Nephrol Dial Transplant (2017) 32: 534–541
doi: 10.1093/ndt/gfw020
Advance Access publication 3 March 2016

Frequent monitoring of mineral metabolism in hemodialysis patients with secondary hyperparathyroidism: associations with achievement of treatment goals and with adjustments in therapy

Keitaro Yokoyama[1,*], Noriaki Kurita[2,3,*], Shingo Fukuma[3,4,5], Tadao Akizawa[6], Masafumi Fukagawa[7], Yoshihiro Onishi[3], Kiyoshi Kurokawa[8] and Shunichi Fukuhara[5,9]

[1]Division of Nephrology and Hypertension, Department of Internal Medicine, The Jikei University School of Medicine, Tokyo, Japan, [2]Department of Innovative Research and Education for Clinicians and Trainees (DiRECT), Fukushima Medical University Hospital, Fukushima, Japan, [3]Institute for Health Outcomes and Process Evaluation Research (iHope International), Kyoto, Japan, [4]Institute for Advancement of Clinical and Translational Science (iACT), Kyoto University Hospital, Kyoto, Japan, [5]Center for Innovative Research for Communities and Clinical Excellence (CIRC2LE), Fukushima Medical University, Fukushima, Japan, [6]Division of Nephrology, Department of Medicine, Showa University School of Medicine, Tokyo, Japan, [7]Division of Nephrology, Endocrinology and Metabolism, Tokai University School of Medicine, Isehara, Japan, [8]National Graduate Institute for Policy Studies, Tokyo, Japan and [9]Department of Healthcare Epidemiology, School of Public Health in the Graduate School of Medicine, Kyoto University, Kyoto, Japan

Correspondence and offprint requests to: Shunichi Fukuhara; E-mail: fukuhara.shunichi.6m@kyoto-u.ac.jp
*K.Y. and N.K. are co-first authors.

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ABSTRACT

Background: Dialysis guidelines in Japan recommend more frequent measurement of mineral metabolism markers than the Kidney Disease: Improving Global Outcomes guidelines. However, the extent to which frequent marker measurement contributes to achievement of target ranges and to therapy adjustment is unknown.

Methods: This multicenter cohort study involved 3276 hemodialysis patients with secondary hyperparathyroidism. Data on laboratory measurements and drug prescriptions were collected every 3 months. Main exposures were frequencies of measuring serum calcium and phosphorus [weekly/biweekly/monthly (reference)] and serum parathyroid hormone (PTH) [monthly/bimonthly/trimonthly (reference)] levels. Outcomes were achievement of guideline-specified ranges of mineral metabolism markers when serum levels were over, and maintenance of ranges when levels were already within, respective specified ranges, use of intravenous vitamin D receptor activator (VDRA) and initiation of cinacalcet use. Associations were examined via generalized estimating equations.

Results: When serum marker levels exceeded the target range, weekly measurement of calcium and phosphorus was positively associated with achievement of the guideline-specified calcium range [adjusted odds ratio (AOR): 1.57, 95% confidence interval (CI) 1.09–2.26] but not phosphorus range (AOR: 0.99, 95% CI 0.74–1.33). Monthly measurement of PTH was positively associated with achievement of the guideline-specified PTH range (AOR: 1.14, 95% CI 1.01–1.27). When serum marker levels were within the guideline-specified range, increased frequency of measurements was not associated with in-range maintenance of marker levels for any of the three mineral markers assessed. Regarding treatment regimen, relatively frequent measurement of serum calcium and phosphorus was positively associated with cinacalcet initiation and relatively frequent measurement of serum PTH with cinacalcet initiation and intravenous VDRA use.

Conclusions: Our results suggest that increasing frequency of measurements is helpful when serum marker levels exceed the target range, partially via adjustment in the therapeutic regimen. We found no evidence that frequent measurements are helpful when mineral levels are already within target ranges.

Keywords: cohort study, mineral metabolism markers, monitoring frequency

INTRODUCTION

Treatment of mineral metabolism abnormalities is important in managing hemodialysis patients with secondary hyperparathyroidism (SHPT), as a body of evidence suggests that the risk of bone-related and cardiovascular complications is increased

under conditions of high serum parathyroid hormone (PTH) levels, hypercalcemia and hyperphosphatemia, possibly via bone remodeling and accelerated vascular calcification [1–3]. To help clinicians recognize abnormalities in mineral metabolism markers, target ranges have been defined for serum PTH, calcium and phosphorus levels in clinical practice guidelines established by the Kidney Disease Outcomes Quality Initiative (KDOQI), Kidney Disease: Improving Global Outcomes (KDIGO) and the Japanese Society for Dialysis Therapy (JSDT) [4–6]. The appropriateness of these target ranges is supported by several studies showing that consistent control of the mineral metabolism makers within their target ranges is associated with improved survival rates among hemodialysis patients [7, 8]. To achieve these guideline-specified target ranges, each guideline outlines rules regarding the frequency of monitoring mineral metabolism markers (Table 1) [4–6]. However, as noted in the guidelines themselves, evidence supporting these recommended frequencies is admittedly scarce.

