different renal units, chi squared analysis confirms that these differences are significant (see Chapter 14).

The Standards

The recommended Standards for these variables in 2001 were:

Serum calcium: 'Total calcium within the normal range quoted by the local pathology laboratory, corrected for serum albumin concentration, or normal serum ionised calcium.' For HD patients, samples should be taken pre-dialysis.

Serum phosphate: HD, pre-dialysis sample, 1.2–1.7 mmol/L.
PD, 1.1–1.6 mmol/L.

Serum intact PTH: Should be maintained at between two and three times the local normal range.

Serum calcium

Measurement

Since different units use different assay methods for calcium and albumin, different correction factors for albumin and different reference ranges for both variables, these are tabulated (Table 10.1). The Renal Registry has used the formula:

$$\text{Corrected calcium} = \text{uncorrected calcium} + [(40 - \text{albumin}) \times 0.02]$$

The registry has either calculated the corrected calcium from the total calcium and the serum albumin or 'back–calculated' the total calcium using the local value for corrected calcium, the serum albumin level and the local correction factor.

The BCG method of albumin measurement overestimates low levels of serum albumin (see Chapter 11). Consequently, when the albumin is low, the calculated corrected calcium will be lower than the 'true' corrected calcium, possibly concealing hypercalcaemia.

City	Hospital	Method (calcium)	Method (albumin)	Ref range (total calcium)	Correcting formula
Birmingham	Heartlands Hospital	CPC	BCG	2.05– 2.60	+0.025(40–Alb)
Bradford	St Luke's Hospital	CPC	BCG	Not reported	+(40–Alb/40)
Bristol	Southmead Hospital	CPC	BCG	2.10–2.65	+0.02(40–Alb)
Cardiff	University of Wales Hospital	Arsenazo	BCG	2.20–2.60	+0.02(40–Alb)
Carlisle	Cumberland Infirmary	Arsenazo	BCG	2.10–2.60	+0.02(40–Alb)
Carshalton	St Helier Hospital	CPC	BCG	2.20–2.60	+0.02(40–Alb)
Coventry	Walsgrave Hospital	Arsenazo	**BCP**	2.22–2.58	–((0.0116×Alb)+0.4652)
Derby	Derby District Hospital	Aresenazo	**BCP**	2.25–2.60	+0.012× (40–Alb)
Exeter	Royal Devon and Exeter Hospital	Arsenazo	BCG	2.20–2.70	+0.02(40–Alb)
Gloucester	Gloucester Road Infirmary	Electrode	**BCP**	2.13–2.63	+0.02(40–Alb)
Hull	Hull Royal Infirmary	Electrode	**BCP**	2.20–2.60	+(–0.016×Alb)+0.59
Leeds	St James's Hospital	CPC	BCG	2.20–2.60	+0.016(46–Alb)
Leeds	LGI	CPC	BCG	2.25–2.60	+(Alb–40) ×0.0225
Leicester	Leicester General Hospital	Arsenazo	BCG	2.10–2.60	+0.02(40–Alb)
Liverpool	Liverpool Royal Hospital	CPC	BCG	2.20–2.60	+0.003(40.4–Alb)
London	Guys St Thomas'	Electrode	**BCP**	2.20–2.60	+0.02(40–Alb)
Middlesborough	South Cleveland	Arsenazo	BCG	2.10–2.60	+0.02(40–Alb)
Newcastle	Royal	Arsenazo	BCG	2.12–2.60	+0.02× (40–ALB)
Nottingham	Nottingham City Hospital	Arsenazo	**BCP**	2.40–2.80	+0.017(43–Alb)
Oxford	Churchill Hospital	Arsenazo	BCG	2.12–2.62	Not reported
Plymouth	Derriford Hospital	CPC	BCG	2.12–2.55	+0.025(40–Alb)
Portsmouth	Queen Alex	CPC	BCG	2.15–2.60	–(Alb×0.017) +0.70
Preston	Royal Preston Hospital	CPC	BCG	2.18–2.63	+0.02(40–Alb)
Reading	Royal Berkshire	Arsenazo	BCG	2.10–2.55	+1–(albumin/41)
Sheffield	Northern General Hospital	Arsenazo	BCG	2.20–2.60	–((0.0175×Alb)+0.7)
Stevenage	Lister Hospital	Electrode	**BCP**	2.20–2.63	+0.025(40–Alb)
Stourbridge	Wordsley Hospital	Arsenazo	BCG	2.20–2.60	+0.02(40–Alb)
Southend	Southend Hospital	CPC	BCG	2.05–2.65	+ (40–Alb) 0.02
Sunderland	Sunderland Royal Hospital	CPC	BCG	2.12–2.65	Not reported
Swansea	Morriston	CPC	BCG	2.15–2.60	+0.02× (40–Alb)
Truro	Royal Cornwell Hospital Trust	CPC	BCG	2.15–2.60	+0.02× (41–Alb)
Wolverhampton	Newcross Hospital	Arsenazo	BCG	2.17–2.66	+1–(alb/40)
Wrexham	Maelor General Hospital	Electrode	**BCP**	2.10–2.65	–((0.071×Alb)+0.692)
York	York District Hospital	CPC	BCG	2.10–2.60	–(Alb× 0.25) +1

Table 10.1: Methods used to measure and 'correct' serum calcium

Results

The new Renal Association Standard for calcium states that the serum calcium, adjusted for albumin concentration, should be between 2.2 and 2.6 mmol/L, measured pre-dialysis in HD patients and PD patients. For current data, given the variability in albumin measurement techniques and local normal ranges, the Registry has calculated compliance using a Standard of 2.25–2.65 mmol/L, which was current in 2001, but will use with the new Renal Association Standard next year.

Figure 10.1 shows the corrected calcium for PD and HD patients combined, and Figure 10.2 what proportion of patients in any unit have values within the range 2.25–2.65 mmol/L. It is apparent that hypocalcaemia is not a significant issue but that several units have median corrected calcium concentrations that lie above the standard range. This probably represents a different approach to calcium metabolism in these units.

Figures 10.3–10.6 show similar data for the same units but with the data split by treatment modality.

There seems to be little difference between HD and HD with regard to corrected calcium, but there is more variability between units in the PD data. Overall, very close to 70% of UK patients are compliant with the Standard, regardless of treatment modality.

In all the figures, units that use the BCP method of measuring serum albumin have been indicated with large blocks. It is interesting that seven out of the eight units using this method have a median corrected calcium *above* the national median. This is the expected result of obtaining a lower serum calcium reading, assuming the use of formulae for correction similar to those used in BCG laboratories. It thus appears that the subsequent clinical response to these readings does not fully modify the corrected calcium obtained back towards the median.

The distribution of differences between units in compliance with the standard is statistically significant for corrected calcium and also for serum phosphate and intact PTH (iPTH).

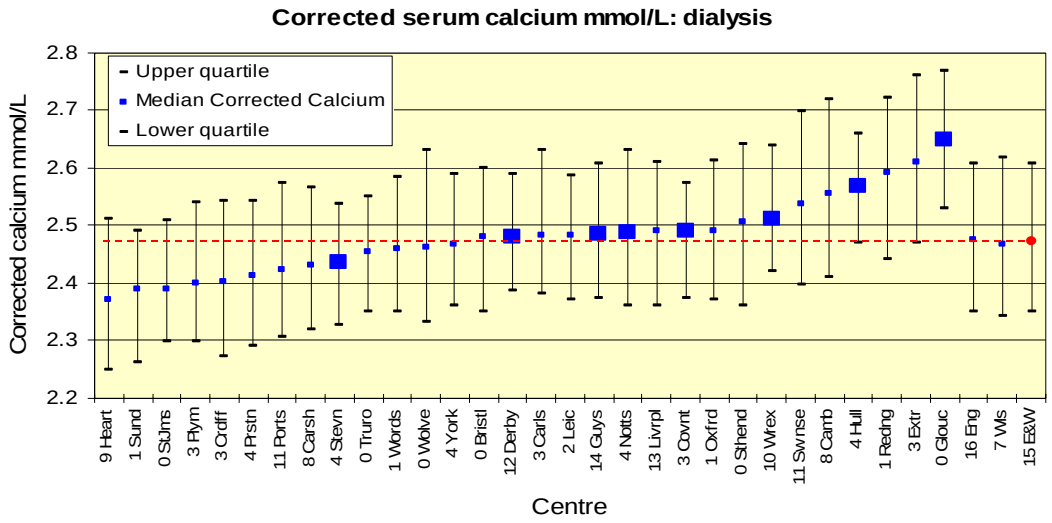

Figure 10.1: Median corrected calcium, all HD and PD patients (large block = BCP centre)

