Chronic Kidney Disease-Mineral and Bone Disorder in Asia

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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.
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, dieticians, 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-

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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.
|                  | Japan     | Korea     | China     | Taiwan    | Hong Kong | Singapore   | Malaysia   | Thailand   |
|------------------|-----------|-----------|-----------|-----------|-----------|-------------|-----------|-----------|
| Dialysis patients, n | 320,448 [52] | 69,986 [53] | 447,644 [54] | 73,339 [55] | 5,009a [56] | 5,912 [57] | 37,629 [58] | 71,121 [59] |
|                  | HD: 311,193 | HD: 62,634 | HD: 385,055 | HD: 1,192 | HD: 5,226 | HD: 3,763   | HD: 21,402 |           |
|                  | PD: 9,255 (as of 2014) | PD: 7,352 (as of 2015) | PD: 6,739 (as of 2015) | PD: 3,817 (as of 2013) | PD: 686 (as of 2014) |           |           |           |
| Estimated percentage of SHPT patients (intact PTH >300 pg/mL) | HD: 14.0 [60] | ND         | HD: 44.5 [61] | ND         | ND         | ND          | HD: 34 [58] | ND         |
|                  | PD: 50.4 [61] |           | PD: 50.4 [61] |           |           | PD: 33 [58] |           |           |
| Dialysis vintage (≥5 years) | 52.9% [52] | HD: 45% [53] | 26.2%b [62] | 49.5% [55] | ND         | HD: 59.7% [63] | HD: 31.9% [58] | ND         |
|                  | PD: 46% [53] |           | PD: 46% [53] |           |           | PD: 44.7% [58] |           |           |
| Guidelines followed | JSDT [22] | KDOQI (or KDIGO) | Chinese guidance for CKD-MBD [64] | KDOQI (and KDIGO) | H.A. Rx protocol (KDIGO) | KDIGO (or KDIGO) | Hemodialysis clinical practice recommendation [65] |           |
| Reimbursement situation | Yes | Yes | 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 (2–9 times the upper limit) |
| Calcium | 8.4–10.0 mg/dL [22] (normal range) | 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 (normal range) |
| Phosphorus | 3.5–6.0 mg/dL [22] (normal range) | 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 (normal range) |

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.
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**

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**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) | ✓     | ✓     | ✓     | ✓      | ✓         | ✓         | ✓        | ✓        |
|           | Alfaro® (alfacalcitriol) | ✓     | ✓     | ✓     | ✓      | ✓         | ✓         | ✓        | ✓        |
|           | Hornel®/Fulstan® (falecalcitriol) | ✓     | ✓     | ✓     | ✓      | ✓         | ✓         | ✓        | ✓        |
|           | Calcitriol generics | ✓     | ✓     | ✓     | ✓      | ✓         | ✓         | ✓        | ✓        |
| IV         | Calcijex® (calcitriol) | ✓     | ✓     | ✓     | ✓      | ✓         | ✓         | ✓        | ✓        |
|           | Zemplar® (paricalcitol) | ✓     | ✓     | ✓     | ✓      | ✓         | ✓         | ✓        | ✓        |
|           | OXarol® (maxacalcitol) | ✓     | ✓     | ✓     | ✓      | ✓         | ✓         | ✓        | ✓        |
|           | Calcitriol generics | ✓     | ✓     | ✓     | ✓      | ✓         | ✓         | ✓        | ✓        |

| P-binder | Renagel®/Phosblock® (sevelamar HCl) | ✓     | ✓     | ✓     | ✓      | ✓         | ✓         | ✓        | ✓        |
|          | Renvela® (sevelamar CO₃) | ✓     | ✓     | ✓     | ✓      | ✓         | ✓         | ✓        | ✓        |
|          | Kiklin® (bixalomer) | ✓     | ✓     | ✓     | ✓      | ✓         | ✓         | ✓        | ✓        |
|          | Riona®/Nephoxil® (ferric citrate) | ✓     | ✓     | ✓     | ✓      | ✓         | ✓         | ✓        | ✓        |
|          | P-Tol®/Velphoro® (sucroferric oxyhydroxide) | ✓     | ✓     | ✓     | ✓      | ✓         | ✓         | ✓        | ✓        |
|          | Calcium-based phosphate-binder generics | ✓     | ✓     | ✓     | ✓      | ✓         | ✓         | ✓        | ✓        |

| Calcimimetics | Regpara® (cinacalcet) | ✓     | ✓     | ✓     | ✓      | ✓         | ✓         | ✓        | ✓        |
|               | Parsabiv® (etelcalcitide) | ✓     | ✓     | ✓     | ✓      | ✓         | ✓         | ✓        | ✓        |

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