Findings from a previous study suggested that the PTH target range specified in the KDOQI guidelines was achieved more often after frequency of monitoring mineral markers was switched from quarterly to monthly [10]. However, given that those results were obtained in a before–after study with no comparison group, conducted at a single center, whether the increased rate of achieving target range PTH levels was due to increased monitoring frequency or due to increased use of cinacalcet or vitamin D receptor activator (VDRA) irrespective of changes in monitoring frequency remains unclear.

Recommended frequencies for monitoring also vary between guidelines, with no firm consensus on optimum frequency (Table 1) [4–6]. In Japan, biweekly or monthly measurement is recommended for calcium/phosphorus [6], which is more frequent than values defined in the KDOQI or KDIGO guidelines [4, 5]. Regarding PTH, trimonthly measurement is recommended in Japan [6], whereas less frequent measurement (every 3–6 months) is recommended in the KDIGO guideline [5]. Further, our previous study on practice patterns at Japanese dialysis facilities revealed that some facilities have adopted 'intensive monitoring' frequencies, such as weekly measurement for serum calcium/phosphorus levels or monthly measurement for serum PTH levels [11]. Examination of how real-world variation in measurement frequency for mineral metabolism markers affects adjustments in therapies and likelihood of achievement of target ranges will help clarify the appropriateness of suggestions in existing guidelines.

Here, to examine the extent to which frequency of marker measurement contributes to achievement of target ranges and to therapy adjustment, we analyzed findings from a prospective, large-scale cohort study of hemodialysis patients with SHPT: Mineral and Bone Disorders Outcomes Study for Japanese CKD Stage 5D Patients (MBD-5D).

MATERIALS AND METHODS

The study protocol and waiver of informed consent were approved by the Central Ethics Committee at Kobe University's School of Medicine (No. 754).

Target population

The target population was chronic kidney disease stage 5D patients with SHPT receiving maintenance hemodialysis. To determine participating facilities, the country was first divided into nine geographical regions, and the number of facilities chosen for each region was made proportional to the number of hemodialysis patients in that region. Facilities were included until the target sample size for the MBD-5D study was reached [12]. Eligible patients were all who met the following two criteria: (i) those receiving hemodialysis at one of the participating facilities as of 1 January 2008 and (ii) either those with iPTH concentration $\geq$180 pg/mL or those receiving an intravenous VDRA (calcitriol or maxacalcitol) or an oral active VDRA (falecalcitriol, the only oral VDRA approved in Japan for SHPT treatment). Patients who had been on dialysis for <3 months were excluded. A total of 3276 patients were registered in the study cohort from among 86 facilities across Japan. Data were collected until January 2011.

Outcomes and exposures

We examined four clinical outcomes: achievement or maintenance of guideline-specified ranges of mineral metabolism markers when serum levels were (i) over or (ii) within ranges, respectively, (iii) use of intravenous VDRA and (iv) initiation of cinacalcet use (see conceptual framework in Figure 1). JSDT-specified target ranges are 3.5–6.0 mg/dL for phosphorus, 8.4–10.0 mg/dL for calcium (albumin-corrected value, see the 'Data collection' section) and 60–180 pg/mL for intact PTH (iPTH) [9]. Regarding intravenous VDRA, use of calcitriol or maxacalcitol was examined.

Table 1. Frequency of monitoring for mineral metabolism markers suggested in guidelines

	KDOQI 2003 [4]	JSDT 2008 [9] and 2012 [6]	KDIGO 2009 [5]
Calcium/phosphorus			
Default	Monthly	Biweekly or monthly	Every 1–3 months
Other than default	More frequently than default[a]	More frequently than default[b]	More frequently than default[c]
PTH			
Default	Trimonthly	Trimonthly	Every 3–6 months
Other than default	More frequently than default[a]	Monthly[d]	More frequently than default[c]

KDOQI, Kidney Disease Outcomes Quality Initiative; JSDT, Japanese Society for Dialysis Therapy; KDIGO, Kidney Disease: Improving Global Outcomes.
[a]Recommended if concomitant therapy for relevant mineral markers is being provided.
[b]Recommended if serum calcium or phosphorus levels deviate from target ranges.
[c]Recommended if concomitant therapy for relevant mineral markers is being provided or if serum levels of relevant mineral markers are abnormal.
[d]Recommended if PTH levels deviate from the target range, if therapies are changed or if active therapy for SHPT is started.

The main exposures were frequencies of measurement for calcium/phosphorus or PTH as a facility policy and were assessed by asking dialysis facility physicians in charge of the MBD-5D study the following: 'In your facility, how often are serum calcium and phosphorus levels usually measured?' with responses of 'weekly', 'biweekly', 'monthly', 'bimonthly', 'when needed' or 'other (with free comments)' and 'In your facility, how often is serum PTH level usually measured?' with responses of 'monthly', 'bimonthly', 'trimonthly', 'every six months', 'when needed' or 'other (with free comments)'.

