Chronic Kidney Disease-Mineral and Bone Disorder in Asia

Masafumi Fukagawa^a Hirotaka Komaba^{a, b}

^aDivision of Nephrology, Endocrinology and Metabolism, Tokai University School of Medicine, and ^bThe Institute of Medical Sciences, Tokai University, Isehara, Japan

Keywords

Cardiovascular events · Chronic kidney disease-mineral and bone disorder · Guideline · Parathyroid · Phosphorus calcium · Survival

Abstract

Background: Chronic kidney disease-mineral and bone disorder (CKD-MBD) is one of the most common complications in patients with CKD. As CKD-MBD is a systemic syndrome, prevention and management should be aimed at achieving better survival and less risk of cardiovascular events and fractures. **Summary:** Although target ranges for serum markers of mineral metabolism have been proposed in several global or local guidelines, these were mostly based on data from non-Asian patients. Additionally, there remain differences in medical and social systems as well as in economic status, even among Asian countries and areas. **Key Message:** Asian CKD patient data needs to be analyzed, published, and shared to establish optimal local strategies for CKD-MBD management.

© 2017 S. Karger AG, Basel

Introduction: Chronic Kidney Disease-Mineral and Bone Disorder as a Systemic Syndrome

The kidney is one of the most important organs in the regulation of mineral metabolism [1]. It is not only the target organ of several regulating hormones, such as parathyroid hormone (PTH) and fibroblast growth factor 23 (FGF23), but also the main organ that activates vitamin D [2]. Thus, in chronic kidney disease (CKD), various abnormalities develop, with secondary hyperparathyroidism (SHPT) being the most common [3]. Such abnormal mineral metabolism in CKD used to be called “renal osteodystrophy” as a disease limited to the bone, but it has recently been renamed to “chronic kidney disease-mineral and bone disorder” (CKD-MBD) as a systemic syndrome [4]. CKD-MBD consists of 3 abnormality categories, including laboratory abnormalities, bone abnormalities, and vascular calcification. For CKD-MBD management, clinicians should correct or prevent these abnormalities in order to decrease the risk of clinical outcomes, including cardiovascular disease, bone fractures, and mortality. Accordingly, the target ranges for serum parameters have recently been determined based on survival risk [5, 6].

It has long been believed that vascular calcification caused by abnormal mineral metabolism is mainly responsible for the elevated cardiovascular risk in CKD [7]; however, several direct or indirect mechanisms in the pathogenesis of cardiovascular disease have recently been revealed [8]. FGF23 is a newly identified phosphaturic hormone that is secreted from osteocytes in response to phosphorus load [9, 10]. In addition to the leading roles in the development of SHPT in CKD [11, 12], it has been demonstrated that this molecule could serve as a marker for mortality and cardiovascular events, especially those associated with heart failure in CKD patients either not yet on or on renal replacement therapy [13, 14]. By elucidating the interactions between FGF23 and multiple organ systems [15], CKD-MBD has been further expanded to include left ventricular hypertrophy [16], hypertension [17], immune dysfunction, inflammation, and iron-deficiency anemia [18–20].

Rationale for CKD-MBD Management

For CKD-MBD diagnosis and management, several clinical guidelines, either global or local, have been published [6, 21, 22] or are soon to be revised further [23]. In these guidelines, the target ranges for serum parameters such as serum phosphorus, calcium, and PTH levels are specified, which are mainly but not completely based on the risk of cardiovascular events and death. Supporting the validity of these targets, more frequent achievement of the target ranges has been shown to be associated with better survival [24]; however, it should be taken into consideration that most of these data were based on observational and not interventional studies.

Another major issue that should be considered is the local implementation of global guidelines. Although many Asian countries adopt such global guidelines, it is sometimes difficult to apply global guidelines to local patients. This is partly due to differences in medical systems and economical status, which result in differences in access to therapeutic modalities. Additionally, the evidence adopted by global guidelines is mainly based on data from non-Asian populations, especially Caucasian patients. This is potentially a serious problem, as it is known that ethnic differences exist in skeletal resistance to PTH, which could influence the optimal target ranges.

Thus, establishment of locally optimal management strategies for CKD-MBD specific to Asian CKD patients is undoubtedly needed. As an initial step to this goal, we

would like to briefly summarize the characteristics and current status of CKD-MBD in various countries and regions in Asia, as well as their original clinical practice guidelines that are based on their own registries and databases, starting with Japan.

