

REVIEW

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CKD 5D Asia—what is common and what is different from the West?

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Abstract

The mission of Kidney Disease: Improving Global Outcomes (KDIGO) is to improve the care and outcomes of kidney disease patients worldwide through the development and implementation of global clinical practice guidelines (CPG). To attain this mission, KDIGO has been publishing CPGs since 2008. Implementation of CPGs is very important, in particular for many developing countries in Asia. This review was written after the first implementation summit of “chronic kidney disease (CKD)-mineral bone disorder (MBD) guideline in Asia” which took place on April 28 to 29, 2018, in Tokyo.

Prevalence of end-stage renal disease (ESRD) is increasing rapidly in Asia. CKD-MBD is a modifiable risk factor of cardiovascular disease (CVD), bone fracture, and mortality, both non-dialysis-dependent and dialysis patients. Concept of CKD-MBD is a newly developed, and the CKD-MBD CPG was published on 2009 and updated on 2017. Unfortunately, very few evidences are available to recommend for daily practice. Many treatment options are based on expert suggestion. Incidence of ESRD especially diabetes mellitus (DM) is very high in Asian countries. More research is needed, in particular using patient-reported outcomes (PRO).

Keywords: Survival, Clinical practice guideline, CKD, KDIGO, CKD-MBD

Background

The mission of Kidney Disease: Improving Global Outcomes (KDIGO) is to improve the care and outcomes of kidney disease patients worldwide through the development and implementation of global clinical practice guideline (CPG) [1]. To attain this mission, KDIGO has published 11 CPGs since 2008 [2–12] (Table 1). More than 30 controversy conferences (CC) were held in many cities worldwide. Core KDIGO efforts are to run the cycle of CC, CPG, implementation, research, clinical practice conference (CPC), and revision and updates. Recent KDIGO implementation activities are summarized in Table 2. Implementation of CPGs is very important, in particular for many developing countries in Asia. KDIGO joint symposiums (CPC) are currently organized with each national or regional society, Asian Pacific Society of Nephrology (APSN), American Society of Nephrology (ASN), and International Society of Nephrology (ISN).

CKD-MBD is an important risk factor of CVD, bone fracture, and mortality, both non-dialysis-dependent and dialysis-dependent CKD patients. CKD-MBD CPG was published on 2009 and has updated on 2017 [4, 12]. Concept of CKD-MBD is a newly developed [13, 14]. There are seven key messages in the updated CPG (Table 3). Unfortunately, very few evidences are available to recommend for daily practice [15–17]. This review was written based on the author’s presentation at the first implementation summit of “CKD-MBD Guideline in Asia” which took place on April 28 to 29, 2018, in Tokyo organized by KDIGO. Invited discussants were from Japan, Korea, China, Taiwan, Hong Kong, Singapore, Thailand, and Malaysia. Prevalence of ESRD is increasing rapidly in Asia. Summary of the meeting will be published by KDIGO.

According to the latest United States Renal Data System (USRDS) [18], the incidence of ESRD especially DM is very high in Asian countries. Unfortunately, data from China and India are not available; however, the number of ESRD patients is roughly increasing 10 to 15% yearly. It is noteworthy that the incidence of ESRD is decreasing in several European countries and also stabilized in Japan. Actually, the sex- and age-specific incidence rates

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Table 1 Clinical practice guideline by KDIGO

1. Hepatitis C in CKD: 2008
2. CKD mineral and bone disorder (CKD-MBD): 2009
3. Care of kidney transplant recipients: 2009
4. Acute kidney injury (AKI): 2012
5. Anemia in CKD: 2012
6. Glomerulonephritis (GN): 2012
7. Blood pressure in CKD: 2012
8. CKD evaluation and management: 2013
9. Lipids in CKD: 2013
10. Living kidney donors: 2017
11. CKD mineral and bone disorder (CKD-MBD): updated 2017

of ESKD requiring RRT have decreased gradually between 2008 and 2012, except among men aged ≥ 80 years in Japan [19]. Recent activities of the Japanese Society of Nephrology (JSN) and other related societies may have contributed for this improvement. Moreover, JSN is collaborating with ISN to advance the knowledge worldwide towards the eradication of kidney disease and to promote all types of related activities that facilitate the spread of awareness, diagnosis, and treatment of kidney disease [20]. However, people live longer and also dialysis patients [21], the number of aged population is increasing, and therefore, the prevalence of ESRD is continuously increasing in Japan, at least several years more.

