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Interprovincial differences in the achievement of K/DOQI targets of mineral metabolism in Canada

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Abstract

Background. Abnormalities in mineral metabolism in chronic kidney disease are associated with increased morbidity and mortality. The Kidney Disease Outcomes Quality Initiative (K/DOQI) clinical practice guidelines were established in 2003 to address issues in the management of mineral and bone metabolism. The goal of this study was to compare (i) mineral metabolism control among Canadian haemodialysis (HD) patients with K/DOQI-defined targets and Dialysis Outcomes and Practice Patterns Study II (DOPPS II) data and (ii) the effect of different treatment strategies.

Methods. A cross-sectional study of 2215 HD patients was conducted. Phosphorus (P), calcium (Ca), intact parathyroid hormone (iPTH) and calcium-phosphate product (CaXP) were analysed. In addition, management was compared between provinces with more or less restricted access to the phosphate binder sevelamer.

Results. K/DOQI targets for P, Ca, iPTH and CaXP K/DOQI targets were met by 59.7%, 58.6%, 29.7% and 83.3%, respectively. A greater proportion of patients were within target compared with those in DOPPS II (2002–2004). Targets were more likely to be reached by patients residing in provinces with formularies allowing less restricted access to sevelamer: P: 61.8% vs 55.7% ($P = 0.01$); CaXP: 85.5% vs 79.1% ($P = 0.0006$). As expected, patients in provinces with more restrictive formularies were more often receiving doses of elemental calcium >1.5 g/day than those with more open listings (62.1% vs 14.0%, $P < 0.0001$) and were less likely to receive sevelamer (14.1% vs 42.4%, $P = 0.0001$).

Conclusion. Mineral metabolism parameters were more frequently within the target range amongst (i) patients in the current study compared with those in the DOPPS II era and (ii) patients in provinces with less restricted access to sevelamer.

Keywords: calcium-based phosphate binders; haemodialysis; mineral metabolism; sevelamer

Introduction

Abnormalities in phosphorus, calcium and parathyroid hormone (PTH) metabolism are common in patients with progressive chronic kidney disease (CKD) [1]. There is a body of evidence indicating that mineral metabolism disturbances are associated with increased morbidity and mortality in CKD patients [1–5]. The Kidney Disease: Improving Global Outcomes (KDIGO) group proposed the term 'chronic kidney disease—mineral and bone disorders (CKD-MBD)' to describe the manifestations of this clinical syndrome as a systemic disorder [6]. CKD-MBD is manifested by any one or a combination of the following: (i) abnormalities of calcium, phosphorus and PTH; (ii) abnormal vitamin D metabolism; (iii) changes in bone turnover, mineralization, volume, linear growth or strength; and (iv) calcification—vascular or other soft-tissue calcification [6].

In 2003, the National Kidney Foundation published the Kidney Disease Outcomes Quality Initiative (K/DOQI) clinical practice guidelines to address issues in the management of mineral and bone metabolism [7]. The K/DOQI clinical practice guidelines consist of evidence- and opinion-based recommendations that aim to provide an integrated clinical action plan for the management of these complex problems throughout the course of CKD [7]. These guidelines have emphasized the importance of control of serum phosphorus, calcium and PTH concentrations in maintenance dialysis patients.

This study describes mineral metabolism management in a cross-section of Canadian adult haemodialysis (HD) patients. In addition, the present study compares mineral metabolism data with the K/DOQI guidelines and to the Dialysis Outcomes and Practice Patterns Study II (DOPPS II: [2002–2004]) observational data [8–10] to identify where improvements need to be made. Lastly, interprovincial comparisons are made to identify differences in treat-

ment strategies and how they impact mineral metabolism management in adult HD patients.

Materials and methods

In an effort to promote the improvement of mineral metabolism management in Canada, the software tool, PhotoGraph^{TM}, was created by Genzyme France Inc. in 2005. Subsequently, Genzyme introduced it in Canada to allow dialysis centres to track bone and mineral metabolism parameters and to assess how effectively patients on dialysis are managed according to the K/DOQI guidelines. Fields in the database include limited demographic information, mineral metabolism parameters and prescribed medications and dosage. The use of PhotoGraph^{TM} began on a clinic-by-clinic project basis. Once a large number of clinics were using this tool, a national study was undertaken to pool the PhotoGraph^{TM} data in order to capture a picture of the management of mineral metabolism within the HD patient population across the country. The software was not used to facilitate patient level prescribing.

