Chapter 9: Serum Phosphate, Calcium, Parathyroid Hormone and Albumin

Summary

- An analysis to assess the contribution of inter-laboratory variation to the 'between-centre performance' indicates that there is no evidence to suggest that laboratory variation influences Registry data for serum phosphate or calcium but there is an influence on serum albumin. The current status of analytical methodology does not allow an accurate assessment of the contribution of inter-laboratory variability to between-centre iPTH differences.

- There has been a year on year improvement in control of serum phosphate in dialysis patients although control remains poor and the variation between units is wide and significant.

- Achievement of the RA phosphate target of <1.8 mmol/L is better on PD (68% of patients) compared to HD (59% of patients).

- The Kings renal unit achieves very good control of serum phosphate in HD patients (76% patients <1.8 mmol/L) through the use of a dietetic prescribing team with support from a pharmacist.

- The median corrected serum calcium for all dialysis patients is 2.42 mmol/L, with 63% of patients achieving a serum corrected calcium within the RA target range.

- There is no significant difference between PD patients and HD patients in terms of achieved serum calcium control.

- Comparative audit of serum calcium remains difficult due to methodological differences, especially in albumin measurement and the use of different correction formulae.

- Using KDOQI calcium phosphate product guidelines of $<4.4\,\text{mmol}^2/\text{L}^2$, 67% of dialysis patients achieve this target although control is better on PD (75%) than on HD (64%). There is wide variation between units.

- Interpretation of iPTH data is complicated by large analytical differences between centres. There is large between-centre variation in the apparent ability of renal centres to achieve the RA target (48% to 88% compliance with the standard).

- In dialysis patients the BCP method of measuring serum albumin gave lower median results than the BCG method.

- For HD patients, the median serum albumin was 38 g/L (BCG) and 34 g/L (BCP). For the BCG technique, 79% of the patients had a serum albumin above 35 g/L: for the BCP technique, 85% of the patients had a serum albumin above 30 g/L.

- PD patients had lower serum albumin compared with those on HD. The median serum albumin was 36 g/L using BCG and 30 g/L using BCP. For the BCG technique, 60% of the patients had a serum albumin above 35 g/L: for the BCP technique, 55% of the patients had a serum albumin above 30 g/L.

Introduction

Traditionally, control of phosphate, calcium and parathyroid hormone metabolism has been regarded as synonymous with control of renal bone disease: recently there has been a shift in emphasis with the increasing realisation that both serum calcium and phosphate control and their balance may also be important in preventing accelerated vascular disease. This chapter presents information relating calcium, phosphate and iPTH control to the RA standards.

For calcium, phosphate and iPTH no separate RA standards are set for different dialysis modalities. Nevertheless, different modalities offer different challenges in achieving metabolic control. Where appropriate, data for HD and PD are shown separately in addition to/instead of the pooled dialysis data.

Table 9.1: Table of data completeness by centre

	Albumin			Uncorrected calcium			Phosphate			iPTH		
	HD	PD	Tx	HD	PD	Tx	HD	PD	Tx	HD	PD	Tx
Bangor	100	100	N/A	100	100	N/A	100	100	N/A	98	92	N/A
Bradford	100	100	97	100	100	97	100	98	95	84	86	22
Bristol	99	100	98	99	100	97	99	100	98	94	99	82
Cambridge	71	100	80	71	100	80	71	100	80	65	95	13
Carlisle	93	94	94	93	94	94	93	94	83	91	94	24
Carshalton	85	99	90	85	99	90	85	99	89	67	77	10
Clwyd	94	100	N/A	94	100	N/A	94	100	N/A	89	31	N/A
Coventry	99	93	81	99	93	81	99	93	81	89	77	20
Cardiff	95	97	96	95	97	96	95	97	96	91	94	16
Derby	88	96	N/A	88	94	N/A	88	93	N/A	0	0	N/A
Exeter	97	100	96	43	5	0	97	100	94	96	100	11
Gloucester	98	100	98	98	100	98	98	100	95	98	94	33
Guys	92	100	81	96	100	92	96	100	92	95	98	18
H&CX	99	99	95	99	99	95	99	99	95	60	89	30
Heartlands	93	100	71	93	100	71	93	100	71	85	75	5
Hull	96	98	81	96	98	81	96	98	81	79	91	16
Ipswich	100	100	96	100	100	96	100	98	98	93	95	37
Kings	96	94	91	96	94	91	93	88	56	93	93	20
Leeds	99	98	94	99	98	93	99	98	93	97	97	23
Leicester	98	99	93	98	99	92	98	99	92	97	91	56
Liverpool	87	96	92	87	96	92	86	96	92	76	78	28
ManWst	69	98	72	69	98	72	69	98	72	64	93	70
Middlbr.	97	100	93	97	100	93	97	100	93	73	86	4
Newcastle	97	98	79	97	98	79	97	98	78	62	73	20
Nottingham	97	100	95	97	100	94	97	100	94	95	96	72
Oxford	99	100	95	99	100	95	95	100	95	84	91	32
Plymouth	86	98	84	86	98	82	86	98	83	73	79	13
Portsmouth	94	88	88	94	82	88	94	81	85	84	43	9
Preston	98	99	68	98	99	67	98	99	64	96	99	30
Reading	98	100	80	98	100	90	98	100	90	95	96	60
Sheffield	100	100	99	100	100	99	100	100	99	98	81	11
Stevenage	93	100	74	90	98	74	89	98	73	83	87	41
Southend	96	100	60	96	52	57	95	100	57	88	68	7
Sundrland	96	100	97	96	100	97	96	100	97	94	100	96
Swansea	72	99	91	72	99	90	72	98	89	63	91	25
Truro	98	97	97	98	94	96	98	94	96	96	91	38
Wirral	9	13	N/A	9	6	N/A	9	6	N/A	17	6	N/A
Wolve.	99	100	90	99	100	90	99	100	85	94	97	35
Words	99	100	89	98	98	89	99	98	89	0	0	0
Wrexham	86	92	98	86	92	92	86	92	92	71	86	57
York	93	100	95	82	88	32	92	100	95	91	81	20
England	N/A	N/A	N/A	92	94	87	93	97	88	81	83	30
Wales	N/A	N/A	N/A	88	97	95	88	97	95	81	89	20
Total	N/A	N/A	N/A	91	94	87	92	97	88	81	84	29

This Chapter also contains data relating to serum albumin concentrations in dialysis patients. These data have been included here in recognition of the inter-relationship between calcium and albumin measurement and the commonality of the problems that affect them.

This year an attempt has again been made to assess the contribution of inter-laboratory variation to the 'between-centre' comparison of renal unit performance. Laboratories in the UK participate in external quality assessment schemes in which their achieved result for a specified analyte is compared with the result from other laboratories. The predominant scheme in the UK is the UK National External Quality Assessment Scheme (UK NEQAS, www.ukneqas.org.uk). Although not all laboratories participate in this scheme, a comparable scheme based in Wales (WEQAS) is also widely used. The organisers of the UK NEQAS scheme have assisted the Registry by providing mean bias data for the laboratories that support renal centres. The bias data is expressed relative to an all laboratory trimmed mean (ALTM) and has been used to assess whether renal centre performance is related to between-laboratory differences. Analysis was undertaken using data from July-December 2002. The analysis is clearly fairly crude and there are important caveats which should be borne in mind when attempting any interpretation. For example, it has not been possible to account for satellite dialysis centres where the biochemical data may be generated from a different laboratory from that used in the main renal unit.

Completeness of data returns

Table 9.1 shows the data completeness for serum albumin, uncorrected calcium, phosphate and iPTH. Completeness of data returns were measured over 6 months for patients on dialysis and 12 months for transplant patients. The Wirral renal unit does not have an automated biochemistry link into the IT renal system (at Liverpool) which accounts for the data being unavailable. Bangor, Clwyd and Wirral do not look after transplant patients.

Serum Phosphate

The Renal Association Standard states:

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

There is no recommendation on the frequency of measurement. This contrasts with the KDOQI guidelines which also set a minimum range for serum phosphate of 1.13 mmol/L and specify that it should be measured monthly.

Although there has been a year on year improvement in serum phosphate control, it remains poor with only 61% of dialysis patients achieving serum phosphate concentrations <1.8 mmol/L and several units having median serum phosphate concentrations above the standard of 1.8 mmol/L. In general, the phosphate control is better on peritoneal dialysis. Overall, 59% of haemodialysis and 68% of peritoneal dialysis patients have serum phosphate under 1.8 mmol/L. The variation between units is wide (Figures 9.1 to 9.5). For both HD ($\chi^2 = 273$, $p < 0.001$) and PD ($\chi^2 = 107$, $p < 0.001$) modalities, the percentage of patients with a serum phosphate below 1.8 mmol/L differed significantly between centres.

The Kings renal unit managed to achieve 76% of HD patients with a serum phosphate <1.8 mmol/L compared with 60% in E&W. Figure 9.3 shows that this high achievement was associated with the smallest inter-quartile range of 0.45 mmol/L compared with 0.74 mmol/L for England and Wales. Enquiries to this renal unit indicate that this tight control of serum phosphate has been achieved through use of a dietician led prescribing and management team for control of serum phosphate. Within this renal unit, dieticians initiate prescribing of calcium based phosphate binders and are also allowed to alter dosing of non-calcium based agents. Calcium based phosphate binders are still used in the majority of patients at this renal unit. Although Figure 9.8 does not show the corrected serum calcium data for HD patients at the Kings renal unit, analysis of the uncorrected calcium data shows that the