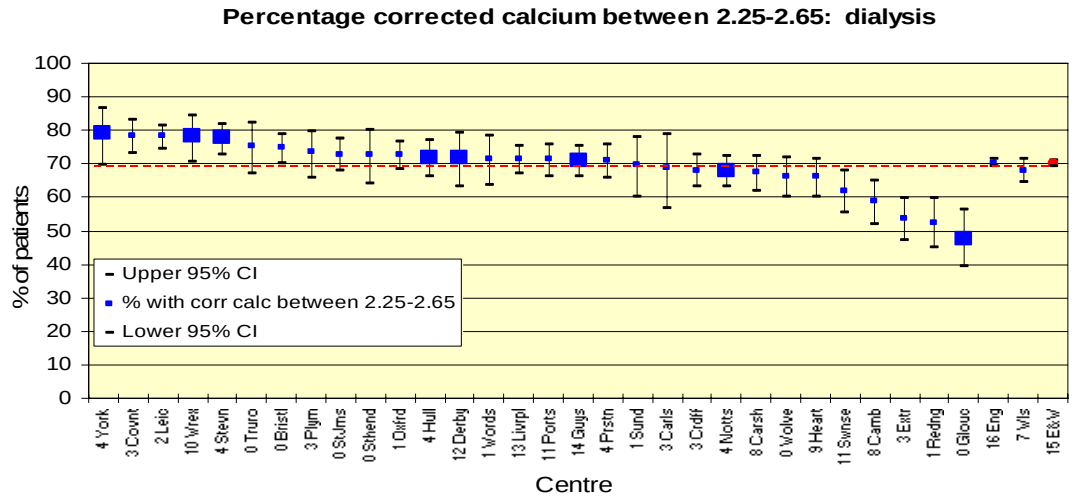

Figure 10.2: Percentage corrected calcium in the range 2.25–2.65 mmol/L: dialysis

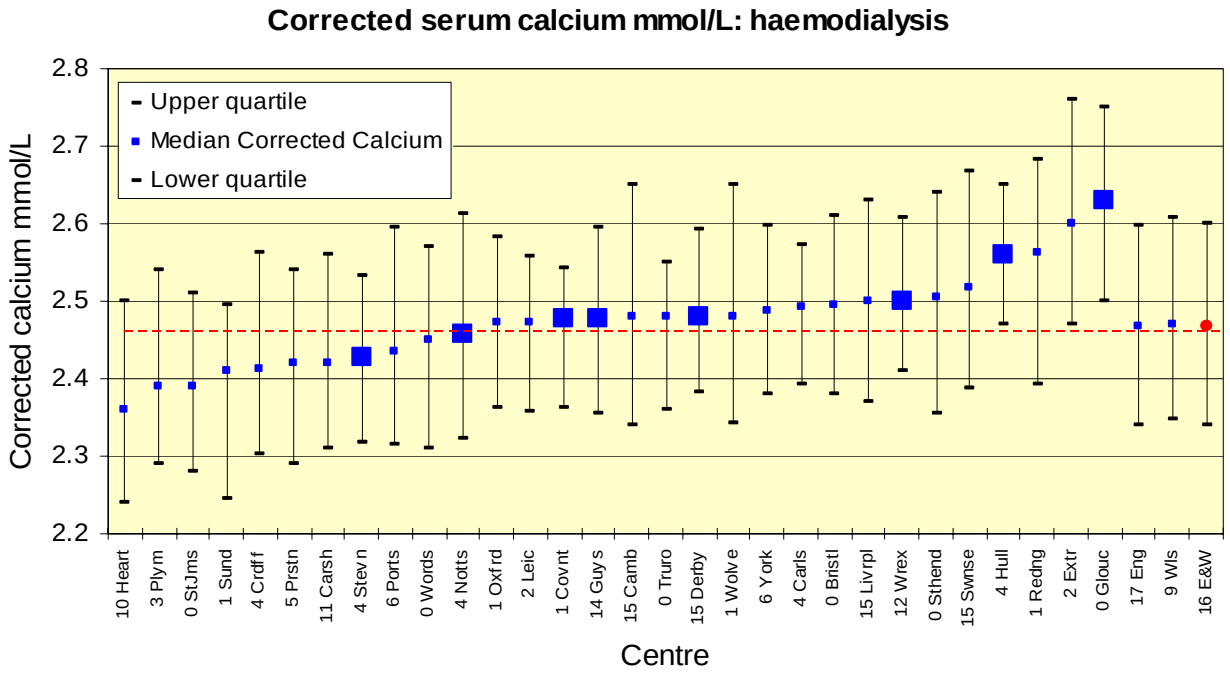

Figure 10.3: Median corrected calcium: HD (large block = BCP centre)

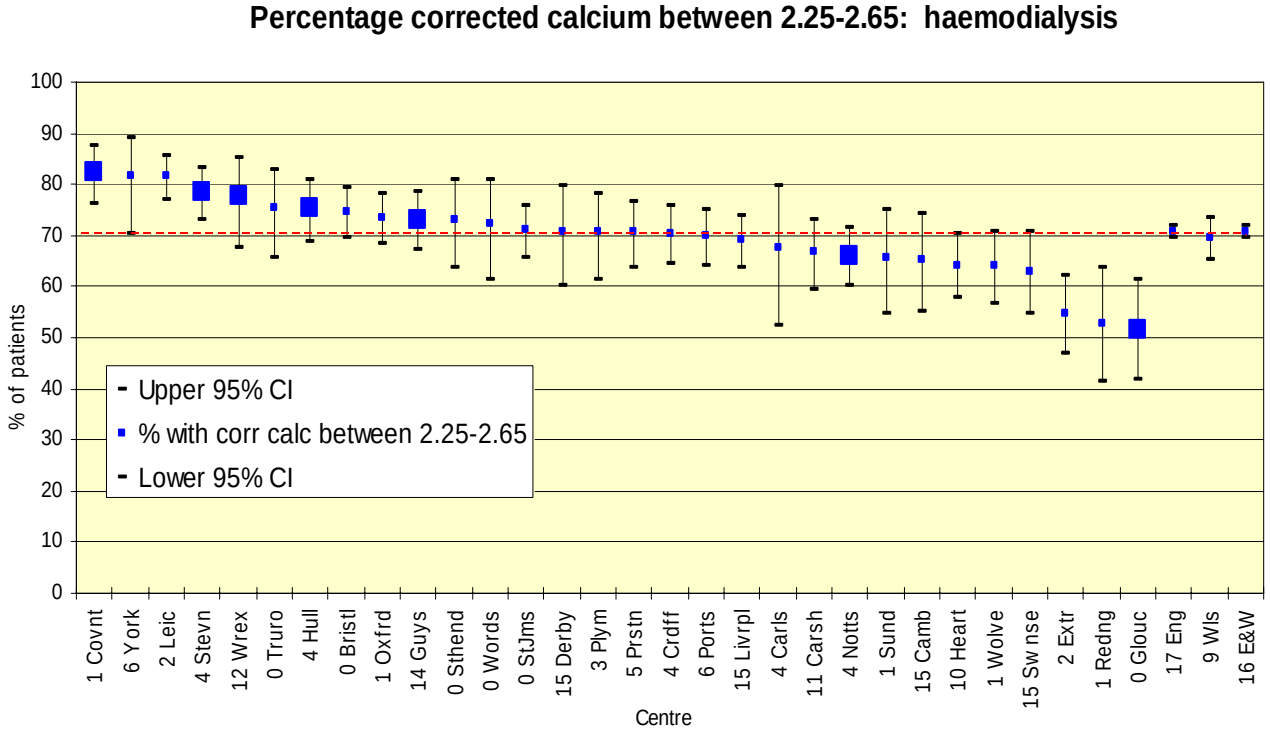

Figure 10.4: Percentage corrected calcium within 2.25–2.65 mmol/L: HD

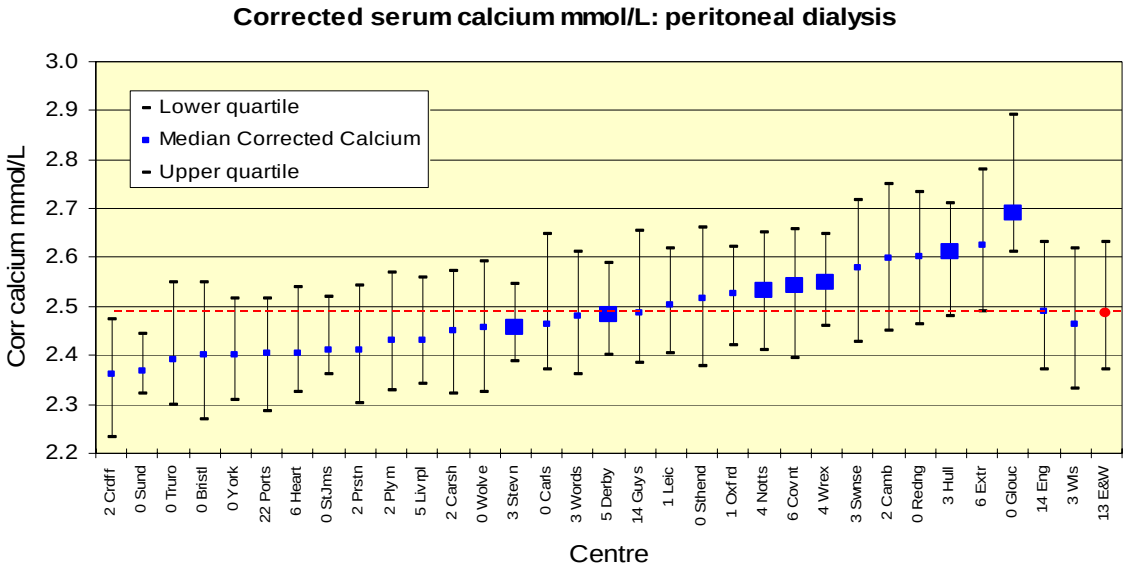

Figure 10.5: Median corrected calcium: PD (large block = BCP centre)