Clinical Practice Pattern and Guideline for CKD-MBD in Japan

Japan is the only non-Western country originally included in the Dialysis Outcomes and Practice Patterns Study (DOPPS). Several analyses of this study revealed much better survival of Japanese hemodialysis patients than other DOPPS countries [25], which could be attributed to unique practice patterns, such as the routine use of arteriovenous fistula and high-standard water purity. In this context, how does their CKD-MBD management contribute to better survival?

By analyzing the registry data for 3-year survival [5], the Japanese Society for Dialysis Therapy (JSDT) released their first guideline in 2008 [26], and by confirming the validity of the suggested target ranges [27] and including the optimal use of cinacalcet hydrochloride [28], a revised version was published in English in 2013 [22]. The target ranges of serum phosphate, calcium, and PTH are shown in Table 1 along with those by other guidelines. The target ranges of serum phosphorus and calcium are comparable with those in other guidelines considering the timing of routine blood sampling [29]; however, a much lower target range has been suggested for PTH. This was not merely because this range was associated with lower mortality but also because the control of serum phosphorus and calcium levels became easier when PTH levels were maintained within this low range of PTH [27]. Furthermore, the dialysis vintage of the Japanese dialysis patients is much longer, indicating that persistently high PTH levels should be avoided to prevent the development of nodular hyperplasia, a more progressive type of parathyroid hyperplasia that is often refractory to medical therapies [3]. The JSDT guideline also recommends considering indications for parathyroid intervention, such as parathyroidectomy and percutaneous ethanol injection therapy, in patients with PTH levels persistently higher than 500 pg/mL. As a result of such a low target range, Japan is the only DOPPS country where the median PTH level has been decreasing [30], even after the release of the Kidney Disease Improving Global Outcomes (KDIGO) guideline, which suggests a higher and more liberal target range for PTH.

Table 1. Different target ranges for dialysis patients

Guideline	Phosphorus	Calcium (corrected)	Intact PTH
KDOQI	3.5–5.5 mg/dL	8.4–9.5 mg/dL	150–300 pg/mL
KDIGO	Normal range	Normal range	2–9 times the upper limit
JSDT*	3.5–6.0 mg/dL	8.4–10.0 mg/dL	60–240 pg/mL

PTH, parathyroid hormone; KDOQI, Kidney Disease Outcomes Quality Initiative; KDIGO, Kidney Disease Improving Global Outcomes; JSDT, Japanese Society for Dialysis Therapy. * 2013 version.

Does a lower PTH level really contribute to better survival in Japanese dialysis patients? The JSDT guideline recommends controlling phosphate and calcium levels first and only then controlling PTH levels. This is because the association of PTH levels with mortality is weaker than that of serum phosphorus and calcium [27], which was also confirmed in another cohort of SHPT patients [31]. Furthermore, new roles for high PTH levels in the development of cachexia, sarcopenia [32], and hyperuricemia [33] have recently been reported in addition to the classic concept of PTH as a uremic toxin [34]. In clinical practice, we have recently shown by propensity-matched analyses of JSDT registry data that the history of surgical parathyroidectomy is associated with better survival and lower cardiovascular risk [35]. It has been shown that cinacalcet treatment could suppress PTH secretion, even in patients with nodular hyperplasia [36]. Importantly, PTH control by the use of cinacalcet was associated with a lower mortality rate in Japanese dialysis patients with moderate-to-severe SHPT [37]. Such beneficial effects may in part be explained by decreased FGF23 levels by this drug [38], as also suggested in the EVOLVE study [39, 40].

In Japan, physicians usually visit patients at every dialysis session and often discuss management strategies with a team consisting of nurses, clinical engineers, dietitians, pharmacists, and social workers. Furthermore, routine laboratory tests for Japanese dialysis patients still remain more frequent than those recommended by the KDIGO, even after the bundling of dialysis fees. We analyzed whether such frequent tests were really beneficial and found that among those who had serum parameters above the upper limit of the ranges, more frequent tests were associated with better achievement of the target ranges [41].

In addition to such an intensive care, new phosphate binders and calcimimetics, which have recently become available in Japan with minimal lag time from that in the

US and EU [42–44], have substantially contributed to better management. Several cohort studies have reported the associations of new drug use and better management and survival [31, 37, 45].

The Landscape of CKD-MBD in Asia

According to national and local registries in Asia, there are extreme variations in renal replacement therapy and management strategies of CKD-MBD among countries and specific areas in Asia (Table 2). There are differences in the mode, doses, and vintage of renal replacement therapy, which can certainly affect the risk of CKD-MBD. Thus, as a premise for better CKD-MBD management, sufficient renal replacement therapy should be provided both in quantity and quality. As noted earlier, because of the paucity of sufficient registry data analyses, many countries and regions, including those who published their guidelines and recommendations in English [46] or in their own language, adopted the target ranges of the Kidney Disease Outcomes Quality Initiative (KDOQI) or KDIGO. As these target ranges are mainly dependent on non-Asian data, they may not be optimal for Asian patients.