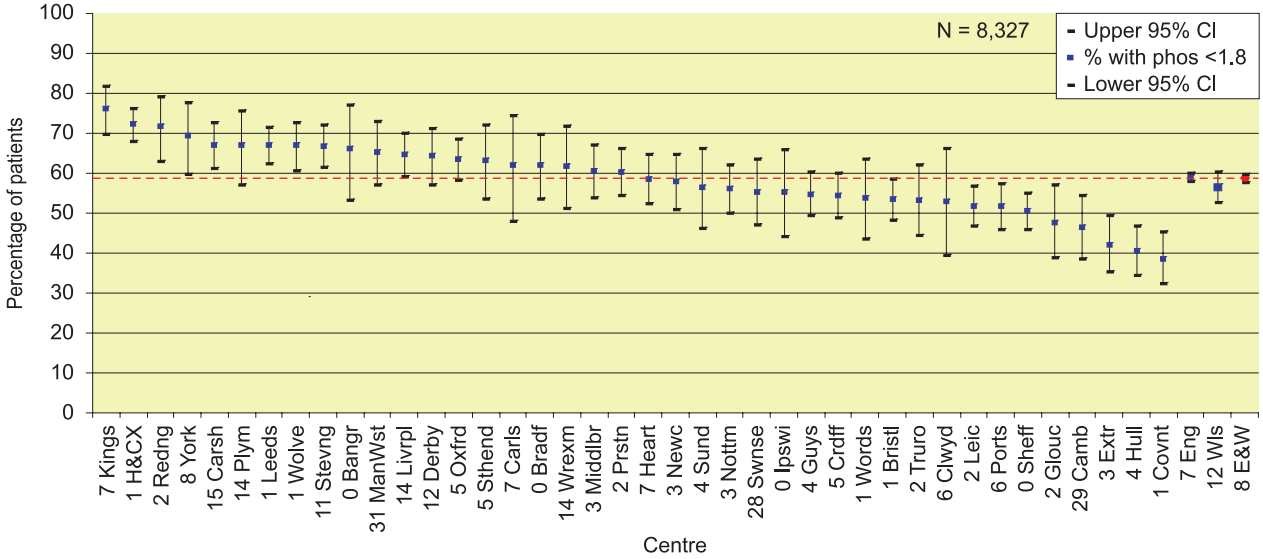

Figure 9.1: Percentage of HD patients in RA range for serum phosphate

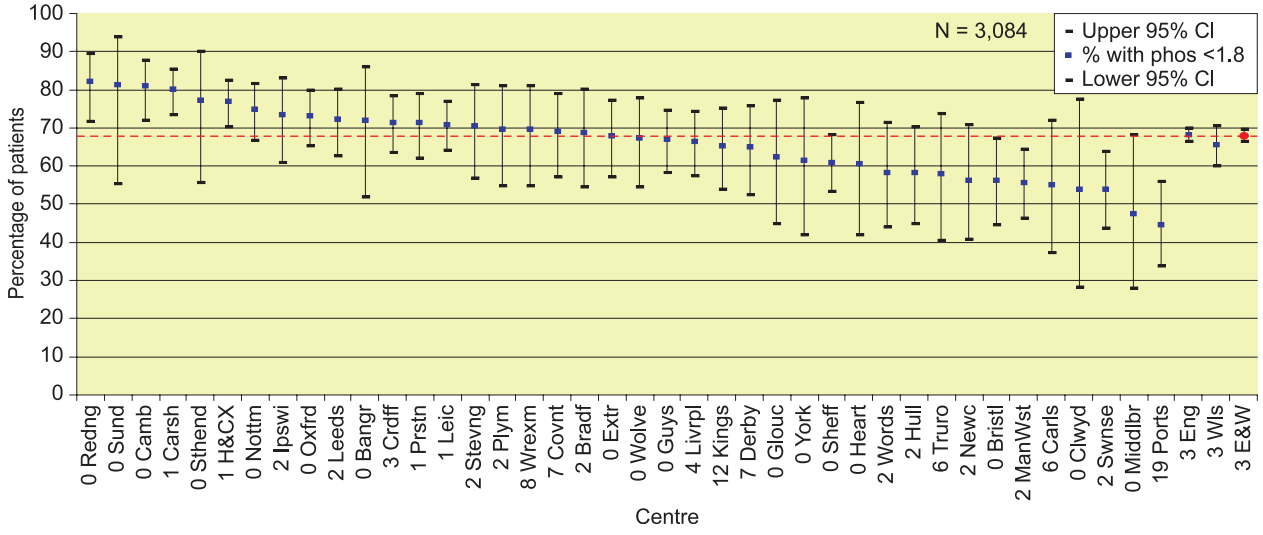

Figure 9.2: Percentage of PD patients in RA range for serum phosphate

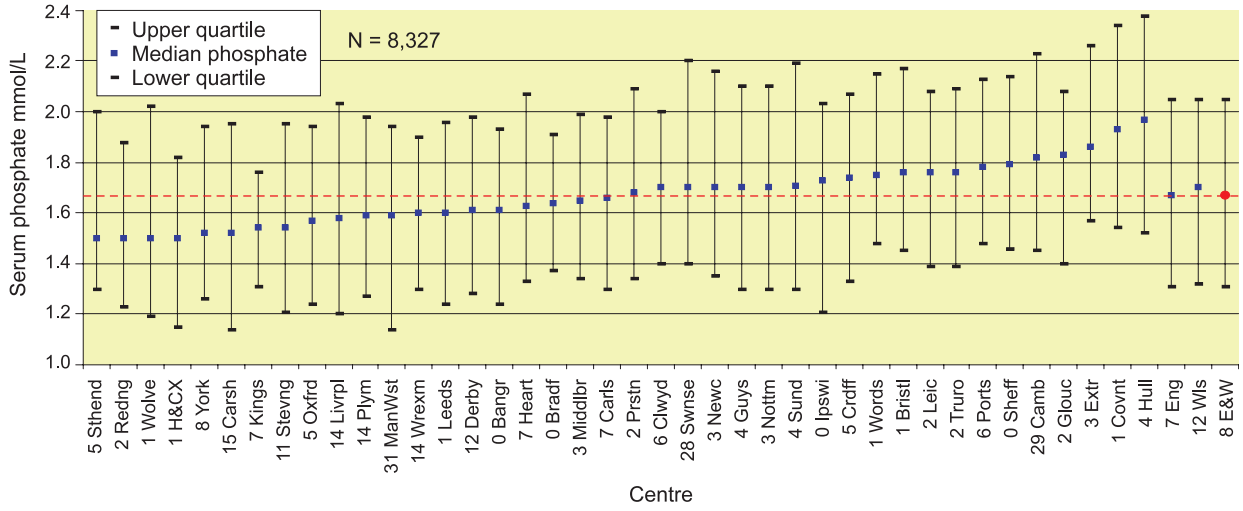

Figure 9.3: Median serum phosphate mmol/L: HD patients

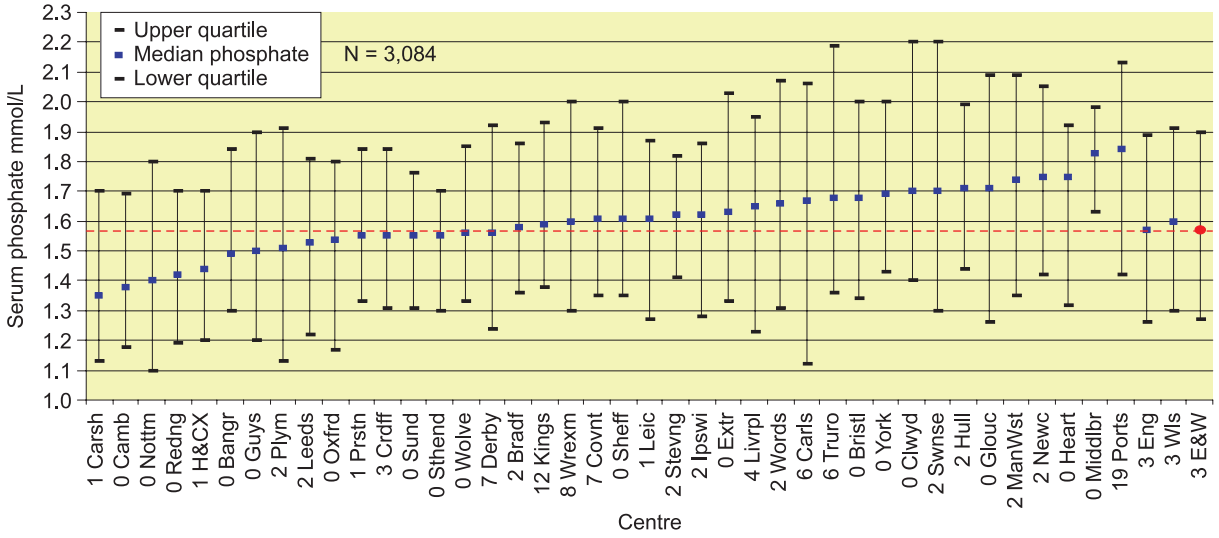

Figure 9.4: Median serum phosphate mmol/L: PD patients

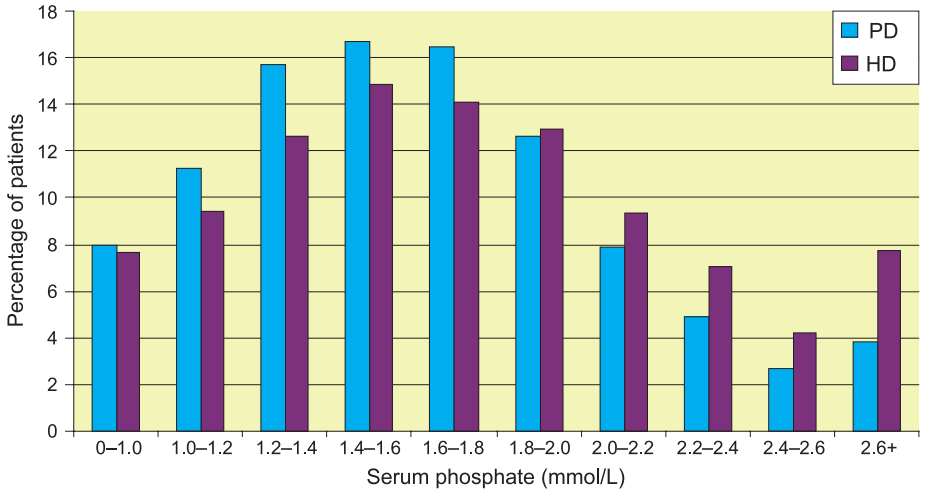

Figure 9.5: Distribution of serum phosphate by PD & HD

median uncorrected calcium at Kings is 2.33 mmol/L compared with 2.36 mmol/L for England and Wales. Achievement of low serum phosphate levels at the Kings renal unit has therefore not been at the expense of higher serum calcium results.

Figure 9.5 shows the difference in control of serum phosphate between HD and PD patients. Almost twice the percentage of HD patients (8%) have a serum phosphate above 2.6 mmol/L compared with 4% of patients on PD.