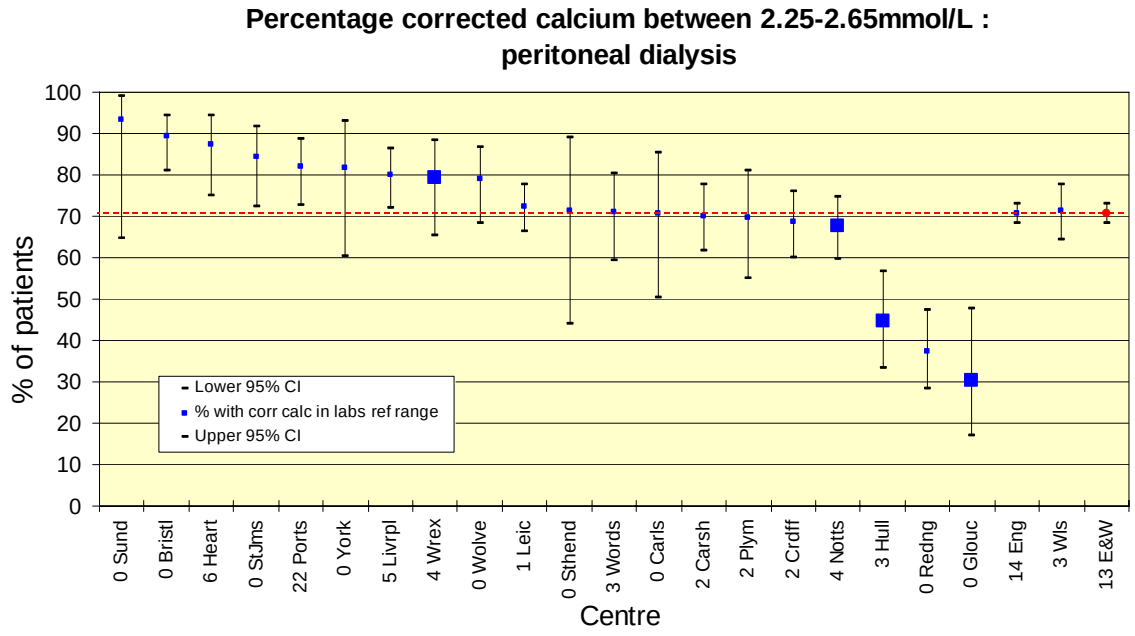

Figure 10.6: Percentage corrected calcium within 2.25–2.65 mmol/L: PD

Changes in calcium over time

The registry has serial data for corrected calcium over 3 years, and there is no visible trend in calcium either for HD or PD patients (Figures 10.7 and 10.8). Renal Units changing albumin methodology (e.g. Exeter) from BCG to BCP show an apparent rise in serum calcium.