A cross-sectional study was conducted. Nineteen HD centres which used the PhotoGraph^{TM} programme were recruited as a convenience sample on a voluntary basis from January 2006 to April 2007. Letters were sent to all centres via e-mail requesting a copy of their PhotoGraph^{TM} datasets stripped of data that might identify individual patients for the purpose of this study. Each centre applied to their local Research Ethics Board and complied with current patient confidentiality requirements, including the exclusive use of non-identified aggregate laboratory data. Data were obtained from British Columbia, Alberta, Ontario, Quebec and New Brunswick. Once all of the datasets were acquired, Inovex Inc., a third-party software company, assessed the datasets for completeness. A sample of 2215 adult patients was identified for inclusion.

The mineral metabolism parameters of interest included serum phosphorus, corrected calcium, intact PTH (iPTH) and calcium-phosphate product (CaXP). In addition, medication data were collected and were analysed by the type of phosphate binder and dosing and use of vitamin D analogues and/or calcimimetics. Corrected calcium was calculated as total calcium (mmol/L) + 0.02[40 − serum albumin (g/L)]. No adjustment for dialysate calcium was made. All iPTH values were reported by centres in picomoles per litre, and centres used their own iPTH test kit without standardization. The pooled data were assessed using the PhotoGraph^{TM} software to compare bone and mineral metabolism parameters with targets set by the K/DOQI guidelines to determine the percentage of patients meeting the guidelines. K/DOQI was chosen as the reference guideline because in the era under study (prior to KDIGO), these were dominant in Canada. SAS 9.1 (SAS Institute, Cary, NC) statistical software was used for all analyses. Furthermore, results were compared with published international results from the DOPPS II (2002–2004) [8–10].

Public drug funding for the phosphate binder sevelamer is more or less restricted in all Canadian provinces (Table 1). Data obtained from provinces with 'less restricted' access to the phosphate binder sevelamer were analysed separately from those obtained from provinces with 'more restricted' access to sevelamer to explore the potential differences in mineral metabolism management. The reimbursement criteria for sevelamer were examined for the five relevant provinces. Whether a province was deemed to have 'less restricted' or 'more restricted' access was determined by the percentage of patients who were prescribed sevelamer. Quebec and New Brunswick were among the 'high-level' access provinces as 42.4% of patients were prescribed sevelamer. In contrast, Ontario, Alberta and British Columbia were deemed to have a 'low level' of drug access as only 14.1% of patients were prescribed sevelamer.

PhotoGraph^{TM} includes only a limited list of baseline patient demographic features (i.e. age, gender and vintage on dialysis). Patient demographics at baseline were compared between patients in provinces with 'more restricted' vs 'less restricted' access to sevelamer for any differences. For this univariate analysis, a Pearson chi-square (χ^2) test was used for discrete variables, and a non-parametric test was used for continuous variables. A P-value of <0.05 was considered to be statistically significant. For vintage, 283 patients had missing values, and so vintage was not included as a factor in the adjusted analysis. All analyses comparing more restricted and less restricted provinces was performed both unadjusted and adjusted for baseline differences in age and gender. Adjusted analysis is presented in the tables but not presented in the figures for clarity since the adjusted results were similar to the unadjusted results.

Results

Table 1 provides information about the criteria for non-calcium-based binder restrictions in the involved provinces (for details, visit the URLs noted as references). Nineteen HD clinics in five provinces (Alberta, British Columbia, New Brunswick, Ontario and Quebec) participated in this study. The study population (n = 2215) was 57.3% male and 42.7% female. The average age was 67.3 ± 14.4 years, with ages of patients ranging from 20 to 95, and the mean time on dialysis amongst the patients without missing data was 3.44 ± 3.71 years (Table 2).