Responses of 'when needed' were excluded for all three markers, as the true frequency was unknown. Given that no facilities cited a frequency of bimonthly for serum calcium/phosphorus measurement (Supplementary data, Table S1), three levels of decreasing frequency were set: weekly/biweekly/monthly (reference, citing KDOQI and JSDT statements) [4, 9]. With regard to frequency of serum PTH measurement, facilities who reported taking measurements every 4 months or less were excluded, as under our study protocol, data on mineral metabolism markers were collected every 3 months (Supplementary data, Table S2). As such, three levels of decreasing frequency were set: monthly/bimonthly/trimonthly (reference, citing KDOQI and JSDT statements) [4, 9].

Covariates

Covariates used in the analyses included baseline (time of entry into cohort) patient characteristics (age, gender, vintage, primary renal disease, cardiovascular disease, lung disease, liver disease, malignancy and history of parathyroidectomy), levels of mineral and bone disorder (MBD)-related serum markers (calcium, phosphorus and iPTH), prescriptions for MBD-related drugs [VDRAs (intravenous VDRAs and oral falecalcitriol, calcitriol and alphacalcidol), cinacalcet and phosphate binders] and other potential confounders (dialysate calcium concentration, Kt/V and serum albumin level).

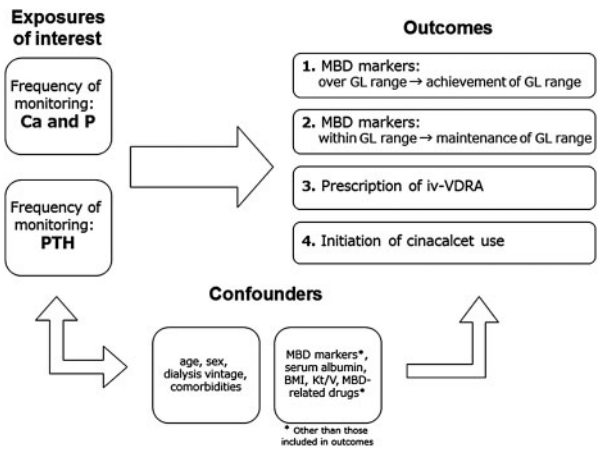

FIGURE 1: Conceptual framework used in regression analyses. MBD markers include serum calcium (Ca), phosphorus (P) and PTH. MBD-related drugs include intravenous VDRAs, phosphate binders and cinacalcet. Guideline (GL) range: target range of MBD markers specified in the JSDT guidelines. Outcome 1 was whether or not future MBD marker levels would achieve their target ranges when their levels were over ranges at previous visit. Outcome 2 was whether or not future MBD marker levels would maintain their target ranges when their levels were within ranges at previous visit. Outcome 3 was whether or not intravenous administration was used in the future. Outcome 4 was whether or not cinacalcet prescription was initiated in the future. BMI, body mass index.

Data collection

Data were collected from 86 dialysis facilities by trained staff. Data on demographics and comorbidities were collected at the time of enrollment (Visit 0). Data on MBD markers and treatments were collected at the time of enrollment (Visit 0) and every 3 months for 3 years (Visits 1–12). Data on other time-dependent variables were collected every 6 months, prospectively. The laboratory data used were values measured closest to the end of each visit. Serum iPTH levels (reference: 10–65 pg/mL) were measured at 73 facilities. Serum whole PTH levels obtained using a third-generation PTH assay (immunoradiometric assay; reference: 9–39 pg/mL) were measured at the other 13 facilities and then converted to iPTH levels by multiplying whole PTH values by 1.7, a method that has been validated in a previous study and is recommended in Japanese guidelines [9, 13]. Serum calcium levels were corrected for albumin concentration using the modified Payne method [corrected calcium = calcium + (4.0 – albumin), when albumin levels were <4.0 g/dL] [14], which is recommended in the Japanese dialysis guideline and thus commonly used in Japanese dialysis settings [9].

Statistical analysis

The analytic model for achieving guideline-specified target ranges is shown in Supplementary data, Table S3. For each 3-month period ending at Visit t, achievement of target range was modeled as a function of treatment-related variables (receipt of VDRAs, phosphate binder or cinacalcet and dialysate calcium concentration) at a given Visit $t-1$, biochemical variables (calcium, phosphorus, iPTH, Kt/V and serum albumin) at Visit $t-2$ and baseline data (measurement frequency, age, gender, primary renal disease and vintage). We fitted generalized estimating equations to estimate odds ratios for likelihood of achieving target ranges based on intra-individual repeated measurements, with a separate model fitted for each mineral metabolism marker (Supplementary data, Table S3). For analyses when mineral metabolism markers exceeded guideline-specified target ranges, sets were restricted to data with mineral metabolism markers at Visit $t-2$ above the upper limits of target ranges. For analyses when mineral metabolism markers were within the target ranges, sets were restricted to data with mineral metabolism markers at Visit $t-2$ within target ranges.