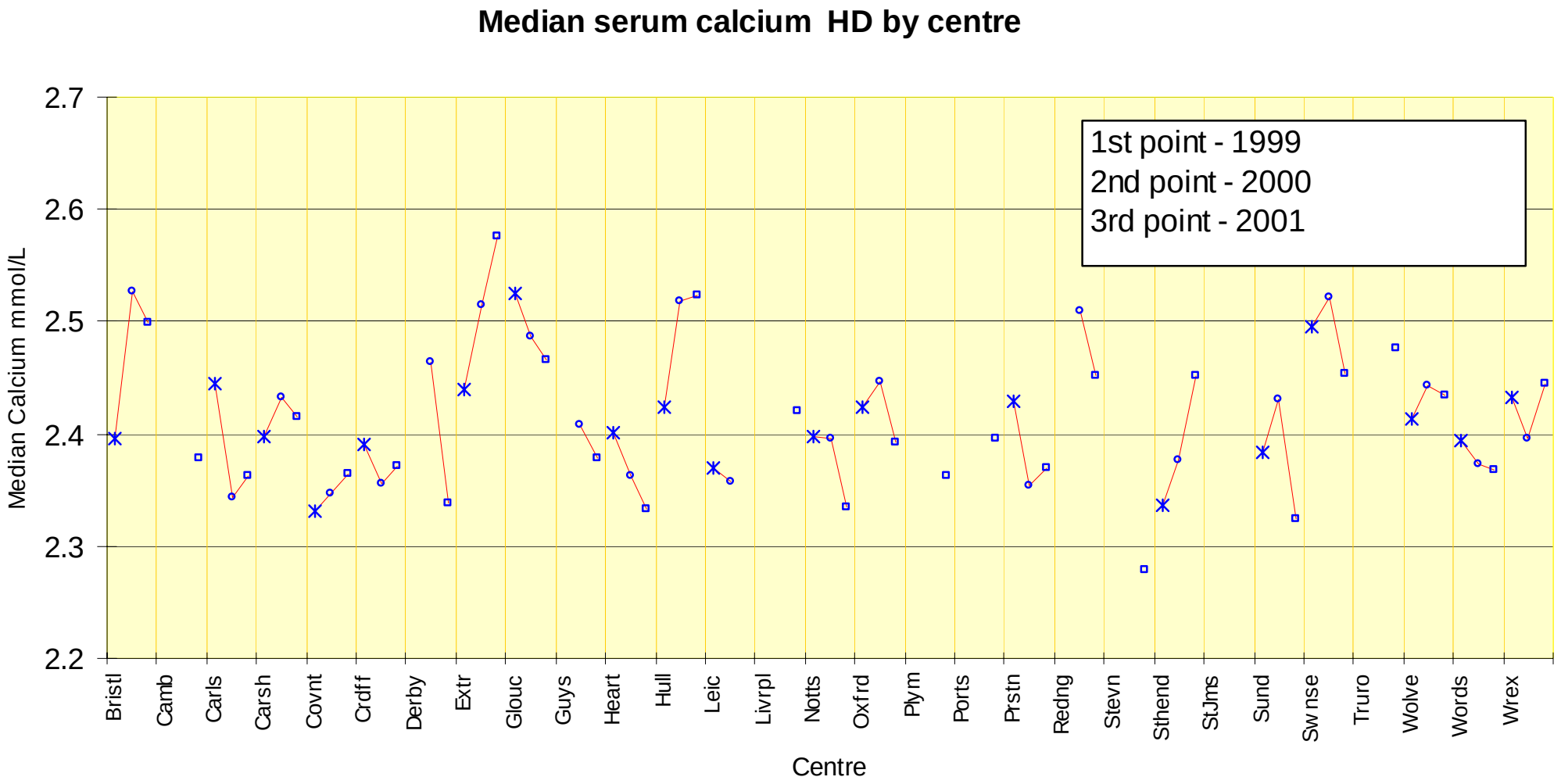

Figure 10.7: Median serum calcium by centre over 3 years: HD

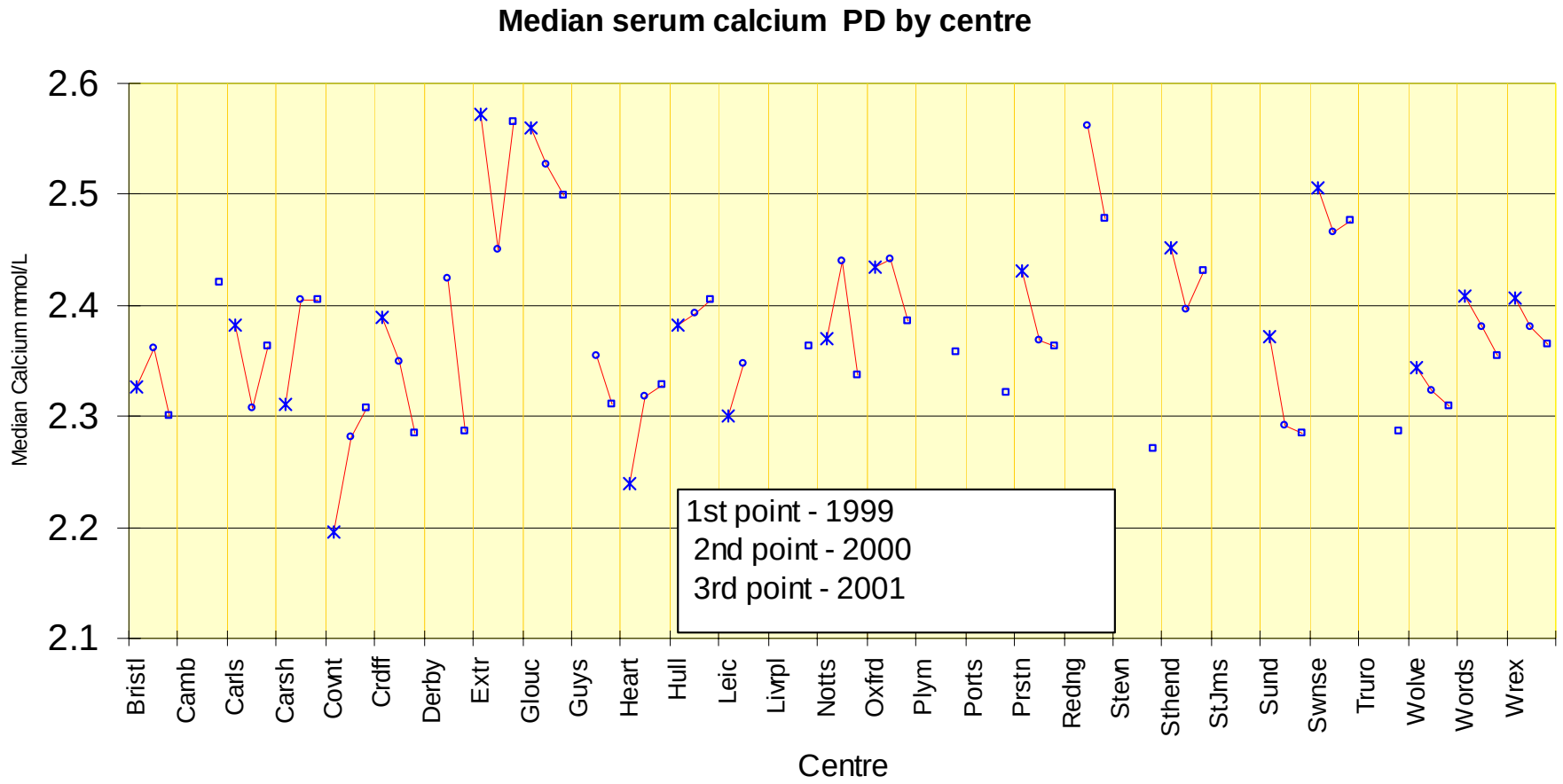

Figure 10.8: Median serum calcium by centre over 3 years: PD

Serum phosphate

Measuring serum phosphate has far fewer problems so audit is easier; the methodologies for measuring serum phosphate are listed in Table 10.2. All centres bar one use the same method, but there is still a variation in the quoted normal range for laboratories using the same method of measurement.

Measurement of phosphate

City	Hospital	Method	Ref range
Birmingham	Heartlands Hospital	PMb	0.80–1.45
Bradford	St Luke's Hospital	PMb	0.80–1.31
Bristol	Southmead Hospital	PMb	0.75–1.35
Cardiff	University of Wales Hospital	PMb	0.80–1.45
Carlisle	Cumberland Infirmary	PMb	0.90–1.50
Carshalton	St Helier Hospital	PMb	0.80–1.40
Coventry	Walsgrave Hospital	PMb	0.75–1.40
Derby	Derby District General	PMb	0.80–1.45
Exeter	Royal Devon and Exeter Hospital	PMb	0.50–2.30
Gloucester	Gloucester Road Infirmary	PMb	0.82–1.55
Hull	Hull Royal Infirmary	PMb	0.70–1.50
Leeds	St James's Hospital	PMb	0.80–1.30
Leeds	LGI	PMb	0.80–1.31
Leicester	Leicester General Hospital	PMb	0.80–1.40
Liverpool	Liverpool Royal Hospital	PMb	0.70–1.40
London	Guys St Thomas'	PMb	0.80–1.50
Middlesborough	South Cleveland Hospital	PMb	0.74–1.40
Newcastle	Royal	PMb	0.80–1.44
Nottingham	Nottingham City Hospital	PMb	0.80–1.40
Oxford	Churchill Hospital	PMb	0.80–1.45
Plymouth	Derriford Hospital	PMb	0.80–1.40
Portsmouth	Queen Alex	PMb	0.80–1.50
Preston	Royal Preston Hospital	PMb	0.80–1.45
Reading	Royal Berkshire	PMb	0.81–1.45
Sheffield	Northern General Hospital	Fish/Sub	0.80–1.40
Stevenage	Lister Hospital	PMb	0.75–1.36
Stourbridge	Wordsley Hospital	PMb	0.80–1.40
Southend	Southend Hospital	PMb	0.80–1.45
Sunderland	Sunderland Royal Hospital	PMb	0.80–1.40
Swansea	Morriston	PMb	0.80–1.40
Truro	Royal Cornwall Hospital Trust	PMb	0.87–1.46
Wolverhampton	Newcross Hospital	PMb	0.80–1.40
Wrexham	Maelor General Hospital	PMb	0.80–1.40
York	York District Hospital	PMb	0.80–1.40

Table 10.2: Methodologies for measurement of serum phosphate
Conversion factor: mg/dL = mmol/L × 3.1

Results

The new Standard for phosphate concentration is that serum phosphate should be below 1.8 mmol/L; the Standard was previously 1.2–1.7 mmol/L pre-dialysis in HD and 1.1–1.6 mmol/L in PD. Centres will have been working towards this Standard during the period of data collection. Figures 10.9–10.14 show these data, first for all dialysis patients and then for

separate dialysis modalities. There is immense variability between patients in serum phosphate level, shown by the wide error bars, and the national median is only just below the standard of 1.8 mmol/L. The distribution of median phosphate concentration suggests that all units find this an almost impossible standard to comply with.

There is a small but significant difference ($p<0.01$) between HD and PD, and the national median is lower in PD patients. Eight units managed to get the upper quartile of the serum phosphate below 1.8 for PD patients, whereas only one centre managed this for their HD patients. Whether this effect is due to better control or globally poorer dietary intake in PD patients is not certain.