More than half of the patients (59.7%) had serum phosphorus concentrations which fell within the K/DOQI target of 1.13–1.78 mmol/L (Figure 1a), with an average concentration of 1.55 ± 0.46 mmol/L. Nearly one-quarter of patients (24.4%) were hyperphosphataemic (i.e. serum phosphorus levels >1.78 mmol/L; Figure 1a). The K/DOQI corrected serum calcium target range is 2.10–2.37 mmol/L, which was met by 58.6% of patients (Figure 1b). The average corrected serum calcium level was 2.28 ± 0.19 mmol/L.

Table 1. Reimbursement status of sevelamer, by province

Province	Public formulary coverage	Criteria	
		'Less restricted' access Treatment of severe renal failure in which calcium therapy is contraindicated, not tolerated, or provides suboptimal control.	'More restricted' access Treatment of dialysis patients with persistent hypercalcaemia and hyperphosphataemia.
AB	No		
BC [38,39]	Yes		√
NB [40]	Yes	√	
ON [41]	Yes		√
QC [42]	Yes	√	

AB, Alberta; BC, British Columbia; NB, New Brunswick; ON, Ontario; QC, Quebec.

Table 2. Patient characteristics

Variables	Overall	'More restricted' access (AB, BC, ON)	'Less restricted' access (NB, QC)	P-value
Age (years)				
n	2215	751	1463	
Mean ± SD	67.3 ± 14.4	66.4 ± 14.8	67.7 ± 14.2	0.04
Gender				
n	2209	750	1458	
Male (*n*, %)	1113 (57.3%)	428 (57.1%)	836 (57.3%)	0.90
Females (*n*, %)	1095 (42.7%)	322 (42.9%)	622 (42.7%)	
Time on HD (years)				
n	1926	468	1458	
Mean ± SD	3.4 ± 3.7	2.7 ± 2.4	3.7 ± 4.0	<0.0001

AB, Alberta; BC, British Columbia; HD, haemodialysis; *n*, number of patients; NB, New Brunswick; ON, Ontario; QC, Quebec; SD, standard deviation.

Hypercalcaemia (i.e. corrected serum calcium concentration >2.54 mmol/L) was noted in 6.6% of patients (Figure 1b). Unlike the previous two parameters, the majority of patients did not attain K/DOQI serum iPTH targets (Figure 1c). Only 29.7% of patients were with a serum target iPTH level between 16.5 and 33.0 pmol/L, with a mean concentration of 41.04 ± 43.71 pmol/L, while 43.1% of patients had iPTH levels >33.1 pmol/L (Figure 1c). The majority of patients were below target serum CaXP levels (83.3%; Figure 1d), with an average concentration of 3.52 ± 1.07 $mmol^2/L^2$. Overall, 11.7% of patients were within the K/DOQI targets for all four mineral metabolism parameters (data not shown).

The percentage of patients who met K/DOQI targets in the current study were compared with the randomly selected patients in the DOPPS II study as a pre-specified end point [10]. More patients were within K/DOQI targets for phosphorus, calcium, iPTH and CaXP control in the current study than in the DOPPS II study (Figure 2) [10]. Since more concurrent data from DOPPS III (2006) are now available, we include this comparison in Figure 2 as well [11]. There is improvement in DOPPS centres from DOPPS II to DOPPS III overall, and the participating centres were within target ranges more frequently than the 2006 DOPPS sample (Figure 2).

Across all 19 centres, 56.1% of patients were prescribed a calcium-based binder (CBB) exclusively and 9.3% sevelamer monotherapy (Table 3). Less than 1% of patients were prescribed aluminium hydroxide as monotherapy; no patients received lanthanum, and 9.8% of patients re-