Analysis of the influence of laboratory bias

An analysis of the potential contribution of laboratory bias to between centre differences has been undertaken using data from the 2003 Registry Report and data supplied by UK NEQAS. No relationship ($p = 0.124$) was observed between the renal centre median serum phosphate and percentage bias relative to the UK NEQAS ALTM using Spearman's rank correlation. The 'between centres' coefficient of variation (CV) for serum phosphate was 6.7% whereas the between-laboratory CV for serum phosphate for all participants in the UK NEQAS scheme using a range of different methods was 4.5%. Taken together, these data suggest that the differences seen between renal centres are greater than can be explained by inter-laboratory variation.

The variability seen therefore suggests that a clinical focus on phosphate control can bring biochemical benefits, which might be translated into future survival benefits.

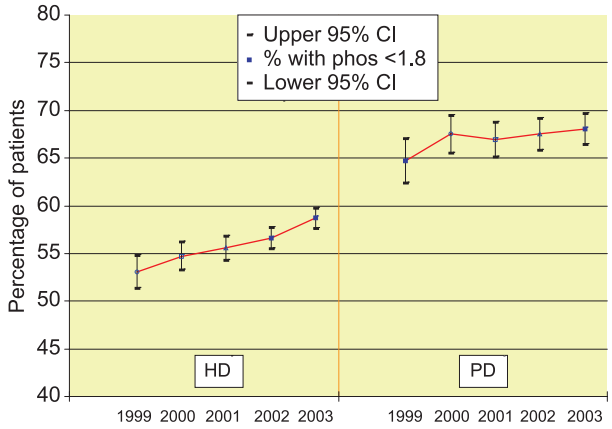

Figure 9.6: Change in percentage of patients achieving serum phosphate <1.8 mmol/L, 1999–2003

Change in achievement of serum phosphate 1999–2003

Figure 9.6 shows the change over 5 years in the percentage of patients achieving serum phosphate <1.8 mmol/L in patients in renal units in England and Wales who have contributed to the Registry throughout that time. Overall, there appears to have been a gradual improvement in the percentage of patients achieving this target for both HD (53.1 to 58.7%) and PD (64.7 to 68.1%).

Change in modality of treatment and effect on serum phosphate

The Registry is able to link biochemical data at individual patient level to changes of modality. Provision of a renal transplant produces a predictable improvement in serum phosphate control. Conversely, switching dialysis modality from PD to HD appears to be associated with a worsening of phosphate control and median rise of 0.2 mmol/L (Figure 9.7).

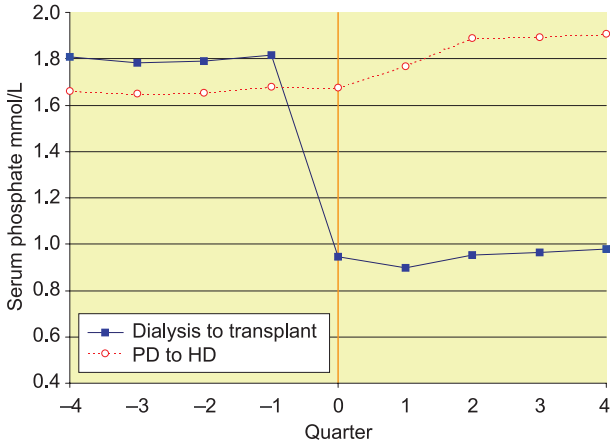

Figure 9.7: Serum phosphate, by quarter, in individual patients before and after modality change

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.***

The KDOQI guidelines advise that serum levels of corrected total calcium should be maintained within the normal range for the laboratory used, preferably toward the lower end (2.10 to 2.37 mmol/L), although the evidence for this is opinion based.

Comparative audit in this area remains difficult due to differences in analytical methods between units, (and even between satellite units managed by one clinical team), different mathematical methods being applied to correct serum calcium for serum albumin concentration and 3 different methods for analysing serum albumin (BCG wet, BCG dry and BCP see the Registry reports 1999–2003). However, as discussed in last year's Registry report[1], 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 and are illustrated in Figures 9.8 to 9.11.

The median corrected calcium is 2.42 mmol/L for HD patients and 2.44 mmol/L for PD patients. Overall, 63% of patients (64% HD, 63% PD) achieved a serum corrected calcium concentration within the RA target range. The variation between units is wide and the percentage of patients with a serum corrected calcium within the RA target range differed significantly between centres for both HD ($\chi^2 = 2023$, $p < 0.001$) and PD ($\chi^2 = 1179$, $p < 0.001$) modalities.

Analysis of the influence of laboratory bias

An analysis of the potential contribution of laboratory bias to between centre differences has been undertaken using data from the 2003 Registry Report and data supplied by UK

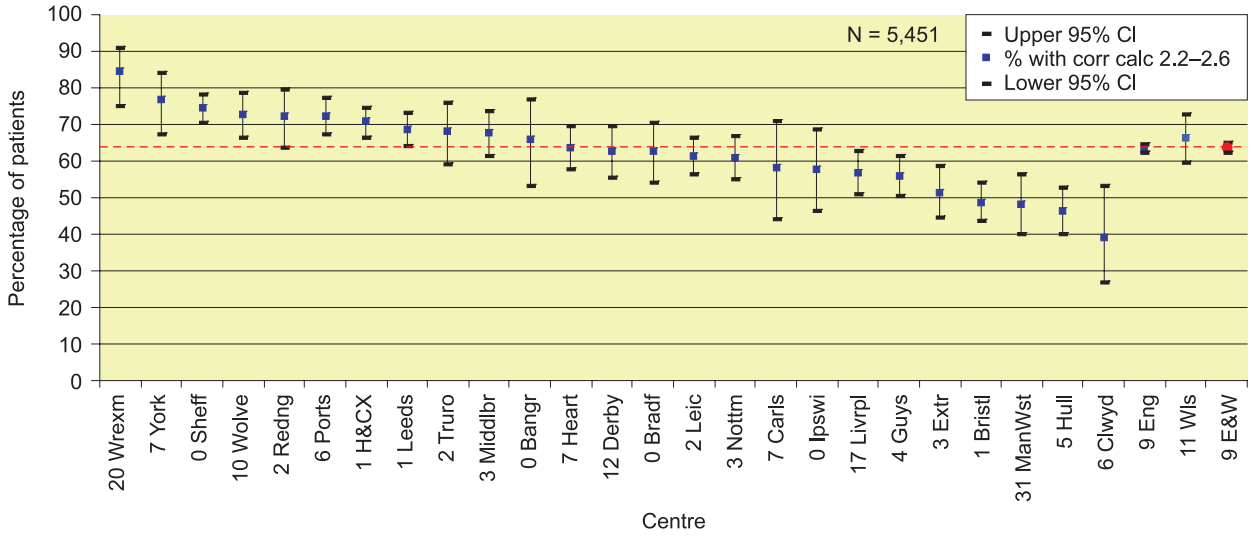

Figure 9.8: Percentage of patients with corrected calcium within 2.2 to 2.6 mmol/L: HD

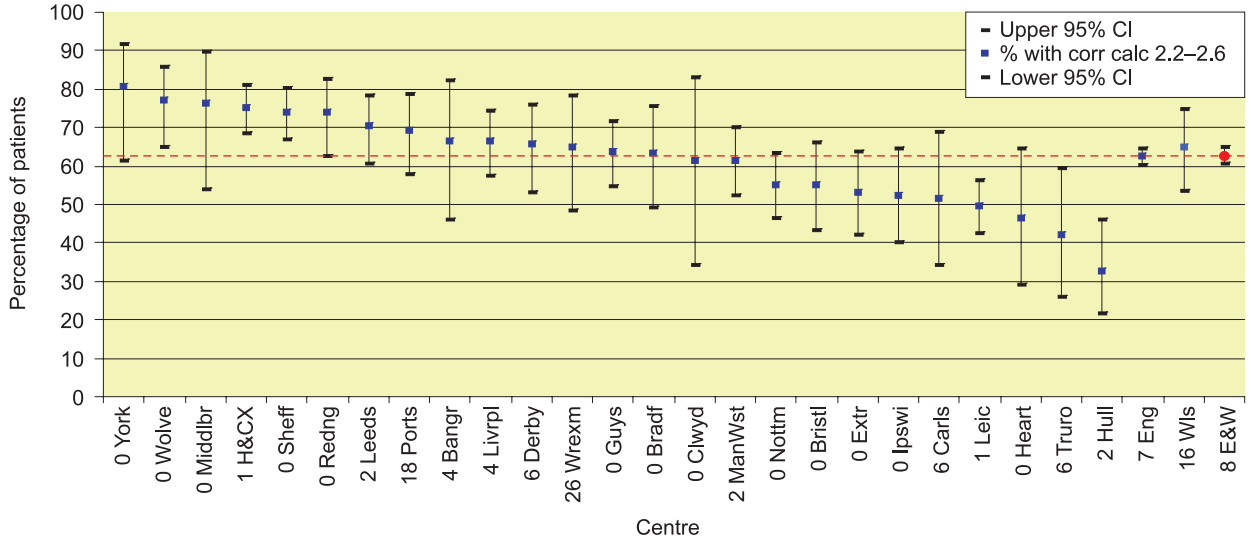

Figure 9.9: Percentage of patients with corrected calcium within 2.2 to 2.6 mmol/L: PD