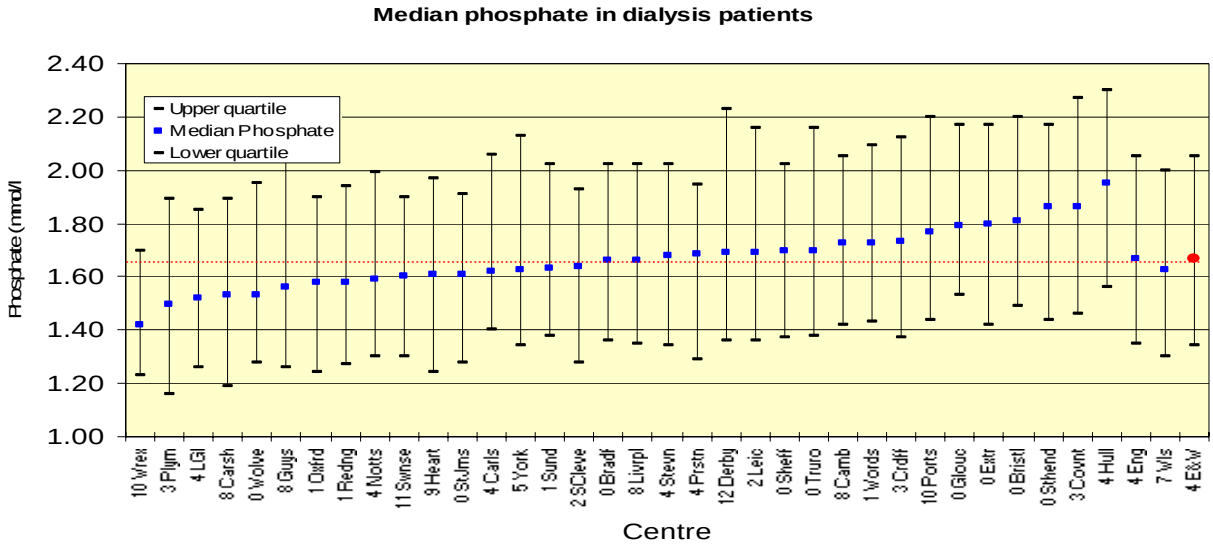

Figure 10.9: Median serum phosphate in all dialysis patients

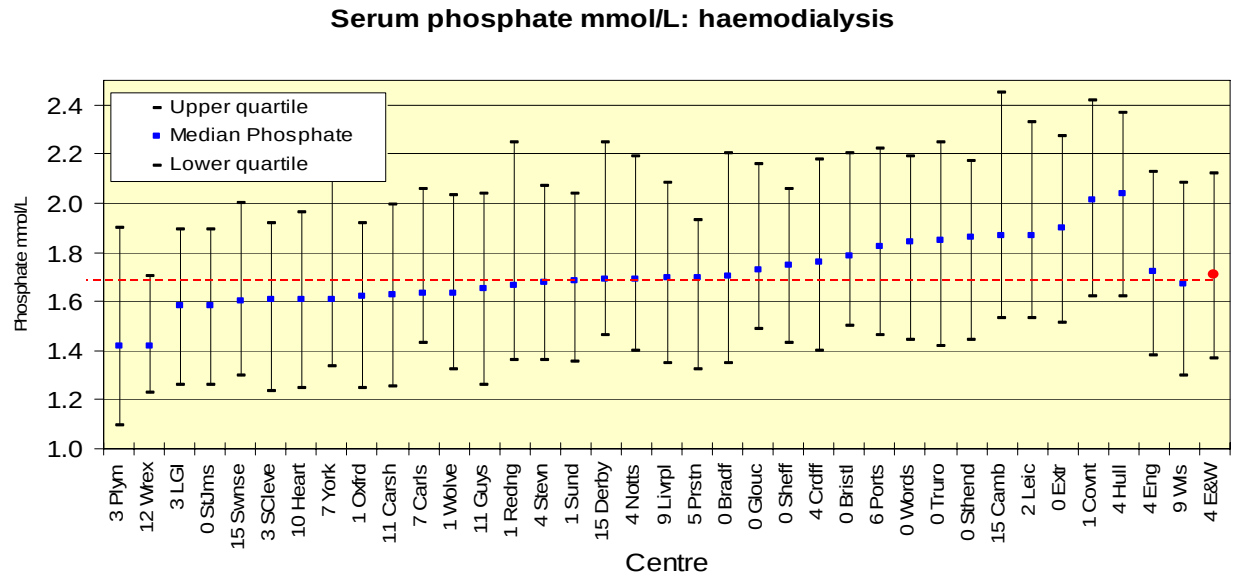

Figure 10.10: Median serum phosphate in HD patients

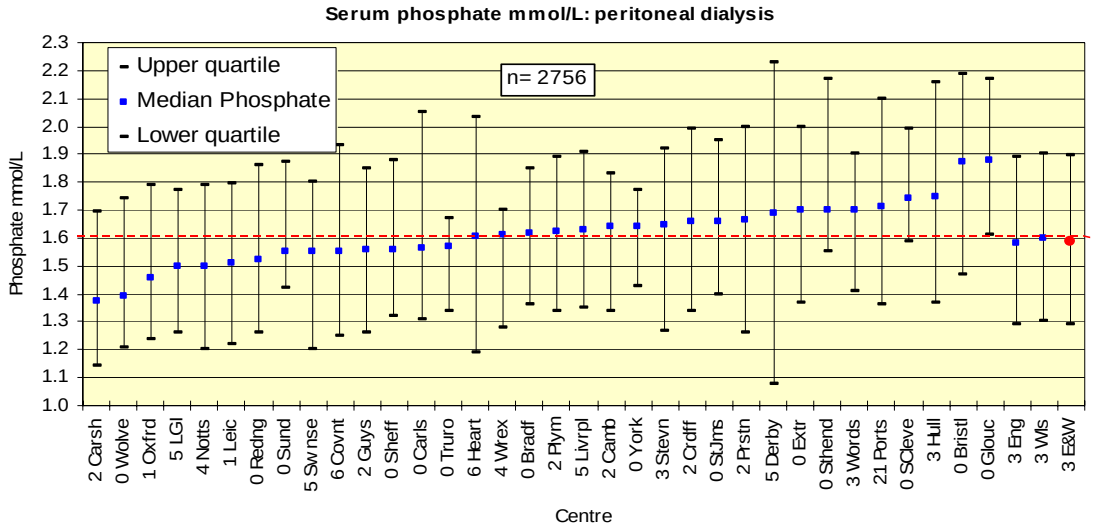

Figure 10.11: Median serum phosphate in PD patients

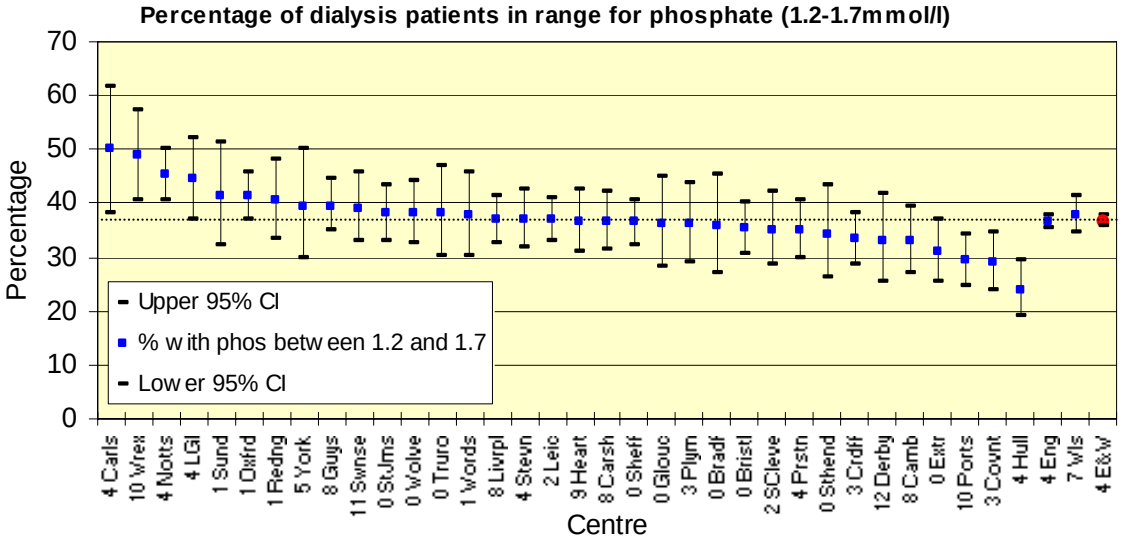

Figure 10.12: Phosphate: percentage compliance with the Standard in all dialysis patients