The analytic model for using intravenous VDRA or starting cinacalcet is shown in Supplementary data, Table S4. For each 3-month period ending at Visit t, use of intravenous VDRA or cinacalcet initiation was modeled as a function of treatment-related variables (receipt of VDRAs, phosphate binder or cinacalcet and dialysate calcium concentration) and biochemical variables (calcium, phosphorus, iPTH, Kt/V and serum albumin) at Visit $t-1$ and baseline data (measurement frequency, age, gender, primary renal disease and vintage). We fitted generalized estimating equations to estimate odds ratios for likelihood of using intravenous VDRAs or starting cinacalcet, with a

separate model fitted for each treatment (Supplementary data, Table S4). Analyses on use of intravenous VDRAs used all data sets, whereas sets used for cinacalcet initiation analyses were restricted to those in which cinacalcet prescription at Visit *t* was not initiated or was initiated for the first time at that visit. Sensitivity analyses restricted to facilities using iPTH were also conducted for the analytic models, both for achieving guideline-specified target ranges and for using intravenous VDRA or starting cinacalcet.

Data missing at baseline were replaced by mean or median values or by predicted values from linear regression models. Missing data were imputed by carrying the last observation forward. We used these simple imputation methods because there were markedly few missing values for MBD-related markers of interest (<0.2% at baseline and ∼2% during follow-up, except for 6% for iPTH).

Statistical significance was set at $P < 0.05$. SAS 9.4 (SAS Institute, Cary, NC, USA) was used for statistical analyses.

RESULTS

Baseline characteristics are shown in Table 2. Across a total of 86 facilities, the mean age was 61.9 years, mean dialysis vintage was 10.1 years, 38.5% of the cases were women, and 44.9 and 24.2% of the cases of primary renal disease were glomerulonephritis and diabetic nephropathy, respectively. Percentages of glomerulonephritis and women in our study population were similar to those of all Japanese dialysis patients in 2007 [15]. At baseline, the proportions of patients with JSDT-specified target ranges of serum calcium (8.4–10.0 mg/dL), serum phosphorus (3.5–6.0 mg/dL) and serum iPTH (60–180 pg/mL) were 65.4, 63.2 and 14.5%, respectively. The proportions of patients receiving VDRA and phosphate binder at baseline were 77.5 and 85.3%, respectively. Cinacalet was not used, as it was not marketed at baseline.

Regarding frequency of monitoring serum calcium/phosphorus as a facility policy, responses of weekly, biweekly and monthly were given by 4, 69 and 9 facilities, respectively (Supplementary data, Table S1). Regarding frequency of monitoring serum PTH, responses of monthly, bimonthly and trimonthly were given by 16, 6 and 33 facilities, respectively (Supplementary data, Table S2).

Table 3 shows the association of frequency of monitoring and likelihood of achieving guideline-specified target ranges. When serum mineral marker levels exceeded the targeted range, weekly measurement of calcium/phosphorus was positively associated with achieving the guideline-specified calcium range [adjusted odds ratio (AOR): 1.57, 95% confidence interval (CI) 1.09–2.26] but not the phosphorus range (AOR: 0.99, 95% CI 0.74–1.33). Monthly measurement of PTH was positively associated with achieving the guideline-specified iPTH range (AOR: 1.14, 95% CI 1.01–1.27). However, when serum marker levels were already within the guideline-specified range, increased frequency of measurements was not associated with in-range maintenance of marker levels for any of the three mineral markers assessed.

Table 2. Study population baseline characteristics

Number of study sites	86
Number of patients	3276
Age [years, mean (SD)]	61.9 (12.7)
Sex (female) (%)	38.5
Dialysis duration [years, mean (SD)]	10.1 (8.2)
Cause of end-stage renal disease	
Glomerulonephritis (%)	44.9
Diabetic nephropathy (%)	24.2
Nephrosclerosis (%)	5.8
Polycystic kidney disease (%)	4.4
Others/unknown (%)	20.8
Comorbidities	
Cardiovascular disease (%)	60.0
Lung disease (%)	7.3
Liver disease (%)	14.0
Malignancy (%)	5.0
History of parathyroidectomy (%)	6.0
Serum albumin [g/dL, mean (SD)]	3.8 (0.4)
Kt/V [mean (SD)]	1.42 (0.29)
Serum calcium[a]	
<8.4 mg/dL (%)	9.9
8.4–10.0 mg/dL (%)	64.8
>10.0 mg/dL (%)	25.3
Serum phosphorus	
<3.5 mg/dL (%)	4.5
3.5–6.0 mg/dL (%)	63.3
>6.0 mg/dL (%)	32.2
Serum iPTH	
<60 pg/dL (%)	2.8
60–180 pg/dL (%)	15.0
>180 pg/dL (%)	82.2
Dialysate calcium	
<3 mg/dL (%)	52.0
≥3 mg/dL (%)	48.0
VDRA	
Intravenous (%)	48.7
Oral (%)	28.8
None (%)	22.5
Phosphate binder	
Both (%)	23.3
Not calcium-based (%)	18.4
Calcium-based (%)	43.6
None (%)	14.7
Cinacalcet[b]	
None (%)	100

SD, standard deviation.
[a]Corrected for albumin concentration using the modified Payne method.
[b]Cinacalcet was not marketed at baseline.