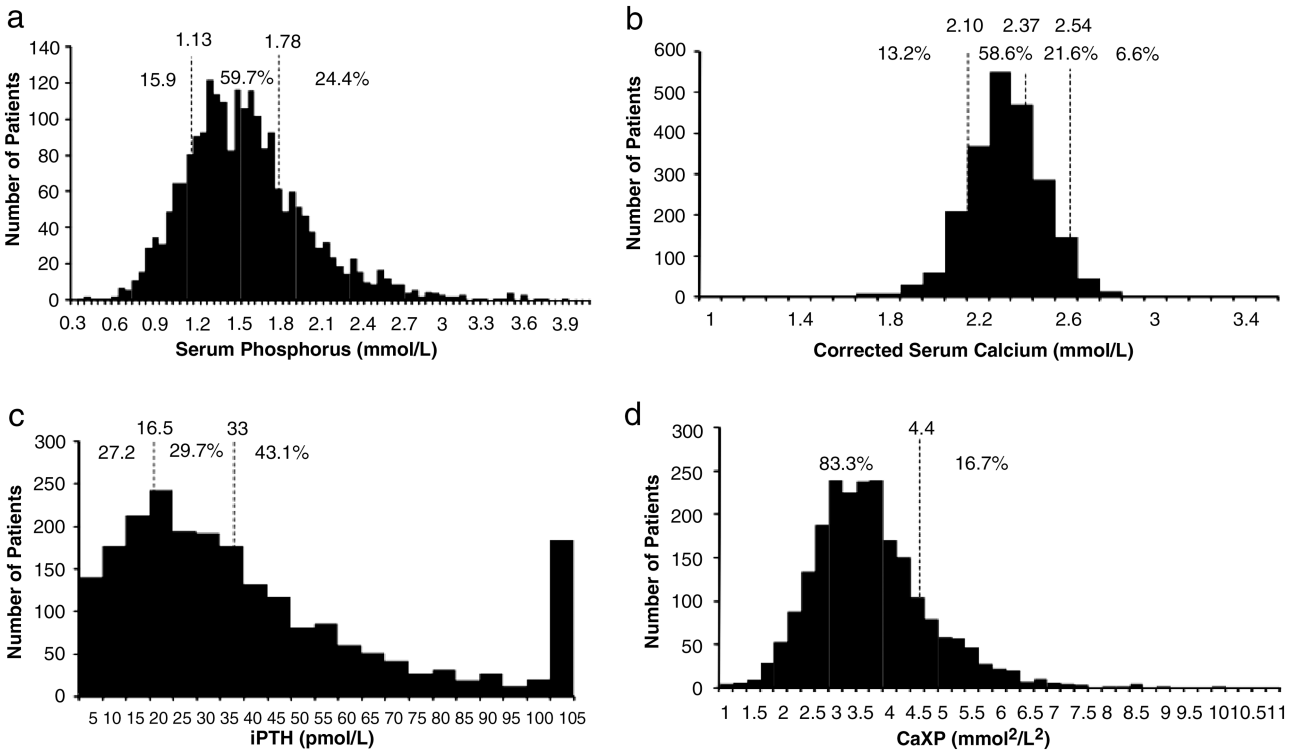

Fig. 1. Distribution of serum concentrations of: (**a**) phosphorus, (**b**) corrected calcium, (**c**) iPTH and (**d**) CaXP.

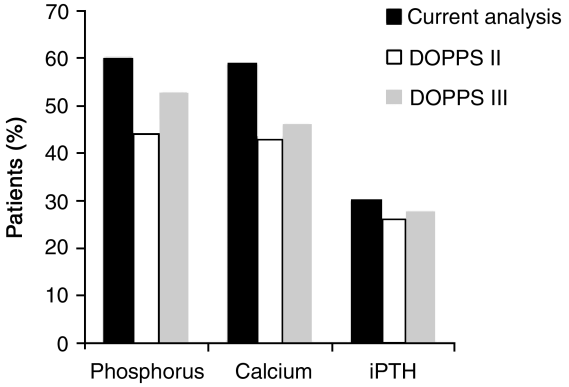

Fig. 2. Percentage of patients who achieved K/DOQI mineral metabolism targets compared with those in the DOPPS II and DOPPS III (2006) studies [10,11].

ceived no phosphate binder (Table 3). Less than 3% of patients received cinacalcet. The average prescribed doses of elemental calcium (from CBBs), sevelamer and aluminium hydroxide were 1.97 ± 1.92 g/day, 5.87 ± 3.51 tablets/day and 2.82 ± 1.00 units/day, respectively (Table 4).