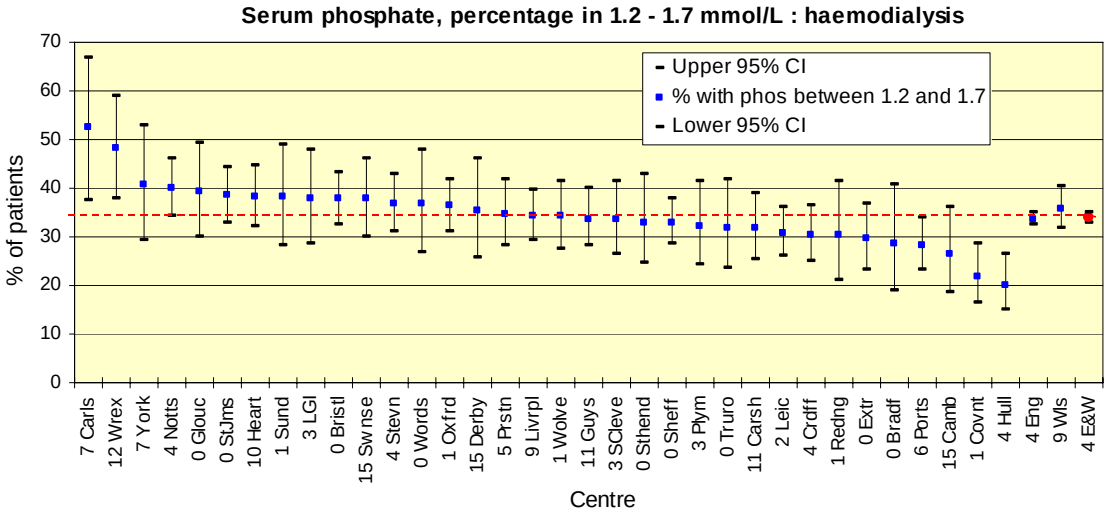

Figure 10.13: Phosphate: percentage compliance with the Standard in HD patients

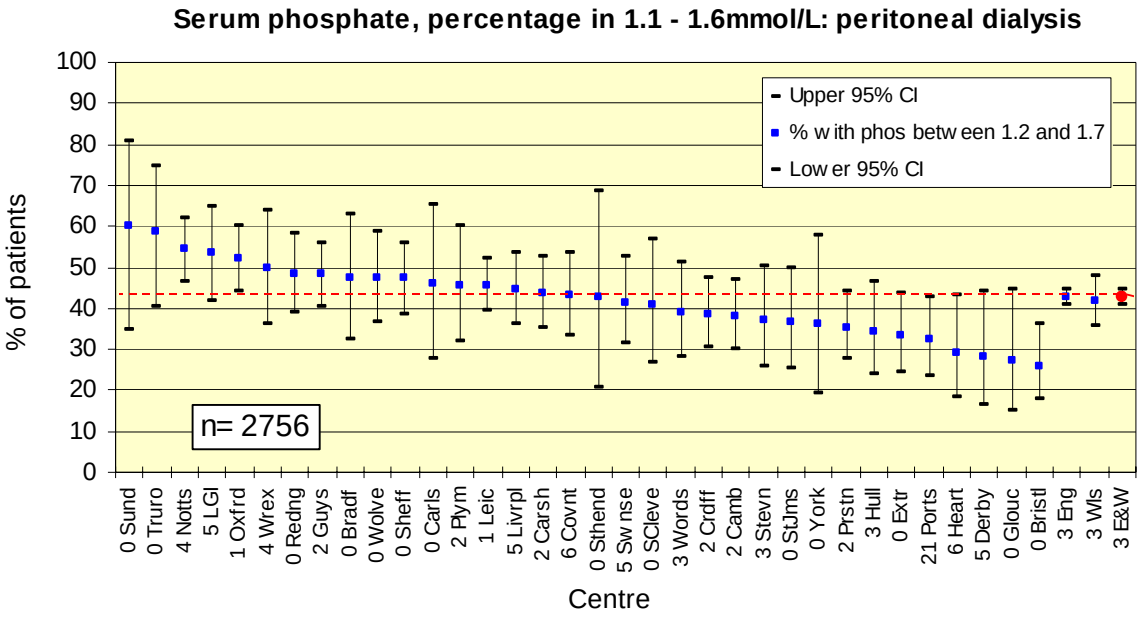

Figure 10.14: Phosphate: percentage compliance with the Standard in PD patients

Changes with time

Figures 10.15 and 10.16 represent the frequency distribution of serum phosphate concentration in 1997, 1999 and 2001. United States Renal Data System data are included for comparison. There is a growing desire to control phosphate better and an increase in the number of phosphate binders available, but these factors have not yet resulted in any measurable change. If change cannot be demonstrated in the next year or two, the cost-effectiveness of the newer phosphate binders will be called into question.

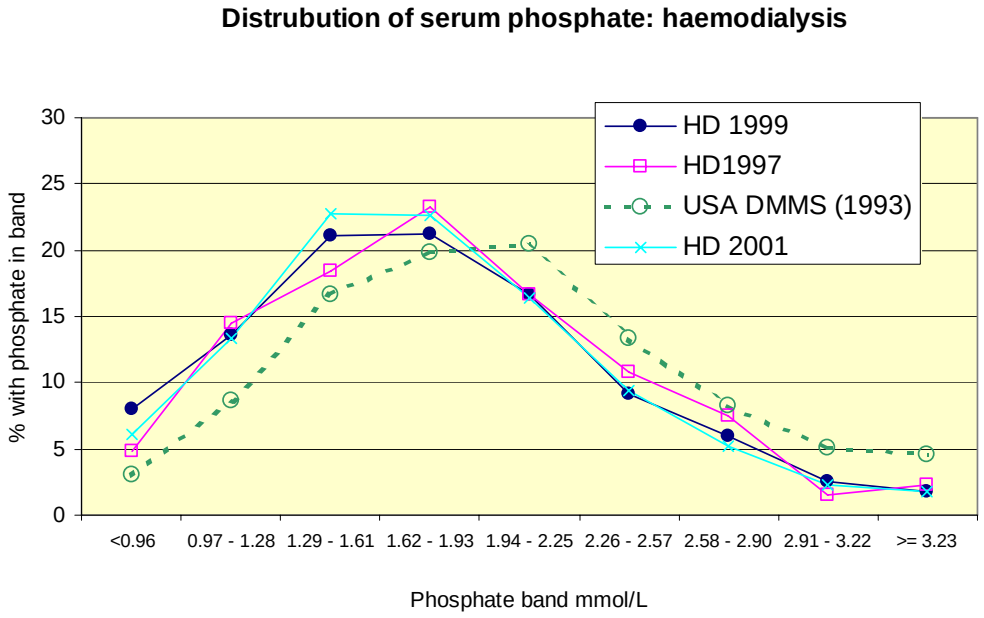

Figure 10.15: Distribution of serum phosphate in HD patients, 1999–2001

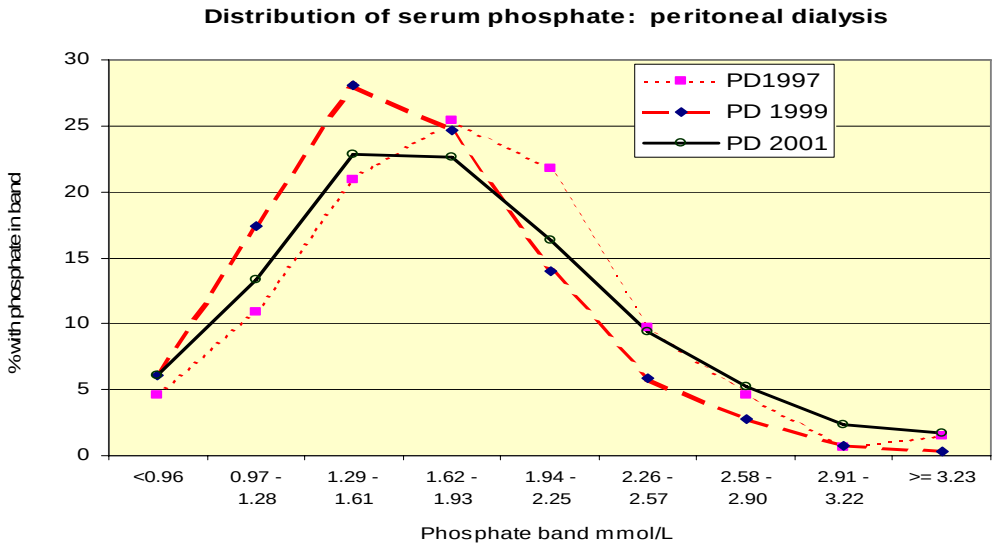

Figure 10.16: Distribution of serum phosphate in PD patients, 1999–2001

Parathyroid hormone

Assays

Different laboratories use different assays and have different reference ranges for PTH. These are tabulated for the various renal centres in Table 10.3.

City	Hospital	Method	Ref range
Birmingham	Heartlands Hospital	Elecsys (P Clark)	30–400 ng/mL
Bradford	St Luke's Hospital	Nichols (LGI)	<65 ng/mL
Bristol	Southmead Hospital	DPC	1.3–7.6 pmol/L
Cardiff	University of Wales Hospital	Nichols	0.9–5.4 pmol/L
Carlisle	Cumberland Infirmary	Elecsys	15–65 ng/L
Carshalton	St Helier Hospital	DPC	3–48 ng/L
Coventry	Walsgrave Hospital	IDS	1.1–4.2 pmol/L
Derby	Derby District General	DPC	12–72 ng/L
Exeter	Royal Devon and Exeter Hospital	DPC	0.6–4.6 pmol/L
Gloucester	Gloucester Road Infirmary	Nichols	0.9–5.4 pmol/L
Hull	Hull Royal Infirmary	DPC	7–53 ng/mL
Leeds	St James's Hospital	Nichols	11–55 ng/mL
Leeds	LGI	Nichols	11–55 ng/L
Leicester	Leicester General Hospital	DPC	1.3–7.6 pmol/L
Liverpool	Liverpool Royal Hospital	Nichols	1.1–6.9 pmol/L
London	Guys St Thomas'	Nichols	10–65 ng/L
Middlesborough	South Cleveland Hospital	DPC	12–72 ng/L
Newcastle	Royal	Nichols	10–65 ng/L
Nottingham	Nottingham City Hospital	DPC	8–78 ng/mL
Oxford	Churchill Hospital	Nichols	1.0–6.1 pmol/L
Plymouth	Derriford Hospital	DPC	12–72 ng/L
Portsmouth	Queen Alex	DPC Immulite	<4.7 pmol/L
Preston	Royal Preston Hospital	Roche Elecys	15–65 ng/L
Reading	Royal Berkshire	DPC	0.7–5.6 pmol/L
Sheffield	Northern General Hospital	Chiron	10–65 ng/L
Stevenage	Lister Hospital	DPC	11–65 ng/L
Stourbridge	Wordsley Hospital	DPC	0.45–5.0 pmol/L

City	Hospital	Method	Ref range
Southend	Southend Hospital	Roche Elecys	1.05–6.9 pmol/L
Sunderland	Sunderland Royal Hospital	DPC	1.3–7.6 pmol/L
Swansea	Morriston	Diasorin	10–50 ng/L
Truro	Royal Cornwall Hospital Trust	DPC	12–7 2ng/L
Wolverhampton	Newcross Hospital	DPC	0.76–7.42 ng/L
Wrexham	Maelor General Hospital	Nichols	0.9–5.4 pmol/L
York	York District Hospital	Nichols	10–60 ng/L

Table 10.3: Laboratory methodology for serum iPTH
Conversion factor: ng/L = pmol/L × 9.5

Results

The Renal Association Standards are based on multipliers of the individual laboratory's normal range. At the time when the data were collected, the recommendation was that iPTH (intact hormone assay) should be maintained at between two and three times the normal range. The data have been standardised between units, by the Registry, to an upper acceptable limit of 23 pmol/L to facilitate comparison.