Access to therapeutic modalities is usually determined by both the availability and reimbursement system. The therapeutic modalities available for CKD-MBD remain quite different among Asian countries and regions, as shown in Table 3 (as of July, 2016). Another important issue is the local reimbursement policy. Except for a few countries, there is no reimbursement system for drugs for intravenous use and for new oral drugs, including non-calcium-based phosphate binders and cinacalcet. Even among countries with reimbursement systems, Korea and Singapore have limitations in the conditions for reimbursement. In Japan, the development of a bundling system has been under way, starting with erythropoiesis-

Table 2. The chronic kidney disease-mineral and bone disorder treatment landscape in Asian countries and regions

	Japan	Korea	China	Taiwan	Hong Kong	Singapore	Malaysia	Thailand
Dialysis patients, <i>n</i>	320,448 [52] HD: 311,193 PD: 9,255 (as of 2014)	69,986 [53] HD: 62,634 PD: 7,352 (as of 2015)	447,644 [54] HD: 385,055 PD: 62,589 (as of 2015)	73,339 [55] HD: 66,600 PD: 6,739 (as of 2015)	5,009 ^a [56] HD: 1,192 PD: 3,817 (as of 2013)	5,912 [57] HD: 5,226 PD: 686 (as of 2014)	37,629 [58] HD: 33,866 PD: 3,763 (as of 2014)	71,121 [59] HD: 49,719 PD: 21,402 (as of 2014)
Estimated percentage of SHPT patients (intact PTH >300 pg/mL)	HD: 14.0 [60]	ND	HD: 44.5 [61] PD: 50.4 [61]	ND	ND	ND	HD: 34 [58] PD: 33 [58]	ND
Dialysis vintage (≥5 years)	52.9% [52]	HD: 45% [53] PD: 46% [53]	26.2% ^b [62]	49.5% [55]	ND	HD: 59.7% [63] PD: 35.9% [63]	HD: 31.9% [58] PD: 44.7% [58]	ND
Guidelines followed	JSDT [22]	KDOQI (or KDIGO)	Chinese guidance for CKD-MBD [64]	KDOQI (and KDIGO)	H.A. Rx protocol (KDIGO)	KDIGO	KDOQI (or KDIGO)	Hemodialysis clinical practice recommendation [65]
Reimbursement situation	Yes	Yes 1. Intact PTH ≥300 pg/mL and corrected serum calcium ≥10.2 2. When patients taken VDRA for 3 months, intact PTH ≥300 pg/mL and corrected serum calcium ≥9.0	No	No	No	No	Yes (partial reimbursement only in MOH hospital)	No
Intact PTH	60–240 pg/mL [22]	150–300 pg/mL (or 2–9 times the upper limit)	2–9 times the upper limit [64]	150–300 pg/mL (or 2–9 times the upper limit)	ND (or 2–9 times the upper limit)	2–9 times the upper limit	150–300 pg/mL (or 2–9 times the upper limit)	130–600 pg/mL [65] (2–9 times the upper limit)
Calcium	8.4–10.0 mg/dL [22]	8.4–9.5 mg/dL (normal range)	8.4–10.0 mg/dL [64] (normal range)	8.4–9.5 mg/dL (normal range)	ND (normal range)	8.4–9.5 mg/dL (normal range)	8.4–9.5 mg/dL (normal range)	9.0–10.2 mg/dL [65]
Phosphorus	3.5–6.0 mg/dL [22]	3.5–5.5 mg/dL (normal range)	3.5–5.5 mg/dL [64] (normal range)	3.5–5.5 mg/dL (normal range)	ND (normal range)	3.5–5.5 mg/dL (normal range)	3.5–5.5 mg/dL (normal range)	2.7–4.9 mg/dL [65]

SHPT, secondary hyperparathyroidism; PTH, parathyroid hormone; HD, hemodialysis; PD, peritoneal dialysis; ND, no data; JSDT, Japanese Society for Dialysis Therapy; KDOQI, Kidney Disease Outcomes Quality Initiative; KDIGO, Kidney Disease Improving Global Outcomes; CKD-MBD, chronic kidney disease-mineral and bone disorder; MOH, Ministry of Health; H.A. Rx protocol, Hospital Authority Treatment Protocol. ^a Only includes patients in public hospitals. ^b Only in Shanghai, as of 2007.