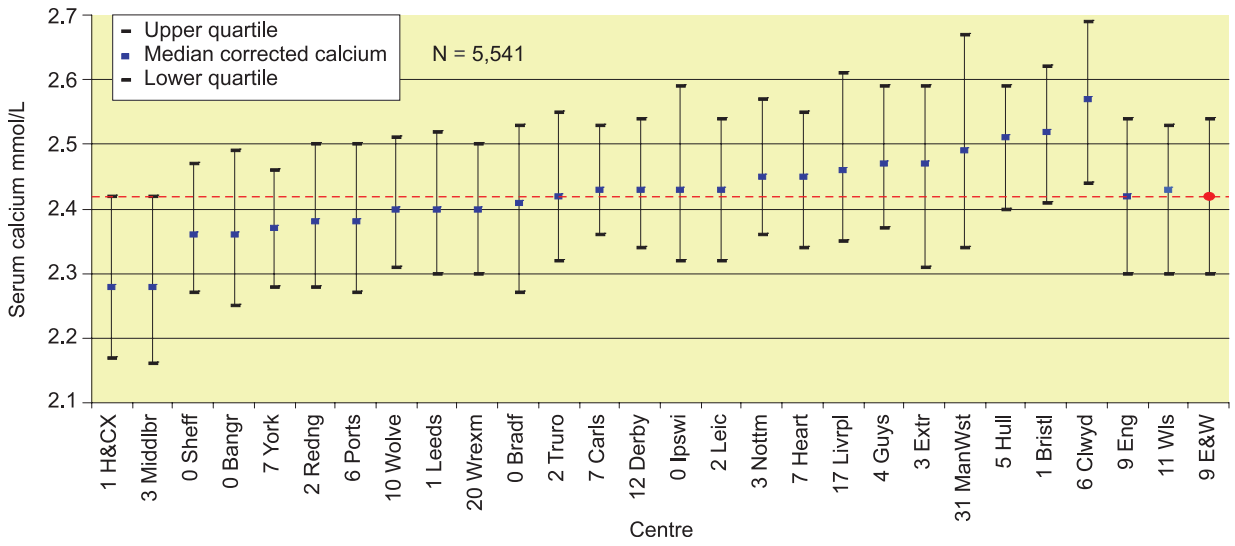

Figure 9.10: Median corrected calcium by centre: HD

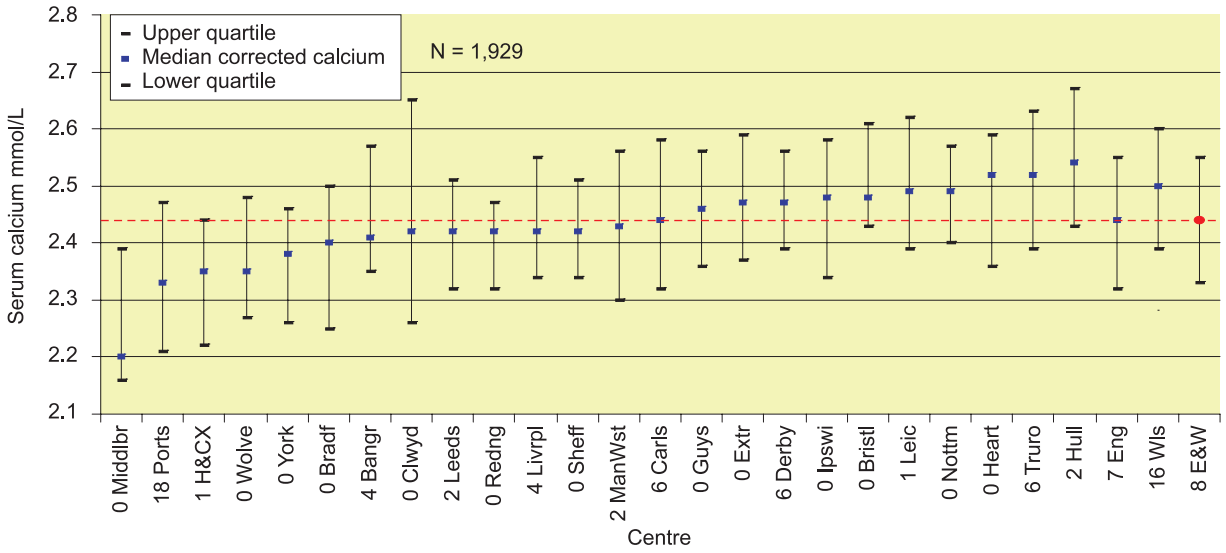

Figure 9.11: Median corrected calcium by centre: PD

NEQAS. No relationship ($p = 0.748$) was observed between median serum corrected calcium and percentage bias of the calcium assay relative to the UK NEQAS ALTM using Spearman's rank correlation. The between centre coefficient of variation (CV) for serum corrected calcium was 2.5%, whereas the between-laboratory CV for serum calcium for all participants in the UK NEQAS scheme using a range of different methods was 3.0%.

Corrected calcium clearly depends on measurement of albumin in addition to calcium. Analysis is complicated by the existence of three different methods used for measurement of serum albumin (bromocresol green (BCG) wet and dry and bromocresol purple (BCP)). However, an earlier Registry report suggested that the correction formulae in use were not necessarily influenced by the choice of albumin method (3rd Registry Report, 2000). Therefore analysis was undertaken comparing median corrected calcium for the centres against the UK NEQAS bias relative to the ALTM data for albumin. This was available from 15 of the laboratories supporting renal centres and ranged from −7.7% to 5.8% (median 1.33%). No relationship ($p = 0.5567$) was observed between median serum corrected calcium and percentage bias of the albumin assay using Spearman's rank correlation.

Taken together, these data suggest that the differences seen between renal centres for (corrected) calcium are not explained by inter-laboratory variation.

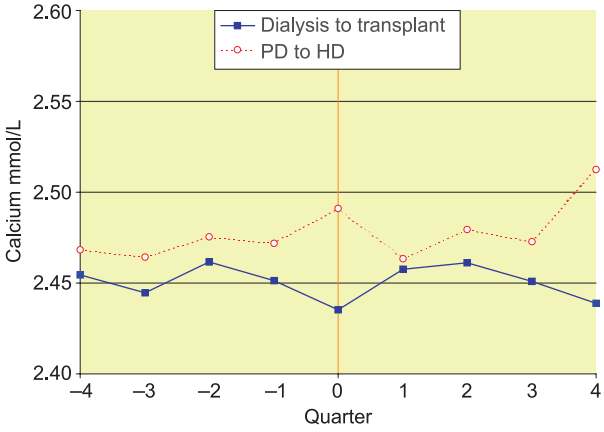

Figure 9.12: Serum corrected calcium, by quarter, before and after modality change

Change in modality of treatment and effect on serum calcium

Neither change in dialysis modality (PD to HD), nor the provision of a renal transplant appear to be associated with clear changes in serum corrected calcium concentration (Figure 9.12).

Calcium/phosphate product

The Renal Association has no standard for the serum calcium phosphate product, but the KDOQI guidelines recommend the product should be less than 4.4 $mmol^2/L^2$ (=55 mg^2/dl^2). Calculating the product using non-corrected serum calcium, more than half (67%) of patients achieve this standard, but the range between units is wide (44% to 82%) (Figure 9.13).

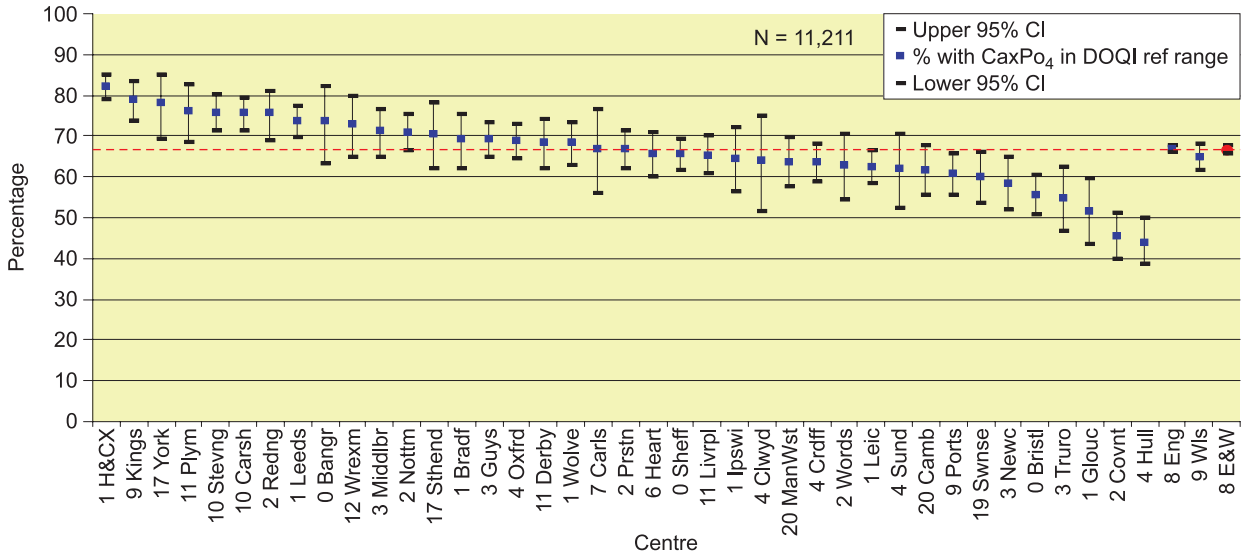

Figure 9.13: Percentage of dialysis patients with calcium phosphate product in the KDOQI recommended range

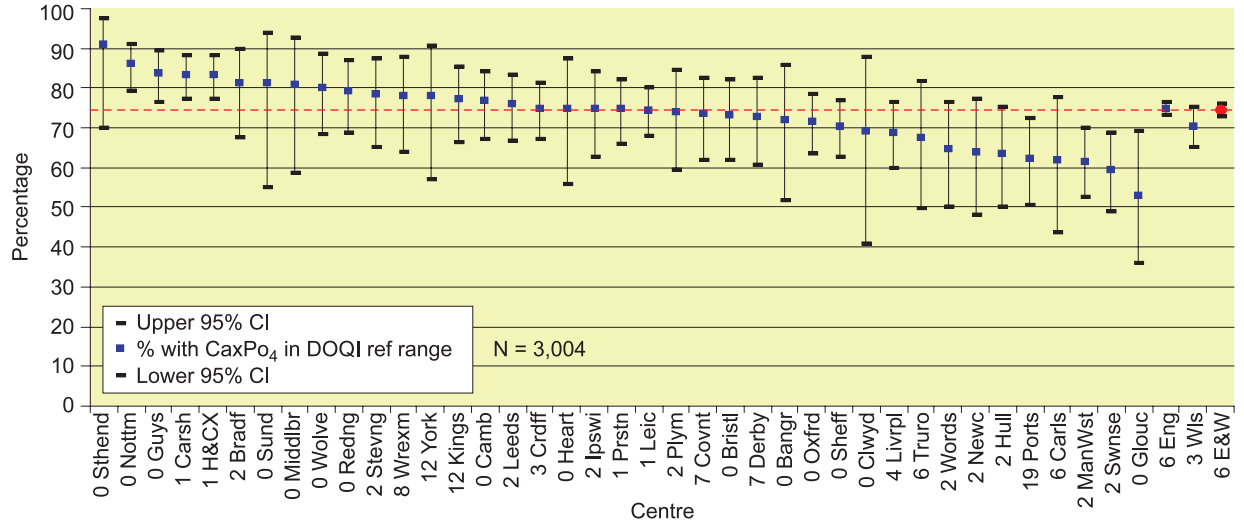

Figure 9.14: Percentage of PD patients with calcium phosphate product in the KDOQI recommended range