Tables 4 and 5 show the association of frequency of monitoring and likelihood of therapy adjustment. Increased frequency of measurement of serum calcium/phosphorus was positively associated with cinacalcet initiation (Table 4). For serum PTH, bimonthly—but not monthly—measurement was associated with cinacalcet initiation (AOR: 1.29, 95% CI 1.01–1.64 and AOR: 1.13, 95% CI 0.95–1.35, respectively). Increased frequency of measurement of serum calcium/phosphorus was not associated with intravenous VDRA administration (Table 5). Monthly PTH measurement was associated with intravenous VDRA administration (AOR: 1.54, 95% CI 1.35–1.76).

Sensitivity analyses restricted to facilities using iPTH assays yielded similar but slightly stronger associations than those presented in Tables 3–5 (Supplementary data, Tables S5–S7, respectively).

Table 3. Association of monitoring frequency with achievement of guideline-specified ranges for each marker

Serum marker	Monitoring frequency	Patients with marker levels OVER range at previous visit			Patients with marker levels WITHIN range at previous visit		
		Sets (*n*)	Proportion (%)[a]	Relative proportion in-range marker levels [OR (95% CI)][b]	Sets (*n*)	Proportion (%)[c]	Relative proportion in-range marker levels [OR (95% CI)][b]
Calcium	Weekly	284	54.9	1.57 (1.09–2.26)	1063	80.1	1.11 (0.89–1.38)
	Biweekly	6892	47.1	1.10 (0.91–1.32)	19 458	78.9	0.96 (0.85–1.09)
	Monthly	1079	44.9	Reference	3145	79.8	Reference
Phosphorus	Weekly	510	49.2	0.99 (0.74–1.33)	861	70.9	0.89 (0.72–1.10)
	Biweekly	8432	47.1	0.92 (0.78–1.09)	18 213	73.9	1.00 (0.90–1.12)
	Monthly	1349	48.6	Reference	3037	74.4	Reference
PTH	Monthly	4429	29.4	1.14 (1.01–1.27)	2991	60.9	0.94 (0.83–1.07)
	Bimonthly	1352	25.1	0.96 (0.80–1.16)	837	58.9	0.93 (0.76–1.13)
	Trimonthly	8563	25.5	Reference	4579	61.5	Reference

[a]Proportion of sets in which mineral marker levels were in the target range when levels had exceeded the range at previous visit.
[b]AORs and 95% CIs were estimated via generalized estimating equations to account for correlation between intra-individual repeated measurements with adjustment for covariates listed in Supplementary data, Table S3.
[c]Proportion of sets in which mineral marker levels were still in the target range when levels had been within the range at previous visit.

Table 4. Association of frequency of monitoring of serum markers with cinacalcet initiation

Serum marker	Monitoring frequency	Initiation of cinacalcet		
		Sets (*n*)	Proportion (%)[a]	Relative proportion of adjustment [OR (95% CI)][b]
Calcium and phosphorus	Weekly	923	7.8	1.96 (1.35–2.84)
	Biweekly	20 830	5.3	1.26 (1.03–1.55)
	Monthly	3423	4.4	Reference
PTH	Monthly	6043	5.1	1.13 (0.95–1.35)
	Bimonthly	1751	6.2	1.29 (1.01–1.64)
	Trimonthly	10 405	5.1	Reference

[a]Proportion of sets in which cinacalcet was first prescribed.
[b]AORs and 95% CIs were estimated via generalized estimating equations to account for correlation between intra-individual repeated measurements with adjustment for covariates listed in Supplementary data, Table S3 (age, sex, vintage, primary diseases, comorbidities, use of MBD-related drugs, calcium concentration in dialysate, Kt/V, serum albumin, phosphorus, calcium and PTH).

Table 5. Association of frequency of monitoring of serum markers with adjustment of intravenous VDRA use

Serum marker	Monitoring frequency	Use of intravenous VDRA		
		Sets (*n*)	Proportion (%)[a]	Relative proportion of adjustment [OR (95% CI)][b]
Calcium and phosphorus	Weekly	1430	55.1	1.11 (0.87–1.42)
	Biweekly	28 303	56.1	1.14 (0.99–1.30)
	Monthly	4591	51.8	Reference
PTH	Monthly	8071	64.1	1.54 (1.35–1.76)
	Bimonthly	2480	43.5	1.02 (0.84–1.24)
	Trimonthly	14 148	49.4	Reference

[a]Proportion of sets in which intravenous VDRA was prescribed at the assessment visit.
[b]AORs and 95% CIs were estimated via generalized estimating equations to account for correlation between intra-individual repeated measurements with adjustment for covariates listed in Supplementary data, Table S3 (age, sex, vintage, primary diseases, comorbidities, use of MBD-related drugs, calcium concentration in dialysate, Kt/V, serum albumin, phosphorus, calcium and PTH).

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DISCUSSION

In this prospective cohort study of hemodialysis patients with SHPT, when serum marker levels exceeded the target range, weekly measurement of calcium/phosphorus was positively associated with achieving the guideline-specified calcium range but not the phosphorus range and monthly measurement of PTH was positively associated with achieving the guideline-specified PTH range. However, when serum marker levels were already within the guideline-specified range, increased frequency of measurements was not associated with in-range maintenance of marker levels for any of the three mineral markers assessed. Our results support the notion proposed by clinical practice guidelines that increased frequency of measurements is helpful when serum mineral marker levels exceed the target range, partially via therapy adjustments, but may not be helpful when levels are already within target ranges.