Table 3. Drugs available for chronic kidney disease-mineral and bone disorder in Asian countries and regions

Drug class	Drugs (generic name)	Japan	Korea	China	Taiwan	Hong Kong	Singapore	Malaysia	Thailand
VDRA	Oral	Rocaltrol® (calcitriol)	✓	✓	✓	✓	✓	✓	✓
		Alfarol® (alfacalcitriol)	✓		✓	✓			
		Hornel®/Fulstan® (falecalcitriol)	✓						
		Calcitriol generics	✓	✓	✓	✓	✓	✓	✓
	IV	Calcijex® (calcitriol)	✓		✓	✓		✓	
		Zemplar® (paricalcitol)		✓	✓	✓	✓	✓	
		Oxarol® (maxacalcitol)	✓						
		Calcitriol generics	✓	✓				✓	✓
P-binder	Renagel®/Phosblock® (sevelamar HCl)		✓		✓	✓			
	Renvela® (sevelamar CO ₃)			✓	✓	✓	✓	✓	✓
	Kiklin® (bixalomer)		✓						
	Riona®/Nephoxil® (ferric citrate)		✓		✓				
	P-Tol®/Velphoro® (sucroferric oxyhydroxide)		✓		✓ [#]		✓		
	Calcium-based phosphate-binder generics		✓	✓	✓	✓	✓	✓	✓
Calcimimetics	Regpara® (cinacalcet)		✓	✓	✓	✓	✓	✓	✓
	Parsabiv® (etelcalcetide)		✓ [#]						

IV, intravenous. Shaded lines, no reimbursement. [#] Approved but not yet launched, as of December 2016.

stimulating agents [47]. These situations will further change depending upon the local status of the economy and government regulations.

Conclusions

As briefly summarized thus far, there remain substantial local variations in the strategies for CKD-MBD management in Asia. Ongoing economic development in these countries and areas will certainly contribute to the improvement of management in the near future. Policies for publishing and sharing of data regarding Asian CKD

patients is most urgently required [48], which should include data on pre-dialysis CKD patients and kidney transplant recipients [49]. Such data should also include cost-effectiveness analyses [50, 51] that take the local medical costs and system into consideration.

Conflict of Interest Statement

M.F. has received honoraria, consulting fees, and/or grant/research support from Bayer Yakuhin, Kyowa Hakko Kirin, ONO Pharmaceutical, and Torii Pharmaceutical. H.K. has received honoraria, consulting fees, and/or grant/research support from Bayer Yakuhin and Kyowa Hakko Kirin.

References

- Fukagawa M, Hamada Y, Nakanishi S, Tanaka M: The kidney and bone metabolism: a nephrologist's view. *J Bone Mineral Metab* 2006; 24:434–438.
- Lawson D, Kodicek E, et al: Identification of 1,25-dihydroxycholecalciferol, a new kidney hormone controlling calcium metabolism. *Nature* 1971;230:228–230.
- Komaba H, Kakuta T, Fukagawa M: Diseases of the parathyroid gland in chronic kidney disease. *Clin Exp Nephrol* 2011;5:797–809.
- Moe S, Drueke T, Cunningham J, et al: Definition, evaluation, and classification of renal osteodystrophy: a position statement from Kidney Disease Improving Global Outcomes (KDIGO). *Kidney Int* 2006;69:1945–1953.
- Nakai S, Akiba T, Kazama J, Yokoyama K, Fukagawa M, Tominaga Y, Iseki K, Tsubakihara Y; Patient Registration Committee of the Japanese Society for Dialysis Therapy: Effects of serum levels of calcium, phosphorus, and intact PTH on survival in chronic hemodialysis patients in Japan. *Ther Apher Dial* 2008;12: 49–54.
- Kidney Disease: Improving Global Outcomes (KDIGO) CKD-MBD Work Group: KDIGO clinical practice guideline for the diagnosis, evaluation, prevention and treatment of chronic kidney disease-mineral and bone disorder (CKD-MBD). *Kidney Int* 2009;76(suppl 113):S1–S130.
- London GM, Guerin AP, Marchais SJ, Metivier F, Pannier B, Adda H: Arterial calcification in end-stage renal disease: impact on all-cause and cardiovascular mortality. *Nephrol Dial Transplant* 2003;18:1731–1740.