Data were compared for patients in provinces with 'less restricted' vs 'more restricted' access to sevelamer. Patients were older (67.7 ± 14.2 vs 65.9 ± 15.0 years, P = 0.04) and had been on HD for a greater number of years (3.68 ± 4.02 vs 2.71 ± 2.35 years, P < 0.0001) in provinces with 'less restricted' access compared with those in 'more restricted' access provinces (Table 2). A greater percentage of patients were within K/DOQI-defined mineral metabolism targets for phosphorus and CaXP in provinces with 'less restricted' access than 'high restricted' access (Figure 3). While the percentages of patients who had achieved K/DOQI-defined targets for corrected serum calcium or iPTH did not differ statistically (data not shown), more patients in provinces with 'less restricted' access to sevelamer had iPTH levels >33.0 pmol/L (45.0% vs 29.3%, P = 0.006), while concentrations <16.5 pmol/L were more commonly reported in the 'low-level' access group (33.4% v s. 24.0%, P < 0.0001).

Prescribing practices differed significantly between provinces with 'more restricted' vs 'less restricted' access. More patients in 'more restricted' access provinces were prescribed CBBs as monotherapy (77.6% vs 45.0%, P < 0.0001; Table 3). Not surprisingly, sevelamer monotherapy was greater in provinces with greater access to the drug compared in those where there was less access (11.0% vs 6.0%, P = 0.0001; Table 3). Moreover, a greater proportion of patients in the 'less restricted' access group received a combination regimen of CBBs and sevelamer than in the 'more restricted' access group (30.2% vs 8.3%, P < 0.0001; Table 3). While more patients were not prescribed any phosphate binder in provinces with less restricted access to sevelamer, this difference was small (10.9% vs 7.9%, P = 0.04; Table 3). A greater percentage of patients were prescribed vitamin D in provinces with less restricted access to sevelamer than in those with more restricted access (59.2% vs 29.6%, P <0.0001; Table 3).

The mean dose of elemental calcium was lower in provinces with less restricted access to sevelamer (1.45 ± 0.90 vs 3.04 ± 2.83 g/day, P < 0.0001, Table 3), and fewer patients exceeded the 1.5-g/day limit suggested by the K/DOQI guidelines (62.1% vs 14.0%, P < 0.0001; Table 4) [7]. Interestingly, patients in provinces with 'more restricted' access to sevelamer received higher doses than those in provinces with less restricted access (7.46 ± 3.92 vs 5.60 ± 3.35 tablets/day, P < 0.0001; Table 3). No differences in the dosing of aluminium hydroxide were observed.

Discussion

In 2006, 16 047 Canadians received HD [12]. While the Canadian Institute of Health Information's (CIHI) and Canadian Organ Replacement Registry's (CORR) annual report provides certain insights into the care of Canadian dialysis patients, they do not collect, track or report clinical mineral metabolism quality indicators [13]. Given that there are 92 HD facilities in Canada [12], our study represents 21% of Canadian facilities and 13.8% of Canadian HD patients. Until this study, the only national mineral metabolism data

Table 3. Distribution of Phosphate Binder Use

Binder therapy	Overall *n* = 2215	'More restricted' access (AB, BC, ON) *n* = 751	'Less restricted' access (NB, QC) *n* = 1464	P-value, Unadjusted	P-value, Adjusted
No binder	9.8%	7.9%	10.9%	0.02	0.04
Monotherapy					
CBB	56.1%	77.6%	45.0%	<0.0001	<0.0001
Sevelamer	9.3%	6.0%	11.0%	0.0001	0.0001
$Al(OH)_3$	0.41%	0.13%	0.55%	0.29	0.18
≥2 binders	24.4%	8.4%	32.6%	<0.0001	<0.0001
CBB + Sevelamer + $Al(OH)_3$	0.68%	0	1.0%	–	–
CBB + Sevelamer	22.1%	8.3%	29.2%	<0.0001	<0.0001
CBB + $Al(OH)_3$	0.86%	0.1%	1.2%	–	–
Sevelamer + $Al(OH)_3$	0.72%	0	1.1%	–	–
Vitamin D	49.2%	29.6%	59.2%	<0.0001	<0.0001

AB, Alberta; $Al(OH)_3$, aluminium hydroxide; BC, British Columbia; CBB, calcium-based phosphate binder; *n*, number of patients; NB, New Brunswick; ON, Ontario; QC, Quebec.