Regarding the appropriate frequency of serum PTH measurements, our present results are consistent with frequencies found in the guidelines of KDOQI 2003 and JSDT. When serum PTH levels exceed the target ranges, KDOQI 2003 and JSDT guidelines recommend more frequent measurements (than trimonthly) [4, 6]. In the present study, monthly—but not bimonthly—PTH measurement was associated with increased likelihood of achieving target ranges when serum values exceed the recommended range. When serum PTH values are already within target ranges, the JSDT guidelines recommend trimonthly measurement [6], which is consistent with our finding that measuring PTH more frequently than trimonthly was not associated with higher likelihood of maintaining target ranges. The relationship between increased frequency of PTH monitoring and greater likelihood of achieving the target range was also supported in part by our finding that increased frequency of measurement was associated with greater likelihood of future VDRA use.

Regarding the appropriate frequency of serum calcium/phosphorus measurements, our present results are partially consistent with frequencies found in the guidelines of JSDT. When the serum calcium/phosphorus levels exceed the target ranges, the JSDT guideline recommends more frequent

measurements (than biweekly or monthly) [6]. In the present study, weekly—but not biweekly—calcium/phosphorus measurement was associated with increased likelihood of achieving target ranges, though only for serum calcium. When serum calcium/phosphorus values are already within the target ranges, the JSDT guidelines recommend biweekly or monthly measurement [6], which is consistent with our finding that measuring calcium/phosphorus more frequently than monthly was not associated with a higher likelihood of maintaining target ranges for both serum calcium and phosphorus.

The relationship between increased frequency of calcium monitoring and greater likelihood of achieving the target range was also supported in part by our findings that increased frequency of calcium/phosphorus measurement was associated with greater likelihood of cinacalcet initiation. Given that cinacalcet has a calcium-lowering effect in addition to its PTH-lowering effect [16, 17], Japanese dialysis physicians will likely prescribe cinacalcet to SHPT patients on the basis of serum calcium values, as serum calcium is measured more frequently than serum PTH. This notion is further supported by our finding that likelihood of cinacalcet initiation dose dependently increased with increased frequency of serum calcium/phosphorus measurements, but not with increased frequency of serum PTH measurements. In contrast to findings for serum calcium, however, likelihood of achieving the target range for serum phosphorus was not associated with measurement frequency, even when serum phosphorus values exceeded the target range. Although the reason for this discrepancy is unclear, it may be associated with difficulties in serum phosphorus management due to excessive dietary phosphorus intake.

Several strengths to this study should be noted. First, we analyzed the association between monitoring frequency and achievement of target ranges using a large-scale cohort study, with adjustment for important potential confounders that vary over time, such as mineral metabolism markers and therapeutic regimens. Secondly, the unique measurement pattern for serum calcium/phosphorus levels (weekly/biweekly) observed in Japanese settings allowed us to analyze the effectiveness of intensive monitoring patterns on the likelihood of achieving target ranges or prescription change. In contrast, a previous before–after study in the USA was only able to examine the change in likelihood of achieving target ranges of PTH, calcium and phosphorus values after switching from trimonthly to monthly [10], which is less frequent than the 'intensive monitoring (weekly/biweekly)' pattern adopted in some Japanese facilities, likely because US facilities comply with the KDIGO guideline, whereas Japanese facilities comply with the JSDT guidelines (Table 1).

In addition to the aforementioned strengths, we also feel that the present findings may positively influence the work of dialysis physicians and experts, for several reasons. First, our results provide supporting evidence for experts to draft clinical practice guidelines regarding optimum monitoring frequency. Of note, however, our findings generally support the KDOQI 2003 guidelines versus the KDIGO 2009 guidelines. Secondly, our findings support the notion that dialysis physicians (particularly in Japan) should order routine measurements judiciously. In Japan's healthcare system, payments for routine measurements such as calcium, phosphorus and PTH evaluation are reimbursed to facilities up to once a month. As such, refraining from facility-wide 'intensive monitoring' (such as every 1–2 weeks) except for patients who receive active SHPT treatment such as VDRA pulse therapy or cinacalcet may aid in facility management. We hope that the next versions of the KDIGO and JSDT guidelines will harmonize and include statements on reasonable monitoring frequency from evidence-based and economic perspectives.