- 8 Fujii H, Joki N: Mineral metabolism and cardiovascular disease in CKD. *Clin Exp Nephrol* 2017;21(suppl 1):53–63.
- 9 Shimada T, Mizutani S, Muto T, Yoneya T, Hino R, Takeda S, Takeuchi Y, Fujita T, Fukumoto S, Yamashita T: Cloning and characterization of FGF23 as a causative factor of tumor-induced osteomalacia. *Proc Natl Acad Sci USA* 2001;98:6500–6505.
- 10 Komaba H, Fukagawa M: Phosphate – a poison for humans? *Kidney Int* 2016;90:753–763.
- 11 Isakova T, Wahl P, Vargas GS, Gutierrez OM, Scialla J, Xie H, Appleby D, Nessel L, Bellovich K, Chen J, Hamm L, Gadebeku C, Horwitz E, Townsend RR, Anderson CA, Lash JP, Hsu CY, Leonard MB, Wolf M: Fibroblast growth factor 23 is elevated before parathyroid hormone and phosphate in chronic kidney disease. *Kidney Int* 2011;79:1370–1378.
- 12 Nakano C, Hamano T, Fujii N, Matsui I, Tomida K, Mikami S, Inoue K, Obi Y, Tsubakihara Y, Isaka Y, Rakugi H: Combined use of vitamin D status and FGF23 for risk stratification of renal outcome. *Clin J Am Soc Nephrol* 2012;7:810–819.
- 13 Gutierrez OM, Mannstadt M, Isakova T, Rauh-Hain JA, Tamez H, Shaf A, Smith K, Lee H, Thadachani R, Jueppner H, Wolf M: Fibroblast growth factor 23 and mortality among patients undergoing hemodialysis. *N Engl J Med* 2008;359:584–592.
- 14 Scialla JJ, Xie H, Rahman M, Anderson AH, Isakova T, Oko A, Zhang X, Nissel L, Hamano T, Grunwald JE, Raj DS, Yang W, He J, Lash JP, Go AS, Kusek JW, Feldman H, Wolf M: Chronic Renal Insufficiency Cohort (CRIC) Study Investigators: Fibroblast growth factor-23 and cardiovascular events in CKD. *J Am Soc Nephrol* 2014;25:349–360.
- 15 Kuro-O M: The FGF23 and Klotho system beyond mineral metabolism. *Clin Exp Nephrol* 2017;21(suppl 1):64–69.
- 16 Faul C, Amaral AP, Oskouei B, Hu MC, Sloan A, Isakova T, Gutierrez OM, Aguillon-Prada R, Lincoln J, Hare JM, Mundel P, Morales A, Schilla J, Fischer M, Solomon EZ, Chen J, Go AS, Rosas SE, Nessel L, Townsend RR, Feldman HI, St John Sutton M, Ojo A, Gadebeku C, Di Marco GS, Reuter S, Kentrup D, Tiemann K, Brand M, Hill JA, Moe OW, Kuro-O M, Kusek JW, Keane MG, Wolf M: FGF23 induces left ventricular hypertrophy. *J Clin Invest* 2011;121:4393–4408.
- 17 Andrukhova O, Slavic S, Smorodchenko A, Zeitz U, Shalhoub V, Lanske B, Pohl EE, Erben RG: FGF23 regulates renal sodium handling and blood pressure. *EMBO Mol Med* 2014;6:744–759.
- 18 Coe LM, Madathil SV, Casu C, Lanske B, Rivella S, Sitara D: FGF-23 is a negative regulator of prenatal and postnatal erythropoiesis. *J Biol Chem* 2014;289:9795–9810.
- 19 Wolf M, Koch TA, Bergman DB: Effect of iron deficiency anemia and its treatment on fibroblast growth factor 23 and phosphate homeostasis in women. *J Bone Mineral Res* 2013;29:1793–1803.
- 20 Singh S, Grabner A, Yanucil C, Schramm K, Czaya B, Krick S, Czaja MJ, Bartz R, Abraham R, DiMarco GS, Brand M, Wolf M, Faul C: Fibroblast growth factor directly targets hepatocytes to promote inflammation in chronic kidney disease. *Kidney Int* 2016;90:985–996.
- 21 National Kidney Foundation: National Kidney Foundation-Kidney Disease Outcomes Quality Initiative (K/DOQI) clinical practice guideline for bone metabolism and diseases in chronic kidney disease. *Am J Kidney Dis* 2003;42(suppl 3):S1–S201.
- 22 Fukagawa M, Yokoyama K, Koiwa F, Taniguchi M, Shoji T, Kazama JJ, Komaba H, Ando R, Kakuta T, Fujii H, Nakayama M, Shibagaki Y, Fukumoto S, Fujii N, Hattori M, Ashida A, Iseki K, Shigematsu T, Tsubakihara Y, Tomo T, Hirakata H, Akizawa T; for CKD-MBD Guideline Working Group, Japanese Society for Dialysis Therapy: Clinical practice guideline for the management of chronic kidney disease-mineral and bone disorder (CKD-MBD). *Ther Apher Dial* 2013;17:247–288.
- 23 Ketteler M, Elder GJ, Evenepoel P, Ix JH, Jamal SA, Lafage-Proust MH, Shroff R, Thadhani RI, Tonelli MA, Kasiske BL, Wheeler DC, Leonard MB: Revisiting KDIGO clinical practice guideline on chronic kidney disease-mineral and bone disorder: a commentary from a Kidney Disease: Improving Global Outcomes controversies conference. *Kidney Int* 2015;87:502–528.