Table 4. Average daily doses of phosphate binders

Binder therapy	Overall	More restricted	Less restricted
Elemental Calcium (g/day)			
n	1643	530	1113
Mean ± SD	1.97 ± 1.92	3.04 ± 2.83	1.45 ± 0.90
Min–max	0.13–30.00	0.25–30.00	0.13–11.25
>1.5 g/day	29.5%	62.1%	14.0%
Elemental Calcium (number of 1250 mg tablets/day)			
n	1643	530	1113
Mean ± SD	3.94 ± 3.84	6.08 ± 5.66	2.90 ± 1.80
Min–max	0.6–60.00	0.5–60.00	0.26–22.50
Sevelamer (number of 800 mg tablets/day)			
n	725	106	619
Mean ± SD	5.87 ± 3.51	7.46 ± 3.98	5.60 ± 3.35
Range	1.00–20.00	1.00–20.00	1.00–18.00
Sevelamer (g/day)			
n	725	106	619
Mean ± SD	4.70 ± 2.80	5.97 ± 3.18	4.48 ± 2.687
Range	4.70–16.00	4.70–16.00	4.70–14.40
$Al(OH)_3$ (number of 600 mg tablets/day)			
n	53	2	51
Mean ± SD	2.82 ± 1.00	3.00	2.82 ± 1.02
Min–max	1.00–6.00		1.00–6.00
$Al(OH)_3$ (mg/day)			
n	53	2	51
Mean ± SD	1692 ± 600	1800	1692 ± 612
Min–max	600–3600.00		600–3600.00

AB, Alberta; $Al(OH)_3$, aluminium hydroxide; BC, British Columbia; Min–max, minimum–maximum; *n*, number of patients; NB, New Brunswick; ON, Ontario; QC, Quebec; SD, standard deviation.

came from the DOPPS II and III studies. DOPPS Canada includes a random sample of 20 HD facilities but studies in detail only a randomly selected subset of incident and prevalent patients in each facility. For example, DOPPS II included 601 patients from Canada [8]. Therefore, this larger study, while not a random sample, demonstrates an important analysis of the management of mineral metabolism among HD patients in a recent Canadian cohort.

The majority of patients were within the K/DOQI-defined targets for serum phosphorus, corrected calcium and CaXP. Based on the K/DOQI guidelines, Canadian centres in 2006–2007 have shown improvement since the 2002–2004 DOPPS II data across all four mineral metabolism parameters. This observation is consistent with international data recently published from the three phases of DOPPS up to 2007 [7,9,10]. These international trends may be due, in part, to the implementation of the K/DOQI clinical practice guidelines and/or to better internal quality improvement practices.

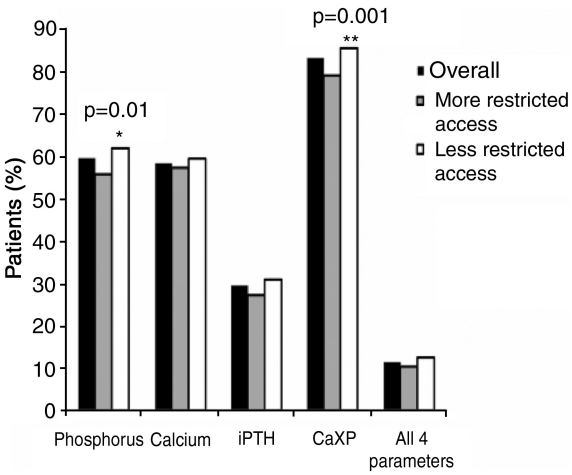

Fig. 3. Percentage of patients who achieved K/DOQI mineral metabolism targets in provinces with 'more restricted' vs 'less restricted' access to sevelamer.