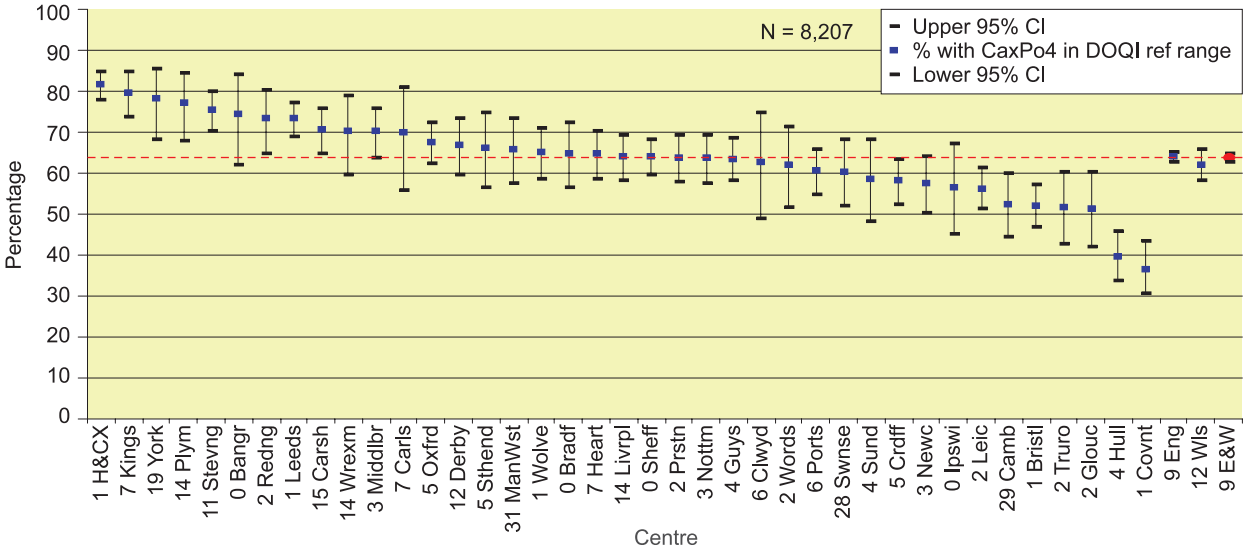

Figure 9.15: Percentage of HD patients with calcium phosphate product in the KDOQI recommended range

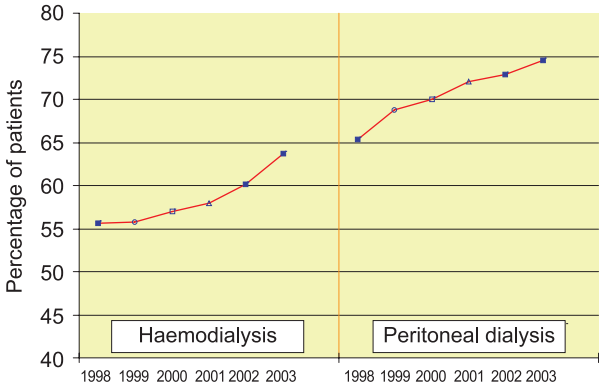

Figure 9.16: Percentage of patients with calcium phosphate product $<4.4\,\text{mmol}^2/\text{L}^2$ in 1999–2003

Control is better on PD, with 75% (range 53–91%) of patients achieving the standard, than on HD (64%, range 37–82%) (Figures 9.14–9.16). The variation between units was significant for both HD ($\chi^2 = 365$, $p < 0.001$) and PD ($\chi^2 = 94$, $p < 0.001$) modalities.

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 iPTH values from different units is difficult due to the variety of methods and reference ranges in use. Laboratories commonly adopt the reference ranges suggested by the assay manufacturer's product information, but for iPTH laboratories may not quote the same upper limit even when using the same methods[2]. The lack of rigour with which some reference ranges have been derived is also an area of concern (ie no manufacturers appear to have established their reference ranges in proven vitamin D replete individuals)[2]. The differing reactivity of the various iPTH methods with the PTH 7–84 fragment known to accumulate in uraemia (see below)[3] is another confounding factor. To enable some form of comparative audit, the Registry has expressed all results in pmol/L and chosen an upper limit of four times the median upper lab value: this equates to 32 pmol/L.

The median iPTH for all dialysis patients (19 pmol/L) lies well within the Standard although the distribution between the centres was wide (6 to 34 pmol/L, Figure 9.17). There was little difference in median iPTH between PD patients (21, range 4 to 55 pmol/L) and HD patients (19, range 6 to 38 pmol/L). Overall, 66% of dialysis patients achieved the RA Standard, but the spread of data between centres was remarkable, ranging from 48% to 87% compliance with the standard (Figure 9.18).

Analysis of the influence of laboratory bias

An analysis of the potential contribution of laboratory bias to between centre differences in

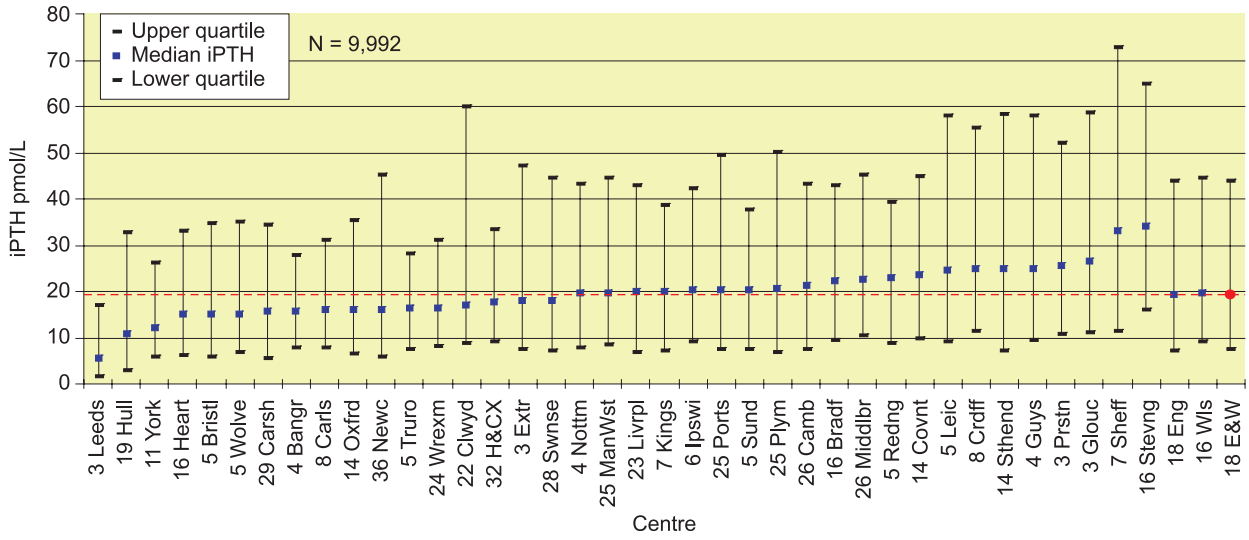

Figure 9.17: Median iPTH by centre: dialysis

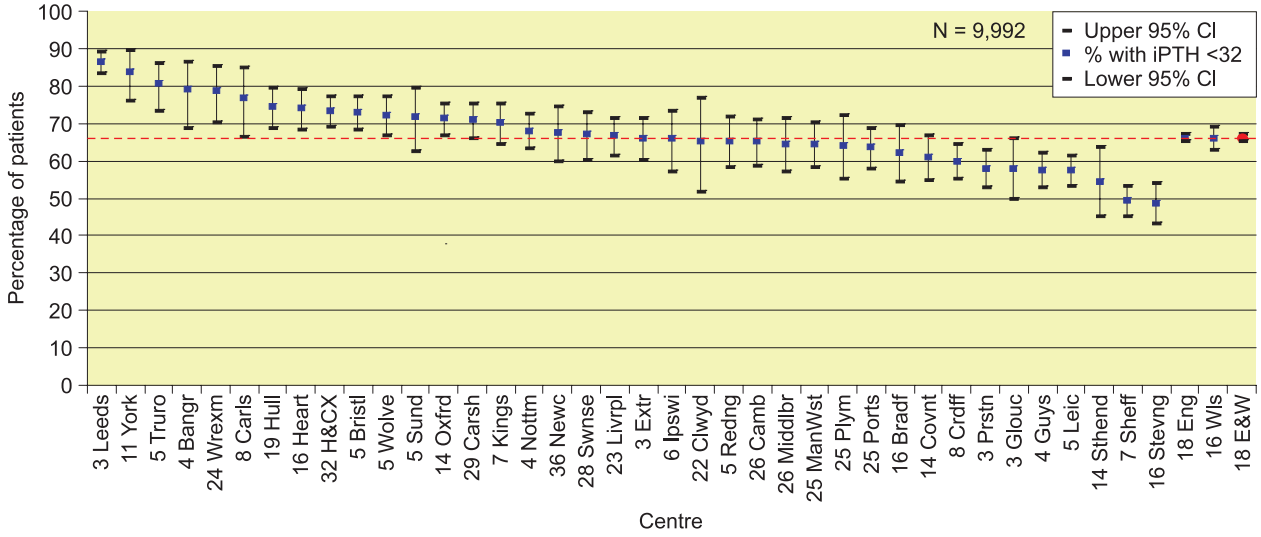

Figure 9.18: Percentage of patients with iPTH <32 pmol/L: dialysis

serum iPTH was undertaken using data from the 2003 Registry report and data supplied by UK NEQAS, which were available from 30 of the laboratories supporting the 35 renal centres which contributed data to the report. Although mean UK NEQAS bias relative to the ALTM varied widely (range −17.3% to 17.8%), this was unrelated ($p = 0.3740$) to the renal centre median serum iPTH using Spearman's rank correlation. Median centre iPTHs for the PD and HD programmes rank in a very different order, despite using the same iPTH assay. Anecdotally, three centres all served by the same laboratory had median iPTHs of 20, 20 and 9 pmol/L. Taken together these observations tend to suggest that differences in patient management and/or case mix probably have a greater influence on centre median iPTH than analytical variation.