- 24 Danese MD, Belozeff V, Smimakis K, Rothman KJ: Consistent control of mineral and bone disorder in incident hemodialysis patients. *Clin J Am Soc Nephrol* 2008;3:1423–1429.
- 25 Goodkine DA, Bragg-Gresham JL, Koenig KG, Wolfe RA, Akiba T, Andreucci VE, Saito A, Rayner HC, Kurokawa K, Port FK, Held PJ, Young EW: Association of comorbid conditions and mortality in hemodialysis patients in Europe, Japan, and the United States: the Dialysis Outcomes and Practice Patterns Study (DOPPS). *J Am Soc Nephrol* 2003;14:3270–3277.
- 26 Guideline Working GROUP, Japanese Society for Dialysis Therapy: Clinical practice guideline for the management of secondary hyperparathyroidism in chronic dialysis patients. *Ther Apher Dial* 2008;12:514–525.
- 27 Taniguchi M, Fukagawa M, Fujii N, Hamano T, Shoji T, Yokoyama K, Nakai S, Shigematsu T, Iseki K, Tsubakihara Y; Committee of Renal Data Registry of the Japanese Society for Dialysis Therapy: Impact of mineral metabolism on mortality in hemodialysis patients: serum phosphate level should be controlled firstly and consistently. *Ther Apher Dial* 2013;17:221–228.
- 28 Fukagawa M, Yumita S, Akizawa T, Uchida E, Tsukamoto Y, Iwasaki M, Koshikawa S; and KRN1493 study group: Cinacalcet (KRN 1493) effectively decreases serum intact PTH level with favorable control of serum phosphorus and calcium levels in Japanese dialysis patients. *Nephrol Dial Transplant* 2008;23:328–335.
- 29 Yokoyama K, Katoh N, Kubo H, Murai S, Imamura N, Shoji R, Yamamoto H, Shigematsu T, Nakayama M, Takasu S, Kono T, Yoshida T, Hosoya T: Clinical significance of the K/DOQI bone guideline in Japan. *Am J Kidney Dis* 2004;44:383–384.
- 30 Tentori F, Wang M, Bieber B, Jacobson S, Andreucci V, Fukagawa M, Frimat L, Mendelssohn DA, Port F, Pisoni RL, Robinson BM: Recent changes in therapeutic approach and association with outcomes in the DOPPS study. *Clin J Am Soc Nephrol* 2015;10:98–109.
- 31 Fukagawa M, Kido R, Komaba H, Onishi Y, Yamaguchi T, Hasegawa T, Kurita N, Akizawa T, Kurokawa K, Fukuhara S: Abnormal mineral metabolism associated with higher absolute mortality in hemodialysis patients with secondary hyperparathyroidism: evidence from marginal structural models used to adjust for time-dependent confounding. *Am J Kidney Dis* 2014;63:979–987.
- 32 Kir S, Komaba H, Garcia AP, Economopoulos KP, Liu W, Lanske B, Hordin RA, Spiegelman BM: PTH/PTHrP receptor mediates cachexia in models of kidney failure and cancer. *Cell Metab* 2016;23:315–323.
- 33 Sugimoto R, Watanabe H, Ikegami K, Enoki Y, Imafuku T, Sakaguchi Y, Murata M, Nishida K, Ishima Y, Tanaka M, Matsushita K, Komaba H, Fukagawa M, Otagiri M, Maruyama T: The down-regulation of ABCG2, a urate exporter, by parathyroid hormone enhances urate accumulation in secondary hyperparathyroidism. *Kidney Int* 2017;91:658–670.
- 34 Klahr S, Slatopolsky E: Toxicity of parathyroid hormone in uremia. *Annu Rev Med* 1986;37:71–78.
- 35 Komaba H, Taniguchi M, Wada A, Iseki K, Tsubakihara Y, Fukagawa M: Parathyroidectomy and survival among hemodialysis patients with secondary hyperparathyroidism: results from a nationwide registry in Japan. *Kidney Int* 2015;88:350–359.
- 36 Komaba H, Nakanishi S, Fujimori A, Tanaka M, Shin J-S, Shibuya K, Nishioka M, Hasegawa H, Kurosawa T, Fukagawa M: Cinacalcet effectively reduces parathyroid hormone secretion and gland hyperplasia regardless of pretreatment gland size in patients with secondary hyperparathyroidism. *Clin J Am Soc Nephrol* 2010;5:2305–2314.
- 37 Akizawa T, Kurita N, Mizobuchi M, Fukagawa M, Onishi Y, Yamaguchi T, Ellis AR, Fukuma S, Brookhart MA, Hasegawa T, Kurokawa K, Fukuhara S: PTH-dependence of the effectiveness of cinacalcet in hemodialysis patients with secondary hyperparathyroidism. *Sci Rep* 2016;6:19612.
- 38 Koizumi M, Komaba H, Nakanishi S, Fujimori A, Fukagawa M: Cinacalcet treatment and FGF23 levels in dialysis patients with secondary hyperparathyroidism. *Nephrol Dial Transplant* 2012;27:784–790.