Well after the completion of our data collection, an international CKD-MBD guideline was published in 2009 [6]. The language of that document does not allow for precise definitions of targets for calcium, phosphate and iPTH, and so comparisons with KDIGO are problematic. In addition, our centres were not acting to achieve the stricter recommendations for phosphate in 2006. However, if one accepts that the assumed targets within KDIGO are normal calcium (2.1–2.6 mmol/L), normal phosphate (0.85–1.45 mmol/L) and iPTH two to nine times the upper limit of normal (14.3 – 64.4 pmol/L), then overall, the study centre patients were within 'target' ranges 83.7%, 42.8% and 61.5% for calcium, phosphate and iPTH, respectively.

We note that two recent publications from France describe results using the PhotoGraph^{TM} software and with comparisons with K/DOQI targets [14,15]. In >9000 patients, improvement in mineral metabolism parameters from 2005 to 2008 was documented. Although our cross section was obtained from 2006 to 2007, in comparison, our Canadian patients were within phosphate target range more commonly and had similar calcium and iPTH outcomes [15].

This study assessed the effect of differences in prescription patterns on mineral metabolism in HD patients. While more patients in the 'less restricted' access group met the

targets for phosphorus and CaXP, compared with those in the 'more restricted' access group, the percentage of patients who achieved the K/DOQI-defined target for corrected serum calcium and iPTH levels were not different between groups. However, more patients in provinces with freer access to sevelamer had elevated iPTH concentrations (i.e. >33.0 pmol/L) than in provinces with more restricted access, while more patients in provinces with restricted access had iPTH levels <16.5 pmol/L. A previous study showed that iPTH concentrations were greater after HD patients were switched from CBBs to sevelamer [16]. It is more difficult to administer vitamin D analogues to patients on CBBs, in particular to patients with elevated serum calcium concentrations. Sevelamer treatment permits increased use of vitamin D agents, which has been associated with increased survival rate in HD patients [17]. We have demonstrated that more patients who resided in provinces with less restricted access to sevelamer were prescribed vitamin D analogues than those in the 'more restricted' access group (59.2% vs 29.6%, $P < 0.0001$).

Opinions regarding the efficacy and cost effectiveness of non-CBBs (i.e. sevelamer, lanthanum) are polarized within the Nephrology community [18–24]. CBBs have historically been the binder of choice since they were assumed to be safe, contain a natural constituent of body chemistry and are inexpensive. However, *in vitro* studies and observational data suggest that calcium load (i.e. from CBBs) may contribute to vascular calcification and subsequent cardiovascular events [25–27]. Despite the widespread use of CBBs, there has been no rigorous assessment that assures that long-term calcium administration is safe [22]. In the largest head-to-head trial performed to date (DCOR, Dialysis Clinical Outcomes Revisited), sevelamer did not show a significant survival benefit over calcium-based binders [28]. However, two very recent meta-analyses of DCOR and other smaller trials show consistent trends in favour of sevelamer [29,30]. Given this controversy and the lack of definitive data, the new 2009 international KDIGO CKD-MBD guidelines take a pragmatic approach. KDIGO does not make a general statement about limiting calcium intake in all dialysis patients as K/DOQI did but does recommend restricting calcium intake in patients with hypercalcaemia and suggests limiting calcium in patients with arterial calcification, adynamic bone disease and/or low iPTH [31].

Of interest, and in contrast to our results, previous direct comparisons of sevelamer with CBBs do not show that sevelamer is more efficacious in achieving guideline targets [32–34]. It is also important to note that the concurrent use of alternative non-CBBs and calcimimetics, (i.e. lanthanum and cinacalcet), was very low and could not be invoked to explain these results. Indeed, both of these drugs are either more restricted than sevelamer in all Canadian provinces or unavailable on public formularies. Perhaps, compliance or other issues in a real world study such as ours are part of the explanation for better control of mineral metabolism parameters with sevelamer. Validation of this result with further investigation is now important, as well as exploration of mechanisms of better control.

The provision of healthcare in Canada is a provincial responsibility; thus, the delivery of healthcare services varies between the provinces. Likewise, Canada does not have a national prescription drug programme, and policy and drug reimbursement differ by province [20,35]. Access to publicly funded drugs is generally restricted to patients over age 65. Each province has its own drug evaluation process based on efficacy, safety and cost effectiveness to determine whether a medication is included in its provincial formulary and eligible for reimbursement from public funding sources [36]. Therefore, public access to the same prescription medications differs widely across the provinces, and there is considerable variation of annual expenditures by Canadians with identical prescription burdens [37].