PTH measurement at the centres was dominated by three major method groups; DPC Immulite ($n = 10$), Nicholl's Institute Advantage ($n = 11$) and Roche Elecsys ($n = 9$). It is known that fragments of PTH (predominantly 7–84) accumulate in uraemia and cross-react to varying extents in so-called 'intact' PTH immunoassays; typically these fragments account for about 50% of the PTH immunoreactivity reported by laboratories[2]. UK NEQAS data have demonstrated differences in recovery of PTH 7–84 varying from 28% with the DPC method, to 53% with the Roche Elecsys method and 58% with the Nicholl's Advantage method (data supplied by UK NEQAS). Therefore the possibility that cross-reactivity with PTH 7–84 was affecting renal centre performance was tested using one-way ANOVA. Mean centre median iPTH was 13.3, 14.8 and 18.5 pmol/L with the DPC, Nicholl's and Roche methods respectively ($p = 0.1198$).

PTH variation between centres is large, as is analytical variation. However, the two do not seem to be obviously related to each other. Variation against the UK NEQAS ALTM may reflect a combination of differences in calibration (there is no international standard for iPTH), varying cross-reactivity with PTH 7–84 and the mixture of samples circulated in the UK NEQAS scheme (typically approximately half of the samples are spiked with uraemic serum). For example, although the DPC method demonstrates the lowest cross-reactivity with PTH 7–84, it typically demonstrates >10% positive bias compared to the UK NEQAS ALTM; the Nicholl's and Roche methods, by comparison, demonstrate >10% negative bias (UK NEQAS Annual Review 2001). This could suggest that the effects of calibration and non-specificity between the different assays are cancelling each other out. Until calibration, standardisation and specificity issues are resolved, it will remain difficult to ascertain the true contribution of analytical variation to centre performance.

The current understanding of renal parathyroid disease is likely to undergo a paradigm shift in the next few years. In addition to the advent of calcimimetic agents and increasing emphasis on reducing calcium phosphate product, the

recognition that so-called 'intact' iPTH assays are not specific for the whole molecule form of PTH may have profound influences on the approach of the nephrological community to renal osteodystrophy. At present it remains unclear whether PTH 7–84 has significant biological activity in vivo[4]. At the very least, given the high prevalence of this circulating truncated form in uraemic patients, the RA standards may require review to accommodate those centres using the third generation, bio-intact (1–84 specific) assays.

Serum Albumin

The Renal Association has no standard for serum albumin.

The RA Standards document 3rd edition[5] recognises the importance of serum albumin as a marker of outcome, but does not recommend setting an audit standard for serum albumin, predominantly due to lack of standardisation of albumin assays between laboratories. Serum albumin concentration is influenced significantly by the dye used in the assay method; either bromocresol green (BCG) or bromocresol purple (BCP). For this report, centres have been separated both by methodology of albumin measurements and by dialysis modality. The difference between BCG and BCP methods in uraemic patients is widely known. In the current report, the influence of between-laboratory variation on centre performance within the BCG method group alone is explored. Too few centres use the BCP method for meaningful analysis.

Haemodialysis

For centres supported by laboratories using BCG methods (n = 28) the median serum albumin was 38 g/L (range 35 to 41 g/L) (Figure 9.19). As anticipated, centres using the BCP method (n = 13) generally had lower albumin concentrations (median 34 g/L, range 33 to 40 g/L) (Figure 9.20). Overall, 79% of patients had serum albumin above 35 g/L for the BCG method (Figure 9.21) and 85% for BCP (Figure 9.22). For both BCG ($\chi^2 = 604$, $p < 0.001$) and BCP ($\chi^2 = 128$, $p < 0.001$) centres, the percentage of patients achieving serum albumin concentrations above these levels differed significantly between centres.

An analysis of the potential contribution of laboratory bias to between-centre differences has been undertaken using data from the 2003 Registry report and data supplied by UK NEQAS. UK NEQAS method group and laboratory bias data were available for 26 of the laboratories supporting these renal centres (17 BCG, 9 BCP). Given the small data available for the BCP group, analysis was only undertaken of the 17 haemodialysis centres with BCG data. Amongst these, there was a relationship between percentage bias relative to the UK NEQAS ALTM and median albumin ($r_s = 0.61$, $p = 0.0089$) using Spearman's rank correlation. This was largely driven by two laboratories using a dry chemistry BCG

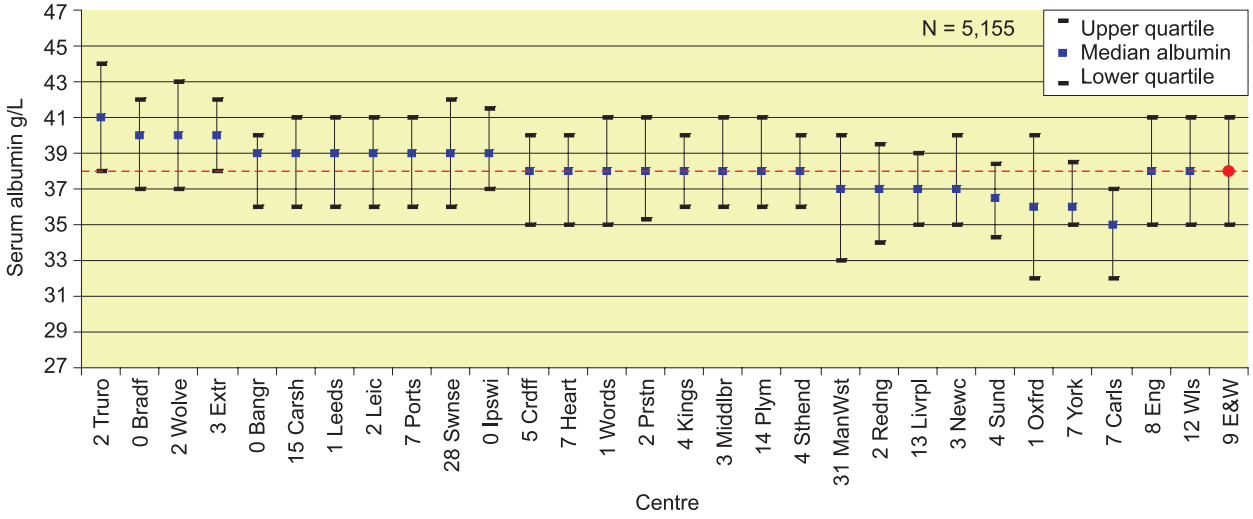

Figure 9.19: Median serum albumin in HD patients by centre: BCG method

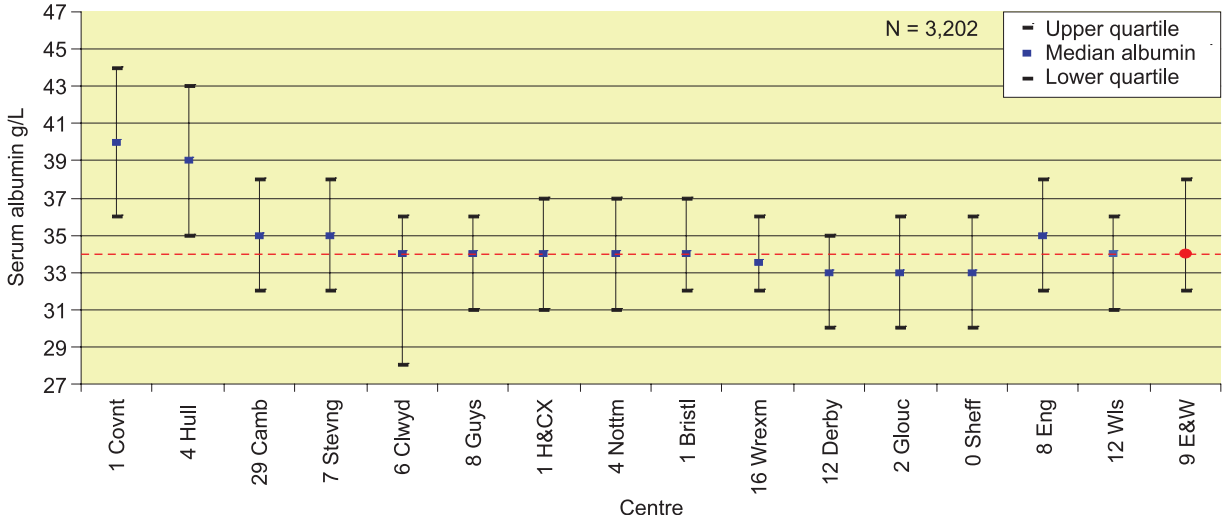

Figure 9.20: Median serum albumin in HD patients by centre: BCP method

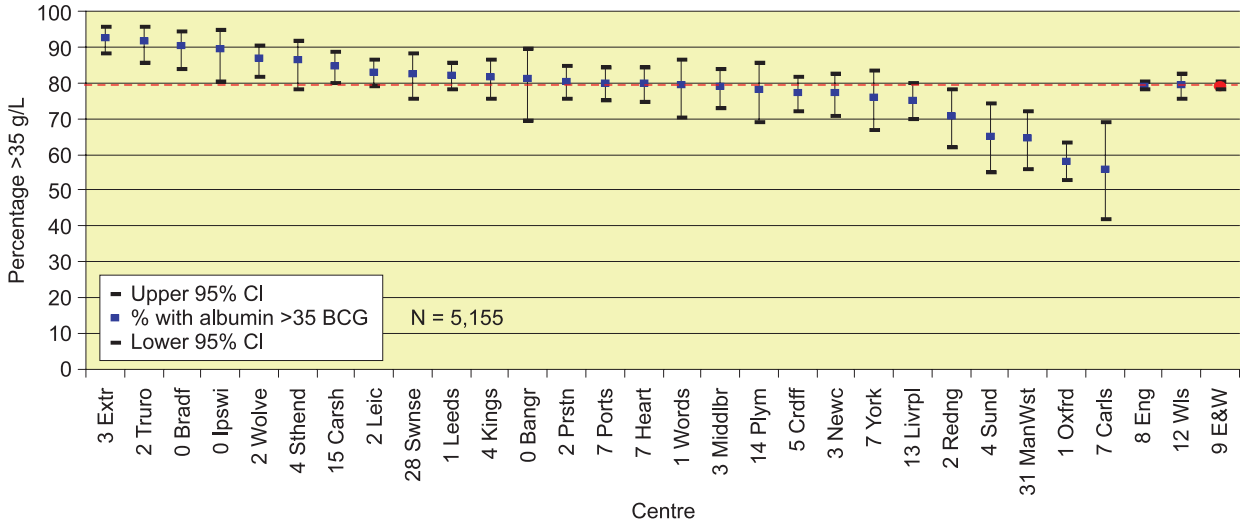

Figure 9.21: Percentage of HD patients by centre with serum albumin >35 g/L (BCG)