- 39 EVOLVE Trial Investigators; Chertow GM, Block GA, Correa-Rotter R, Druke TB, Floege J, Goodman WG, Herzog CA, Kubo Y, London GM, Mahaffey KW, Mix TC, Moe SM, Trotman ML, Wheeler DC, Parfrey PS: Effect of cinacalcet on cardiovascular disease in patients undergoing dialysis. *N Engl J Med* 2012;367:2482–2494.
- 40 Moe SM, Chertow GM, Parfrey PS, Kubo Y, Block GA, Correa-Rotter R, Druke TB, Herzog CA, London GM, Mahaffey KW, Wheeler DC, Stolina M, Dehmel B, Goodman WG, Floege J; Evaluation of Cinacalcet HCL Therapy to Lower Cardiovascular Events (EVOLVE) Trial Investigators: Cinacalcet, fibroblast growth factor-23, and cardiovascular disease in hemodialysis: the Evaluation of Cinacalcet HCL Therapy to Lower Cardiovascular Events (EVOLVE) trial. *Circulation* 2015;132:27–39.
- 41 Yokoyama K, Kurita N, Fukuma S, Akizawa T, Fukagawa M, Onishi Y, Kurokawa K, Fukuhara S: Frequent monitoring of mineral metabolism in hemodialysis patients with secondary hyperparathyroidism: associations with achievement of treatment goals and with adjustments in therapy. *Nephrol Dial Transplant* 2016, Epub ahead of print.
- 42 Yokoyama K, Hirakata H, Akiba T, Fukagawa M, Nakayama M, Sawada K, Kumagai Y, Block G: A randomized double blind placebo-controlled trial of JTT-751 (ferric citrate hydrate) on hyperphosphatemia in patients with non-dialysis dependent chronic kidney disease. *Clin J Am Soc Nephrol* 2014;9:543–552.
- 43 Koiwa F, Yokoyama K, Fukagawa M, Terao A, Akizawa T: Efficacy and safety of surroferic oxyhydroxide compared with sevelamer hydrochloride in Japanese haemodialysis patients with hyperphosphatemia: a randomized, open-label, multicenter, 12-week phase III study. *Nephrology (Carlton)* 2017;22:293–300.
- 44 Fukagawa M, Yokoyama K, Shigematsu T, Akiba T, Fujii A, Kuramoto T, Odani M, Akizawa T: A phase 3, multicenter, randomized, double-blind, placebo-controlled, parallel-group study to evaluate the efficacy and safety of etelcalcitide (ONO-5163/AMG 416), a novel intravenous calcimimetic, for secondary hyperparathyroidism in Japanese haemodialysis patients. *Nephrol Dial Transplant* gfw408.
- 45 Komaba H, Kakuta T, Suzuki H, Hida M, Suga T, Fukagawa M: Survival advantage for hemodialysis patients starting lanthanum carbonate for uncontrolled hyperphosphatemia. *Nephrol Dial Transplant* 2015;30:107–114.
- 46 Hwang E, Choi B-S, Oh K-H, Kwon YJ, Kime C-H: Management of chronic kidney disease-mineral and bone disorder: Korean working group recommendations. *Kidney Res Clin Pract* 2015;34:4–12.
- 47 Hasegawa T, Bragg-Gresham JL, Pisoni RL, Robinson BM, Fukuhara S, Akiba T, Saito A, Kurokawa K, Akizawa T: Changes in anemia management and hemoglobin levels following revision of bundling policy to incorporate recombinant human erythropoietin. *Kidney Int* 2011;79:340–346.
- 48 Hamano T, Sakaguchi Y, Fujii N, Isaka Y: Clinical features of CKD-MBD in Japan: cohort studies and registry. *Clin Exp Nephrol* 2017;21(suppl 1):9–20.