The new recommendation is that iPTH should be less than four times the upper limit of normal, presumably reflecting the view that adynamic bone disease represents a theoretical rather than a real risk.

Figures 10.17 and 10.18 show the very wide variation in PTH within and between units, with the percentage compliance varying from 80% in Wrexham to less than 40% in Cambridge.

Figures 10.19–10.23 show these data split according to dialysis modality.

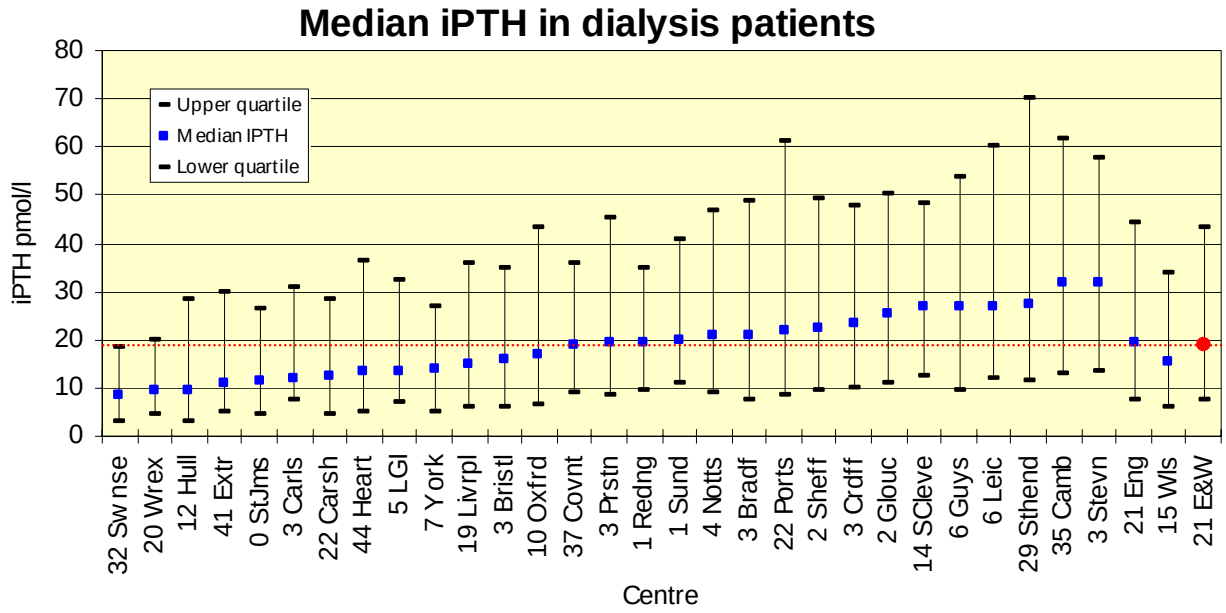

Figure 10.17: Median iPTH in all dialysis patients

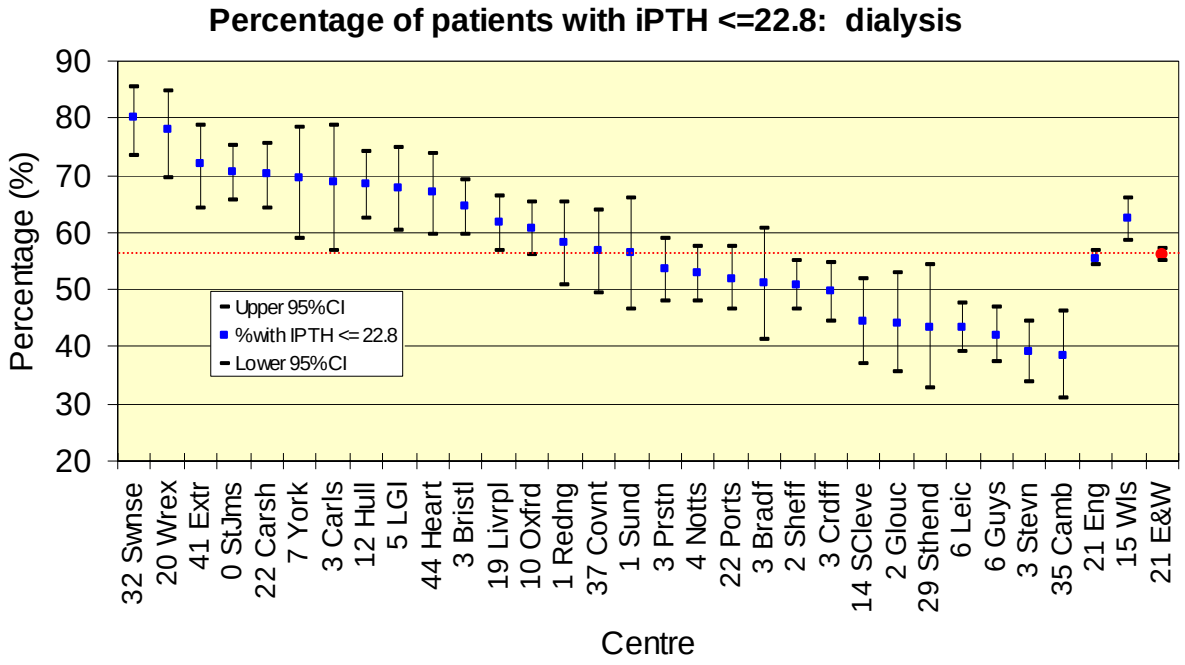

Figure 10.18: Percentage of patients with iPTH < 22.8 pmol/L in all dialysis patients