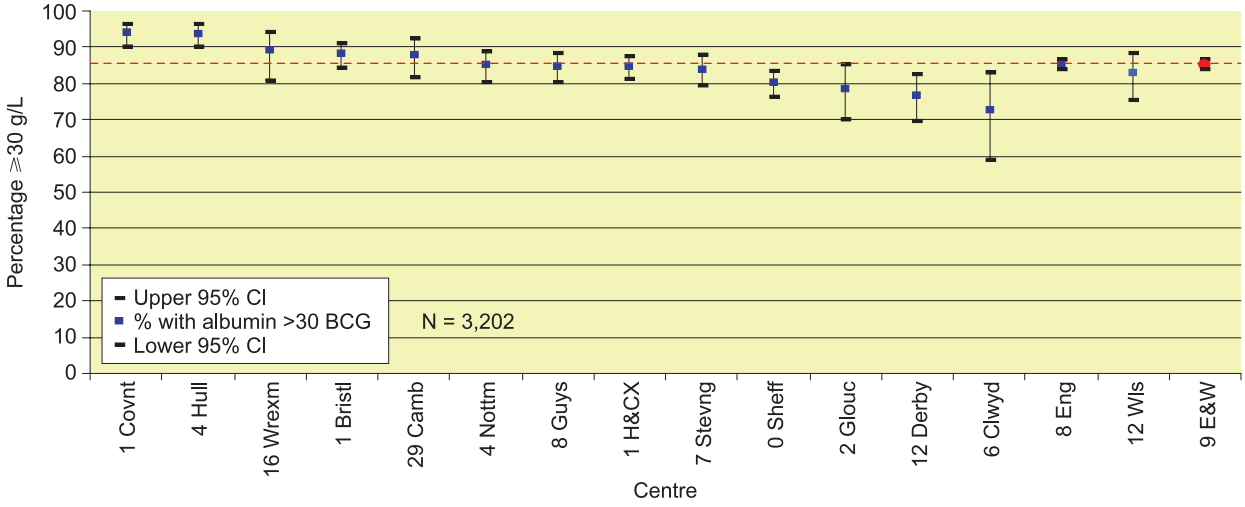

Figure 9.22: Percentage of HD patients by centre with serum albumin >30 g/L (BCP)

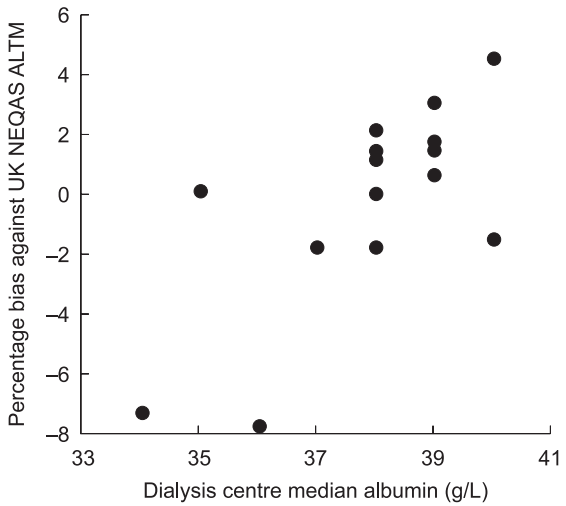

Figure 9.23: Analysis of percentage bias against UK NEQAS ALTM

method, which have low median patient serum albumin (Figure 9.23).

Peritoneal dialysis

Serum albumin is generally lower in PD patients than in HD patients, predominantly due to peritoneal protein losses[6]. Furthermore, peritoneal albumin clearance increases with time on treatment due to increasing effective peritoneal surface area[7]. For centres supported by laboratories using BCG methods (n = 27) the median serum albumin was 36 g/L (range 33 to 38 g/L) (Figure 9.24). As anticipated, centres using the BCP method (n = 13) generally had lower albumin concentrations (median 30 g/L, range 28 to 32 g/L) (Figure 9.25). Overall, 59% of patients had serum albumin above 35 g/L for the BCG method (Figure 9.26) and 55% for BCP (Figure 9.27). For both BCG ($\chi^2 = 138$, $p < 0.001$) and BCP ($\chi^2 = 32$, $p = 0.0015$) centres, the percentage of patients achieving serum albumin concentrations above these levels differed significantly between centres. The data indicate how difficult it is to keep serum albumin above the recommended minimum in patients treated by peritoneal dialysis.

Analysis of the influence of laboratory bias

An analysis of the potential contribution of laboratory bias to between centre differences has been undertaken using data from the 2003 Registry report and data supplied by UK NEQAS. UK NEQAS method group and laboratory bias data was available for 26 of the laboratories supporting these renal centres (17 BCG, 9 BCP). Given the small amount of data available for the BCP group, analysis was undertaken of the 17 PD centres with BCG data only. Amongst these, there was no relationship between percentage bias relative to the UK NEQAS ALTM and median albumin ($r_s = 0.47$, $p = 0.0545$) using Spearman's rank correlation.

Although BCP results clearly demonstrate lower mean albumin concentrations in dialysis patients, in quality assessment samples generally there is no clear relationship between bias relative to the ALTM and method group. Indeed, amongst laboratories supporting renal centres, of the seven laboratories demonstrating the