- 49 Hirukawa T, Kakuta T, Nakamura M, Fukagawa M: Mineral and bone disorders in kidney transplant recipients: reversible, irreversible and de novo abnormalities. *Clin Exp Nephrol* 2015;19:543–555.
- 50 Goto S, Komaba H, Moriwaki K, Fujimori A, Shibuya K, Nishioka M, Kim J-I, Yoshiya M, Shin J-S, Hasegawa H, Taniguchi M, Fujii H, Nishi S, Fukagawa M: Clinical efficacy and cost-effectiveness of lanthanum carbonate as second-line therapy in hemodialysis patients in Japan. *Clin J Am Soc Nephrol* 2011;6:1375–1384.
- 51 Komaba H, Moriwaki K, Goto S, Yamada S, Taniguchi M, Kakuta T, Kamae I, Fukagawa M: Cost effectiveness of cinacalcet hydrochloride for hemodialysis patients with severe secondary hyperparathyroidism. *Am J Kidney Dis* 2012;60:262–271.
- 52 JSDT registry data as of the end of 2014. http://www.jsdt.or.jp/overview_confirm.html (accessed December 26, 2016).
- 53 Jin DC, Yun SR, Lee SW et al: Current characteristics of dialysis therapy in Korea: 2015 registry data focusing on elderly patients. *Kidney Res Clin Pract*. 2016;35: 204–211.
- 54 Chinese National Renal Data System: The annual congress of Chinese Society of Nephrology 2016, Blood Purification Forum. Xiamen Shi, Fujian Sheng, China, May 5–7, 2016.
- 55 2015 Annual Report on kidney disease in Taiwan. http://w3.nhri.org.tw/nhri_org/rl/lib/NewWeb/nhri/ebook/39000000425236.pdf (accessed December 26, 2016).
- 56 Leung CB, Cheung WL, Li PK: Renal registry in Hong Kong – the first 20 years. *Kidney Int Suppl* (2011) 2015; 5:33–38.
- 57 Singapore renal registry annual registry report 1999–2014. <https://www.nrdo.gov.sg/docs/librariesprovider3/Publications-Kidney-Failure/report-1999-till-2014-interim.pdf?sfvrsn=0f> (accessed December 26, 2016).
- 58 22nd report of the Malaysian dialysis and transplant registry 2014. http://www.msn.org.my/Doc/PublicDoc_PB/Publication/mdtr22nd/content.pdf (accessed December 26, 2016).
- 59 Thailand renal replacement therapy registration report 2014. http://www.nephrothai.org/images/10-11-2016/1.TRT-report-2014_3-11-59_final_.pdf (accessed December 26, 2016).
- 60 JSDT registry data as of the end of 2015. http://www.jsdt.or.jp/overview_confirm.html.
- 61 Kong X, Zhang L, Zhang L, et al: Mineral and bone disorder in Chinese dialysis patients: a multicenter study. *BMC Nephrol* 2012;13: 116.
- 62 Lin X, Yan Y, Ni Z, et al: Clinical outcome of twice-weekly hemodialysis patients in Shanghai. *Blood Purif* 2012;33: 66–72.
- 63 Singapore renal registry report No.10. <https://www.nrdo.gov.sg/docs/librariesprovider3/Publications--Kidney-Failure/singapore-renal-registry-annual-registry-report-1999-2013-preliminary.pdf?sfvrsn=0> (accessed December 26, 2016).
- 64 Chinese Society of Nephrology. 2013: Guidance for diagnosis and treatment of mineral and bone disorder in chronic kidney disease.
- 65 Hemodialysis clinical practice recommendation 2014. <http://www.nephrothai.org/en/%E0%B8%AB%E0%B8%99%E0%B8%B1%E0%B8%87%E0%B8%AA%E0%B8%B7%E0%B8%AD%E0%B9%82%E0%B8%A3%E0%B8%84%E0%B9%84%E0%B8%95%E0%B8%99%E0%B9%88%E0%B8%B2%E0%B8%AA%E0%B8%99%E0%B9%83%E0%B8%88/343-hemodialysis-clinical-practice-recommendation-2014-en>.