However, despite the strengths, we feel that several limitations to this study warrant mention. First, we were unable to address potential factors that might improve mineral metabolism, such as frequency of patient–doctor contact and diet instruction by a dietitian to restrict dietary phosphorus. Of note, we did adjust for treatment variables, including VDRA, cinacalcet and phosphate binder administration, which would be prescribed as a result of patient–doctor contact. We therefore believe that any influence of absence of information on patient–doctor contact on our analysis is negligible. Regarding diet instruction, educating patients on eating behavior has been reported to be effective in reducing serum phosphorus levels [18]. However, given that the effectiveness of diet instruction varies by approach [18], with no standardized approaches established, and is provided on an individual basis, we were unable to predict in which direction and to what extent the association between monitoring frequency and achievement/maintenance of targeted phosphorus levels might be confounded by diet instruction. Secondly, frequency of measurement was determined on the basis of facility-level policy, which may not be consistently applied to all patients within a facility. To compensate for this issue, we excluded facilities that reported measuring frequencies on an individual basis. Thirdly, precise methods for assays measuring iPTH or whole PTH were not available and thus were unable to be accounted for. As was noted in the DOPPS study [3], inability to control for differences in assays may lead to increased variability in levels of PTH, which may have biased results toward the null (i.e. toward non-significant associations). Indeed, sensitivity analyses restricted to facilities using iPTH assays yielded similar but slightly stronger associations than those from primary analyses without restriction. Fourth, precise methods for assays measuring serum albumin levels (e.g. bromocresol purple or bromocresol green) were not available [19]; thus we were unable to assess how much corrected calcium values were affected by serum albumin assays. Fifth, we were unable to examine associations between monitoring frequency with adjustment for phosphate binders because data on dosage were unavailable and were recorded as multinomial categories.

In conclusion, our results suggest that increasing frequency of measurements is helpful when serum marker levels exceed the target range, partially via adjustment in the therapeutic regimen. We found no evidence that frequent measurements are helpful when mineral levels are already within target ranges. Dialysis experts should take these results into account when generating the next version of clinical practice guidelines.

SUPPLEMENTARY DATA

Supplementary data are available online at http://ndt.oxfordjournals.org.

ACKNOWLEDGEMENTS

We would like to thank the MBD-5D study advisory investigators as follows: Masashi Suzuki (Shinrakuen Hospital), Yoshindo Kawaguchi (Shiomidai Hospital), Akira Saito (International University of Health and Welfare Atami Hospital), Yoshiki Nishizawa (Osaka City University Graduate School of Medicine), Yusuke Tsukamoto (Shuwa General Hospital), Satoshi Kurihara (Tsukinomori Clinic), Takashi Akiba (Tokyo Women's Medical University), Eriko Kinugasa (Showa University Northern Yokohama Hospital), Yuzo Watanabe (Kasugai Municipal Hospital), Yoshihiro Tominaga (Nagoya Daini Red Cross Hospital), Takashi Shigematsu (Wakayama Medical University), Masaaki Inaba (Osaka City University Graduate School of Medicine), Jun Minakuchi (Kawashima Hospital), Hideki Hirakata (Fukuoka Red Cross Hospital), Naoki Kimata (Tokyo Women's Medical University), Fumihiko Koiwa (Showa University Fujigaoka Hospital), Ryoichi Ando (Musashino Red Cross Hospital), Junichiro J. Kazama (Niigata University), Takatoshi Kakuta (Tokai University School of Medicine), Hirotaka Komaba (Tokai University School of Medicine), Daijo Inaguma (Nagoya Daini Red Cross Hospital), Eiji Ishimura (Osaka City University Graduate School of Medicine), Hideki Tahara (Osaka City University Graduate School of Medicine), Kazuhiko Tsuruya (Kyushu University) and Akira Fujimori (Konan Hospital).

FUNDING

The MBD-5D study is supported by research grants from Kyowa Hakko Kirin. We thank Noriko Nagata (iHope international) for her editorial assistance with this manuscript.

CONFLICT OF INTEREST STATEMENT

The MBD-5D study is supported by research grants from Kyowa Hakko Kirin (manufacturer of intravenous calcitriol, cinacalcet hydrochloride and sevelamer hydrochloride). Kyowa Hakko Kirin had no input on the design, analysis or interpretation of the data, nor on preparation, review or approval of the manuscript. T.A. has acted as a consultant for and received grants (research support) from Kyowa Hakko Kirin and is a member of the Speakers' Bureau of Kyowa Hakko Kirin. S.F. has acted as a scientific advisor for and received grants (research support) from Kyowa Hakko Kirin. M.F. has acted as a consultant for and received honoraria and received grants (research support) from Kyowa Hakko Kirin. The other authors have no conflicts of interest to disclose.

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APPENDIX

The following investigators also participated in this study: Nobuo Hashimoto (H•N•MEDIC), Mari Ishida (Kitasaito Hospital), Toshiyuki Date (Date Clinic), Kiyotaka Yabuki (Yabuki Hospital), Hideki Tanida (Tendo Onsen Yabuki Clinic), Fumitoshi Yamauchi (San-ai Hospital), Mikihiko Fujishima (Yahaba Clinic), Tomohito Matsunaga (Eijinkai Hospital), Jun Urae (Ishinomaki Clinic), Hiroshi Kawaguchi (Iwaki Urological Hospital), Ikuo Takahashi (Kisen Hospital),