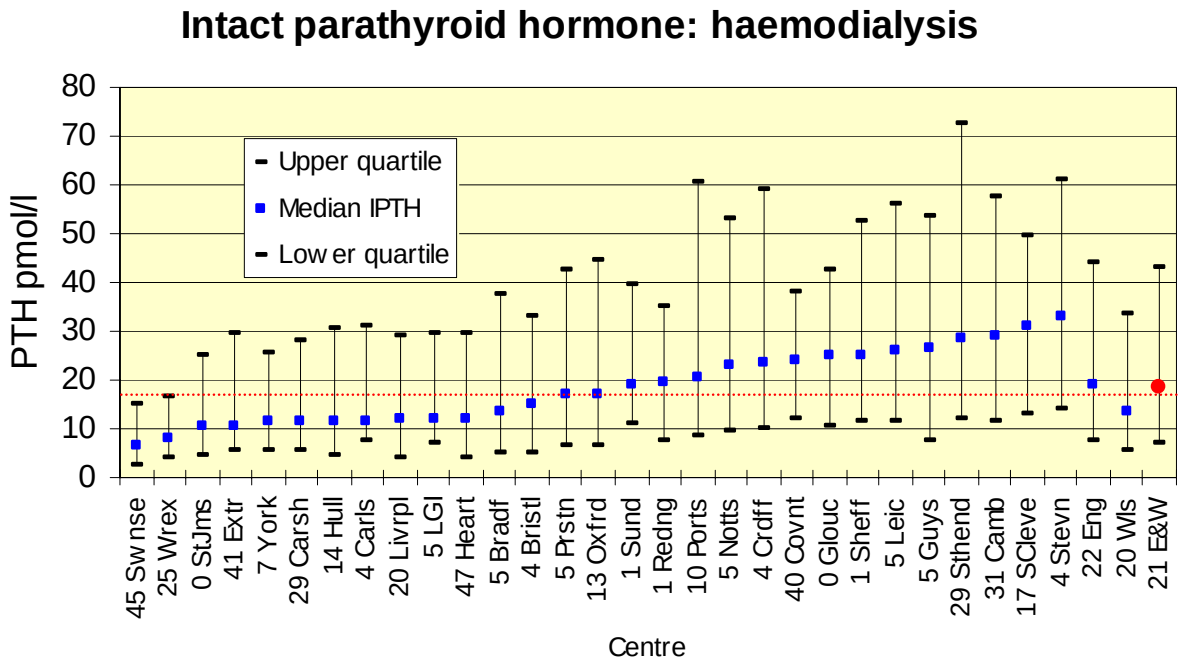

Figure 10.19: Median iPTH in HD patients

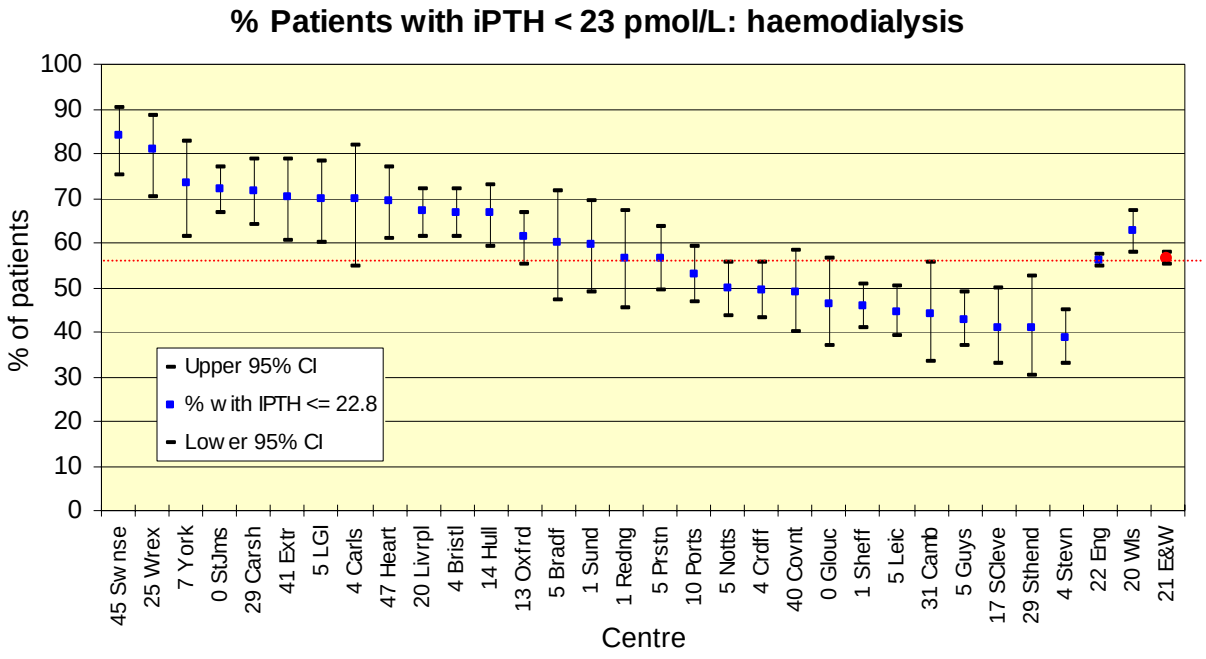

Figure 10.20: Percentage of patients with iPTH <23 pmol/L in HD patients

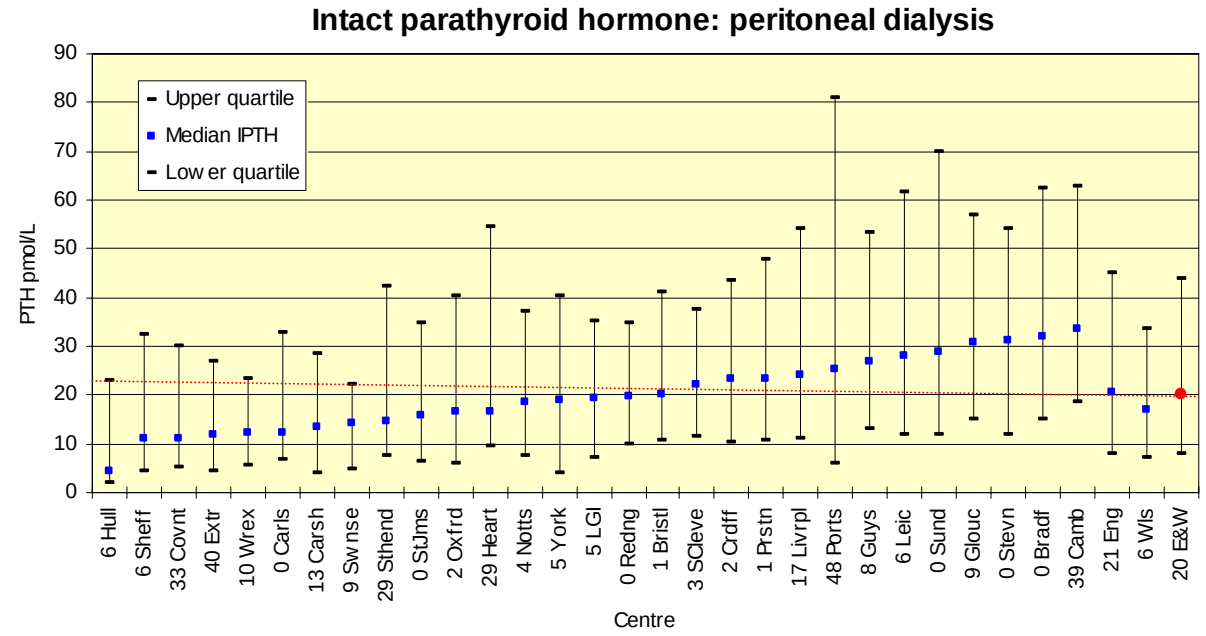

Figure 10.21: Median iPTH in PD patients

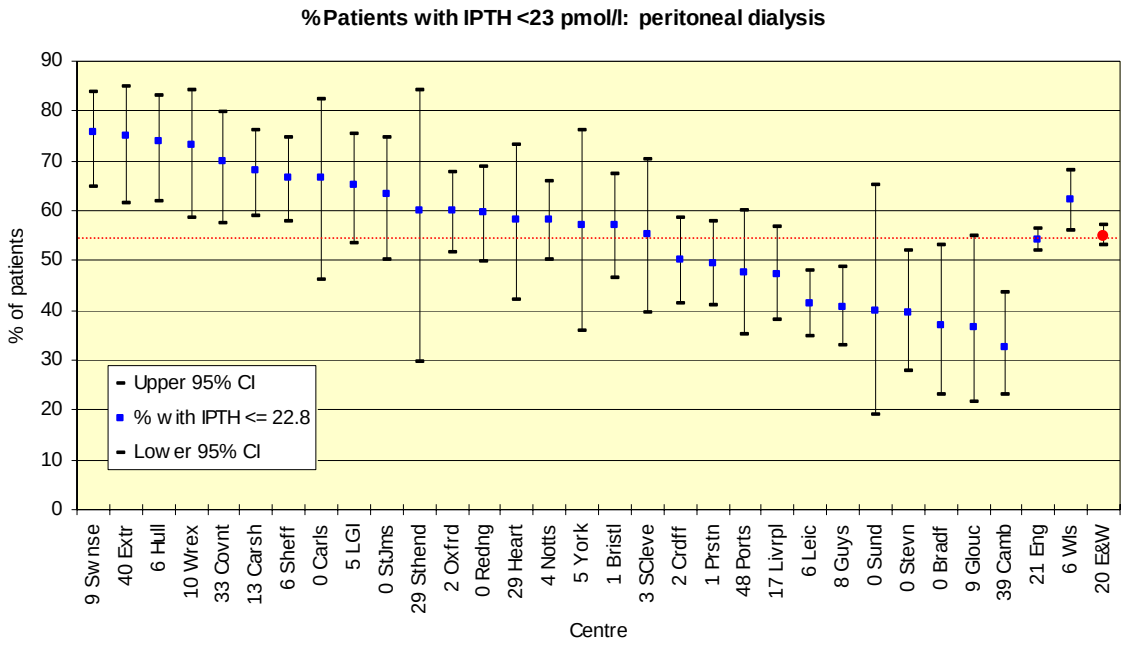

Figure 10.22: Percentage of patients with iPTH <23 pmol/L in PD patients

Conclusion

Achieving a good control of calcium metabolism is a desirable aim with expected benefits to patients in terms of controlling both bone and vascular disease. Comparative audit, particularly of serum calcium, is difficult because different assays, ranges and corrections are made in different units. Despite the difficulties, the data demonstrate that this is an area in which there is considerable variability between units and in which the renal community struggles to achieve agreed standards, many units failing to do so. This is particularly true of serum phosphate – even the best units can manage only 50% compliance with the Standard. Although this may lead to a slackening of the Standard, it is to be hoped that comparative audit will reduce the variability and bring centres with poorer results closer to their competitors.