Sevelamer is a restricted drug on public formularies in all Canadian provinces except Alberta, where it is not listed at all. Nonetheless, the restrictions differ, being more liberal in some provinces than in others. Both lanthanum and cinacalcet are more restricted than sevelamer in all provinces. This study shows that differences in drug access between Canadian provinces are associated with differences in clinical management of mineral metabolism. The policy set by the Canadian Society of Nephrology states that interprovincial differences in drug access should be eliminated.

This study has several limitations. First, this study used a convenience sample, and participating facilities may not have entered all patients, which could introduce bias. However, the demographics of the current study resemble those within the CORR report of the Canadian HD population [13], and the study includes the largest number of Canadian HD patients to date. Confidence in these data is further suggested by the similarity of these results to Canadian data published in DOPPS II and III [9,10]. A second limitation is that the facilities were recruited over 18 months, which may introduce bias. In addition, this study did not follow patients over time. Rather, mineral metabolism parameters were gathered for a patient on a given day, and progression of disease was not assessed. While medication data (i.e. type of binder, dose) were entered into the PhotoGraph™ programme, the date of initiation or duration of its use was not. Furthermore, only a limited amount of demographic data was collected, and information which pertained to dialysis vintage was missing for 283 patients at one centre in Ontario. Therefore, we were unable to fully adjust for baseline differences in demographics and comorbid conditions in our comparison of patients within provinces with more or less restricted access to sevelamer. Finally, all cross-sectional studies have potential for missing data and other sources of bias and consequently report associations only that can simply generate a hypothesis for further evaluation.

In conclusion, this study shows that, based on K/DOQI guidelines, Canadian centres have shown improvement over time relative to DOPPS II across all four mineral metabolism parameters. Moreover, better control of mineral metabolism was associated with patients who resided in provinces with less restricted access to sevelamer. Further studies are needed to determine whether this improvement was due to the impact of K/DOQI guidelines, the increased use and availability of sevelamer, both or whether other factors we did not consider played a role. Of even more fundamental importance are studies to show whether these different treatment approaches lead to different hard outcomes and associated costs.

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(See related article by Pelletier *et al*. Mineral and bone metabolism in dialysis: towards unified patient care? *Nephrol Dial Transplant* 2011; 26: 7–9.)

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Disappearance of glomerular IgA deposits in childhood IgA nephropathy showing diffuse mesangial proliferation after 2 years of combination/prednisolone therapy

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Abstract

Background. The prognosis of children with severe IgA nephropathy showing diffuse mesangial proliferation is poor. However, the prognosis can be improved by combination therapy (prednisolone + azathioprine or mizoribine + warfarin + dipyridamole) or prednisolone alone over a 2-year period, and disappearance of glomerular IgA deposits is often observed. Details of the incidence and clinicopathological significance of glomerular IgA disappearance remain unclear.

Methods. To investigate this phenomenon, we retrospectively screened and analysed 124 consecutive children (age ≤18 years at first biopsy) with newly diagnosed severe IgA nephropathy showing diffuse mesangial proliferation, who received combination therapy or prednisolone alone for 2 years and underwent repeat biopsies.

Results. Among these patients, 90 received combination therapy, and 34 received prednisolone alone. After 2 years of treatment, 27 of the patients (21.8%) showed disappearance of glomerular IgA. Logistic analysis showed that IgA disappearance was associated with less severe urinary protein excretion at the end of treatment. Kaplan–Meier analysis of the long-term course revealed a significant difference in proteinuria-free survival after the 2-year treatment period between the patients with IgA disappearance and those without (P = 0.008; log-rank test). The Cox proportional hazards model showed that disappearance of glomerular IgA after the treatment was a factor significantly associated with proteinuria-free survival in both univariate and multivariate analyses.

Conclusions. The present results suggest that disappearance of IgA after 2 years of treatment indicates milder disease severity, even in patients with diffuse mesangial proliferation, and is a prognostic factor related to proteinuria-free survival.

Keywords: children; deposit; immunosuppressant; proteinuria; steroid