Yoshiko Tanaka (Shinjuku-Koshin Clinic), Hideo Kobayashi (Suda Clinic), Maki Takahashi (Suda Naika Clinic), Tatsuya Nonaka (Seishokai Memorial Hospital), Hideto Emoto (Tokai Hospital), Kyosuke Nishio (Shinkoiwa Clinic), Atsushi Hayama (Moriyama Rehabilitation Hospital), Toshio Shinoda (Kawakita General Hospital Dialysis Center), Takashi Kono (Mihama Narita Clinic), Takahiro Mochizuki (Kameda Medical Center), Yasuo Kimura (Shin-Kashiwa Clinic), Noriyoshi Murotani (Chiba Social Insurance Hospital), Satoshi Yamaguchi (Asahi Hospital), Taichi Nakanishi (Kurihama Clinic), Kiyoshi Ozawa (Yokosuka Clinic), Takashi Nagaoka (Sagamihara Clinic), Takao Suga (Bousei Hiratsuka Clinic), Masakazu Suda (Suda Medical Clinic), Yoshikazu Goto (Saiyu Soka Hospital), Michio Kuwahara (Shuwa General Hospital Hemodialysis Clinic), Hiromi Shimoyama (Yuai Clinic), Kimihiko Matsuyama (Misato Kenwa Clinic), Kazue Ueki (Toho Hospital), Kyoko Ito (Heisei Hidaka Clinic), Katsuhiko Miyamoto (Seseragi Hospital), Takashi Ishizu (Tukuba Central Hospital), Shuichi Kikuchi (Ohba Renal Clinic), Masaki Kobayashi (Tokyo Medical University Ibaraki Medical Center), Mitsuyoshi Furuhashi (Maruyama Hospital), Masanori Wakabayashi (Bousei Dai-ichi Clinic), Kazuyoshi Nakamura (Fujidaiichi Clinic), Hirotake Kasuga (Kaikoukai Central Clinic), Itsuo Yokoyama (Nagoya Memorial Foundation Narumi Clinic), Chikao Yamazaki (Masuko Clinic SUBARU), Kijun Nagata (Sawada Hospital), Yasumasa Kawade (Suzuka Kidney Clinic), Toshiaki Kawanaka (Ishikiriseiki Hospital), Yoshihiro Tsujimoto (Inoue Hospital), Mikio Okamura (Ohno Memorial Hospital), Shigeki Okada (Okada Clinic), Senji Okuno (Kidney Center Shirasagi Clinic), Harumi Nagayama (Nagayama Hemodialysis Clinic), Shuji Okazaki (Nagayama Hospital), Yoshinori Tone (Fujii Clinic), Ibuki Yajima (Ibuki Clinic), Kouji Shibuya (Sumiyoshigawa Hospital), Kunihiko Yoshiya (Hara Genitourinary Hospital), Morihiro Kondou (Otowa Kinen Hospital), Satoru Yamazaki (Tojinkai Hospital), Ryoichi Miyazaki (Fujita Memorial Hospital), Katsuhiko Arimoto (Shigei Medical Research Hospital), Misaki Moriishi (Nakajima Tsuchiya Clinic), Takahito Nasu (Tokuyama Central Hospital), Seiichi Obayashi (Kinashi Obayashi Hospital), Yuzuru Sato (Sato Junkankika Naika), Takao Tanaka (Ohji Hospital), Hidetoshi Nakamura (Kokura Daiichi Hospital), Nobuhiko Koga (Shin-Koga Clinic), Harumichi Higashi (St Mary's Hospital), Kougi Yuu (Takahashi Naika Clinic), Asako Kitamura (Chikuho Social Insurance Hospital), Tomoji Matsumae (Murakami Memorial Hospital), Katsushige Abe (Jinikai Hospital), Masahiro Kawatomi (Kawatomi Internal Medicine Clinic), Motoko Tanaka (Akebono Clinic), Chisa Nogami (Kumamoto Urological Hospital), Etsuo Yoshidome (Ikeda Hospital), Shinyu Miyagi (Okinawa Daiichi Hospital), Satoshi Nakazato (Chibana Clinic), Yoshiki Shiohira (Tomishiro Central Hospital) and Kiyoyuki Tokuyama (Tokuyama Clinic).

Received: 16.10.2015; Editorial decision: 22.1.2016

ORIGINAL ARTICLE

Nephrol Dial Transplant (2017) 32: 541–547
doi: 10.1093/ndt/gfw037
Advance Access publication 6 April 2016

Lung ultrasound: a novel technique for detecting fluid overload in children on dialysis

Marco Allinovi[1,2], Moin Saleem[1,3], Paola Romagnani[2,4], Peiman Nazerian[5] and Wesley Hayes[1,3]

[1]Bristol Children's Renal Unit, Bristol Royal Hospital for Children, Bristol, UK, [2]Paediatric Nephrology Unit, Meyer Children's Hospital, Florence, Italy, [3]University of Bristol, Bristol, UK, [4]University of Florence, Florence, Italy and [5]Department of Emergency Medicine, Careggi University Hospital, Florence, Italy

Correspondence and offprint requests to: Wesley Hayes; E-mail: weshayes@doctors.org.uk

ABSTRACT

Background: Optimizing the target weight of infants and children on dialysis remains an important clinical challenge. The use of ultrasound to detect fluid overload in adult patients on dialysis is receiving growing attention. We hypothesized that fluid overload can be quantified in infants and children receiving dialysis using lung ultrasound.