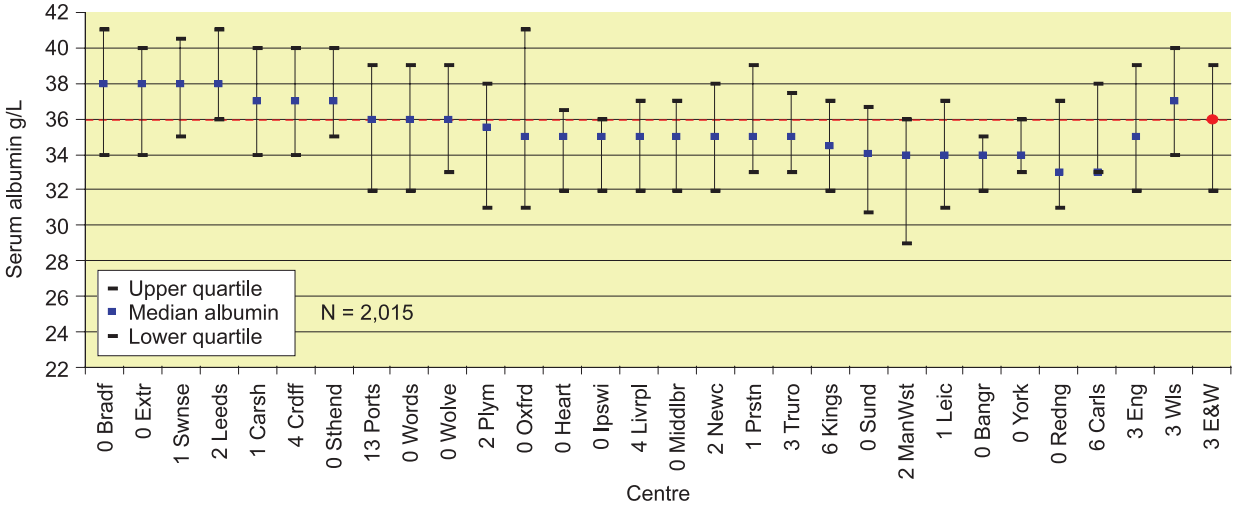

Figure 9.24: Median serum albumin in PD patients by centre: BCG method

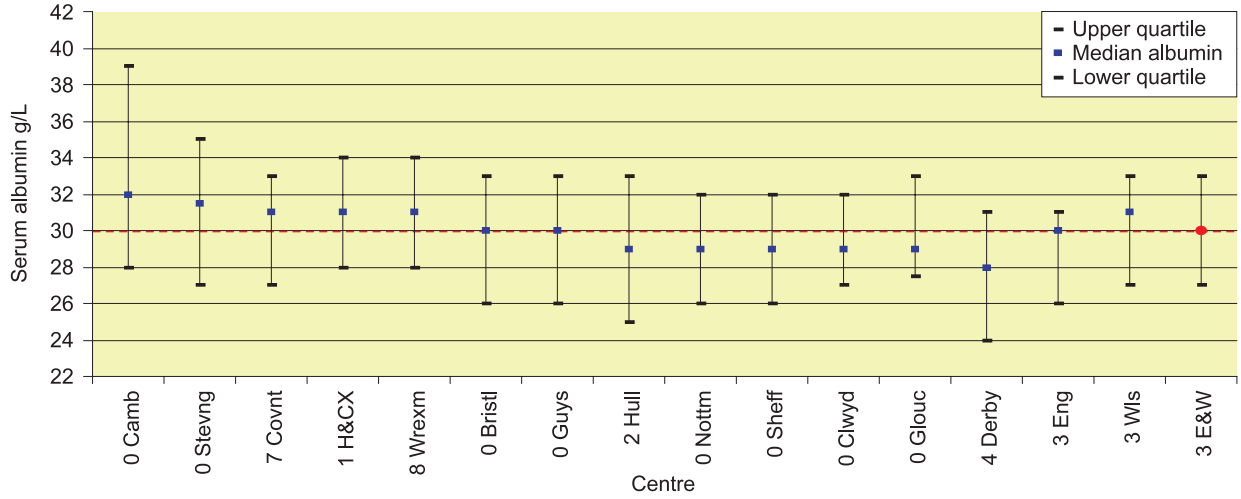

Figure 9.25: Median serum albumin in PD patients by centre: BCP method

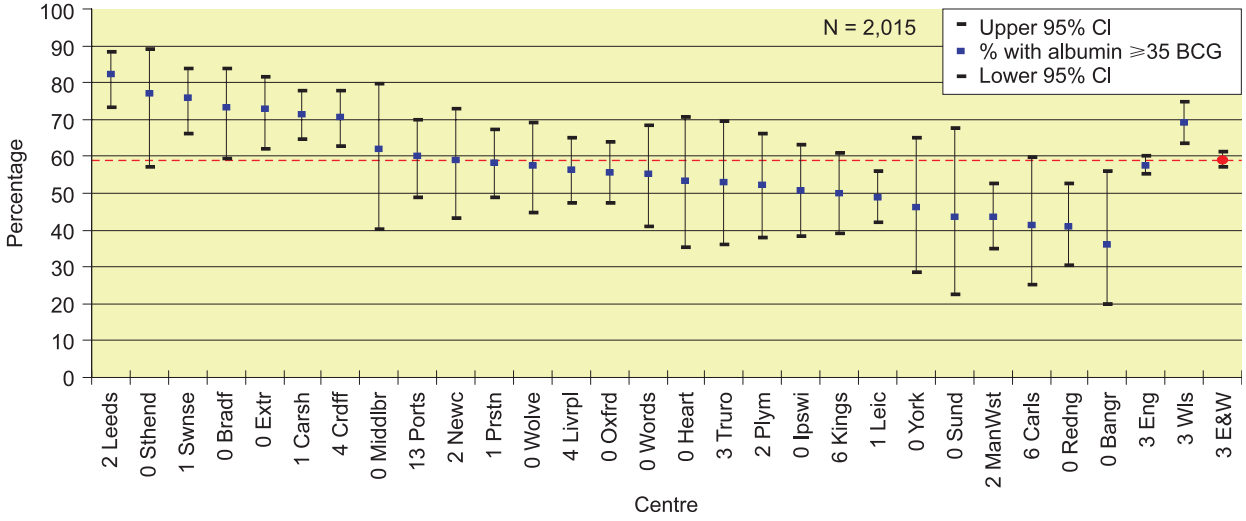

Figure 9.26: Percentage of PD patients by centre with serum albumin >35 g/L (BCG)

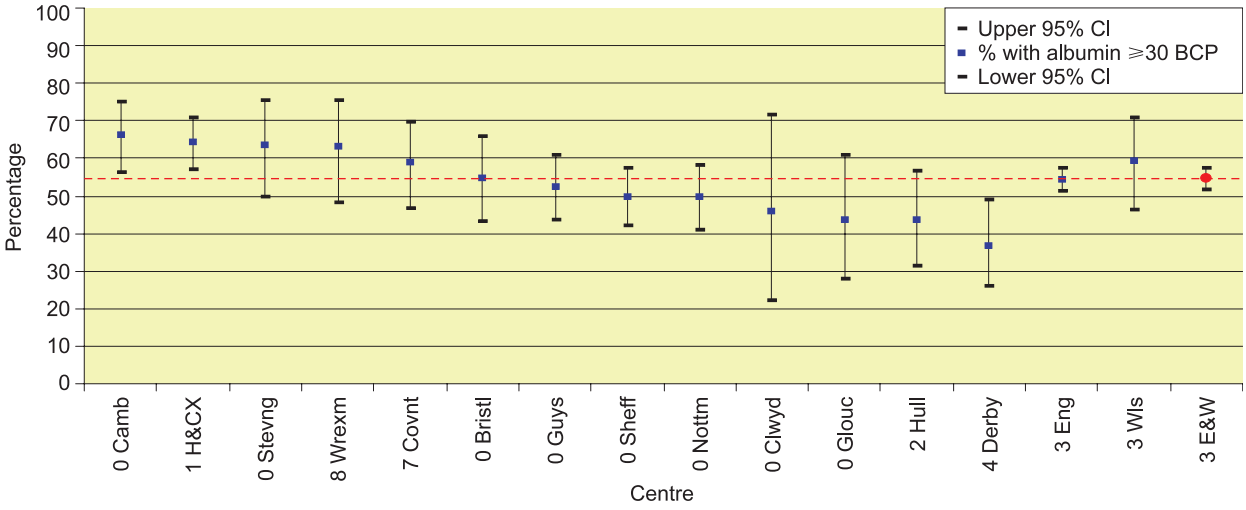

Figure 9.27: Percentage of PD patients by centre with serum albumin >30 g/L (BCP)

most positive bias compared with the UK NEQAS ALTM, five used BCP. This could reflect differing reactivity of the quality assessment material with the BCG/BCP methods compared with uraemic patient samples, or the relative paucity of 'low-range' albumin distributions in the UK NEQAS scheme. The situation is also confused by the use of dry-chemistry BCG methods, which appear to give lower results in dialysis patients. In December 2002, the between-laboratory CV for serum albumin for all participants in the UK NEQAS scheme using a range of different methods was 5.1%. When broken down into method groups, between-laboratory agreement was 3.2%, 3.9% and 3.7% for the BCG, BCP and dry-chemistry methods respectively. Overall, between-centre albumin variation does not greatly exceed laboratory variation and there is some evidence that laboratory variation may contribute to between-centre differences.

Effect of time on treatment

Figure 9.28 demonstrates the effect of time on treatment on the percentage of patients with serum albumin in the target range for both HD and PD. Over time, on HD, the number of patients with higher serum albumin rises, probably due to reduced survival of patients with lower serum albumin. In contrast, over time on PD, serum albumin tends to fall. Possible explanations are increasing peritoneal protein clearance associated with high peritoneal transport due to the cumulative effect of repeated peritonitis and glucose exposure and informative censoring (ie loss of 'fitter' patients to transplantation)[7].

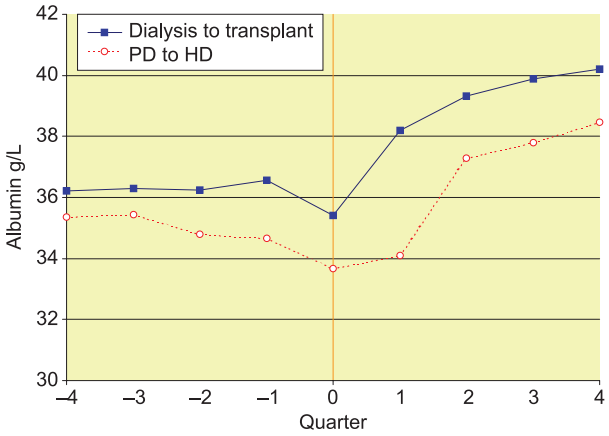

Figure 9.29: Serum albumin, by quarter, before and after modality change

Effect of modality change

Provision of a renal transplant or switching dialysis modality from PD to HD produces predictable increases in serum albumin concentration (Figure 9.29).

Serum Albumin – Discussion

Previous reports from the UK Renal Registry and other publications[18] have recognised the difficulties in using serum albumin as an audit measure in patients with renal failure. BCG is the more commonly used method but tends to overestimate serum albumin when compared with (gold-standard) antibody based methods, especially at lower levels of serum albumin as are often seen in RRT patients. BCG is known to react non-specifically with other protein fractions (α1, α2 and β globulins) in serum, which tend to be over-represented in hypoalbuminaemic situations, eg in an acute phase reaction.

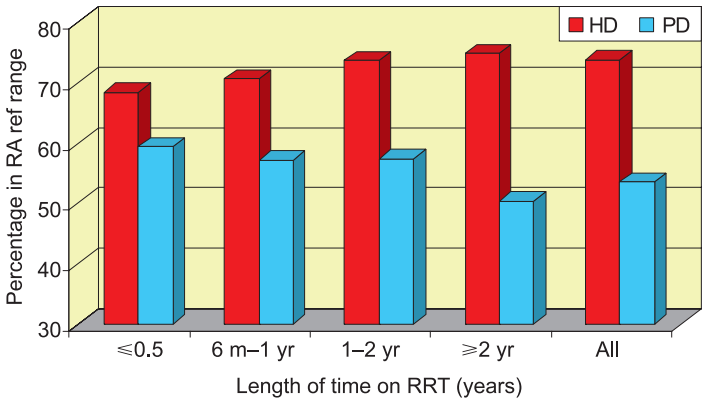

Figure 9.28: Changes over time on HD and PD in percentage of patients with serum albumin >35 g/L (BCG) or >30g/L (BCP)

There have been calls for laboratories to switch to use of BCP[9] but the situation is not straightforward. Not all BCG methods are equal, with the relative interference from non-albumin protein being in part dependent on the time period over which the reaction is monitored (non-albumin proteins react more slowly than albumin itself)[10,11]. Further, dry-slide BCG methods have in fact been reported to show a slight negative bias (−1 g/L) when compared with immunological assays[12] and would appear from the present data to contribute significantly to differences between renal centres. Although some authors have demonstrated improved accuracy of BCP methods compared with BCG in uraemic patients[8], others have shown significant underestimation of serum albumin by BCP methods in haemodialysis patients [13,14]. This may relate to the presence of an inhibitor of the BCP dye-binding reaction[15] which accumulates in haemodialysis patients but not in patients being treated with PD[16]. Other unexplored factors may be important: for example, HD is known to result in loss of cysteine from its mixed disulphide bond, so that the proportion of mercaptalbumin is higher after treatment[17]. It is known that mercaptalbumin is less reactive with BCP methods than its oxidised non-mercaptalbumin form[18].

As reflected in the RA standards, it is widely accepted that BCG gives serum albumin results approximately 5 g/L higher on average than BCP in a renal patient population[19,20]. The present Registry data give some credence to the equivalence of these two standards, with roughly equivalent numbers of dialysis patients achieving the RA minimum albumin concentration with BCG and BCP methods. However, the Registry data support the RA stance that it is not appropriate to set an audit standard for serum albumin. It is clear that analytical influences are significant, but there is no clear pointer as to which method is most appropriate in uraemic patients and whether they can be applied equally to PD and HD patients. There are almost certainly other confounding factors; for example the effect of social deprivation alluded to above. Further, at the individual patient level there is little that can be done to correct hypoalbuminaemia (apart from changing RRT modality).

As concluded in previous Registry reports, although serum albumin measurement is useful clinically at the individual patient level, the value of between-centre comparative audit and continuing to present these data is questionable.

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