Survival of dialysis patients

The Japanese Society for Dialysis Therapy (JSDT) has been conducting nationwide survey on dialysis facilities and patients since 1983. According to the annual report of JSDT, the annual crude mortality rates have been stable at around 9.5%, even though there is a rapid increase in the number of patients: 37,000 (1983) to 320,000 (2015). As the prevalence of DM and mean age of prevalent patients are increasing, overall mortality risk should be decreasing. The response rates have been stable at around 97% except in 1989 which was less than 90% due to the miss-conduct of the JSDT. JSDT has

Table 2 Recent KDIGO implementation activities

1. Dissemination of printed guideline supplements at major nephrology Congresses from the KDIGO booth in exhibit hall
2. Translations—multiple language translations of both full text and executive summary
3. Educational Symposia—live, expert presentations on KDIGO guidelines, usually held in collaboration with local, regional, or international nephrology societies to explain the recommendations and science behind them
4. Implementation tools—development of educational materials based on KDIGO guidelines, including speaker's guides, reference tools, and webinars
5. Implementation summits—a new KDIGO program designed to help implement a KDIGO guideline in a specific region or country, taking into account local issues such as insurance, reimbursement policies, and local guidelines
6. KDIGO app—access to all KDIGO guidelines on the Smartphone app, available for free download from the iTunes Store and Google Play

Table 3 Key messages of the updated KDIGO CKD-MBD guideline (cited from the KDIGO speaker's guide)

1. Prospective studies evaluating BMD testing in adults with CKD represent a substantial advance since the original guideline from 2009, making a reasonable case for BMD testing if the results will impact future treatment.
2. It is important to emphasize the interdependency of serum calcium, phosphate, and PTH for clinical therapeutic decision-making.
3. Phosphate-lowering therapies may only be indicated in the case of "progressive or persistent hyperphosphatemia".
4. New evidence suggests that excess exposure to exogenous calcium in adults may be harmful in all severities of CKD, regardless of other risk markers.
5. It is reasonable to limit dietary phosphate intake, when considering all sources of dietary phosphate (including "hidden" sources).
6. The PRIMO* and OPERA** studies failed to demonstrate improvements in clinically relevant outcomes but did demonstrate increased risk of hypercalcemia. Accordingly, routine use of calcitriol or its analogs in CKD G3a-G5 is no longer recommended.
7. No consensus was reached to recommend cinacalcet as first-line therapy for lowering PTH in all patients with SHPT and CKD G5D.

*PRIMO study [15]

**OPERA study [16]

published many papers written in English such as clinical practice guidelines, proposals, and guides [22–39].

Dialysis Outcomes and Practice Pattern Study (DOPPS) is a prospective observational, international collaborative study [40]. According to the DOPPS, adjusted survival in Japan is better than that of the Europe and USA [41, 42]. So far, there is no clear-cut explanation for this observation [43] although overall mortality risk has been decreased significantly in the USA [44]. According to the DOPPS, several unique practice patterns in Japan were noted. This practice pattern is the long-term tradition of Japanese dialysis physicians, nurses, technicians, and others. We defined "conventional HD is 4 h, three times per week" in 2015 [34]. Many Japanese are quite punctual. Regular visits to the bed-side by physician and nurses also contribute to the early detection of symptoms and signs of dialysis complication. I believe the adherence to this practice of "conventional HD" is one of the key factors explaining the better survival in Japan [45]. However, as aged HD patients are increasing, demands for life support such as diet and transportation are increasing and become a social burden. Compared to the general population, dialysis patients seem to be plus 15 to 20 years of their calendar age. Further studies are necessary to understand the life expectancy gains in ESRD patients [46].

Better management of secondary hyperparathyroidism may retard the progression of complication related to CKD-MBD [47]. Regarding the CKD-MBD GLs and treatment, new drugs come. GL comes later. Even KDIGO2017 information on ferric citrate or etelcalcetide have not included. Generally speaking, even though treatment is recommended based on randomized control trial (RCT), we have to be careful when applying to individual patient. There may be racial differences in side-effects. In JSDT,

there are two GLs on CKD-MBD written in English [24, 32]. The suggested target of intact PTH was 60–180 pg/ml [24] and updated to 60–240 pg/ml [32] lower than that of the West (up to nine times higher than the upper limit). Again, there may be racial differences in interdependency in Ca, Pi, and PTH.

Clinical research

Several years ago, interesting debate was published [48]. As noted, dialysis therapy has been conducted by experience-based medicine as associated with very few RCT [49]. Possible explanation for this observation may be related to too many factors related to high mortality among dialysis patients. Firstly, they should be managed under “conventional HD.” Unless otherwise, there would be no drugs to replace the dialysis itself.

In the Nephrology subspecialty, the number of RCT has been the lowest among many subspecialties. In non-CKD patients, there was a problem of “outcome.” Incidence of “hard outcomes” such as death or ESRD is relatively low; therefore, it requires many subjects and long-term follow-up. It has been difficult for pharmaceutical companies to support RCT. Recently, a decline rate of eGFR has been proposed as a surrogate marker of CKD outcome [50, 51]. Fortunately, data for eGFR by using Japanese formula [52] is broadly available for general screening and many medical facilities in Japan. Change in proteinuria is also helpful as a surrogate marker of CKD outcome [53]. In the near future, the number of RCT may increase in nephrology field. But, for dialysis patients, there would be no such surrogate marker, so far.

Currently, shift in the research focus is proposed [54]. They suggested (1) more qualitative methods used in social sciences, (2) more PRO, (3) unmet needs for studies to elucidate racial and ethnic differences in quality of life (QOL) issues, (4) research and policy changes should be driven by experienced practitioners with current patient contact to ensure that they are relevant to patient needs, (5) support research to improve QOL and discourage cookie-cutter survival studies, and (6) QOL metrics (pain, depression) needs to be incentivized in clinical practice to drive-related research efforts. The 36-Item Short-Form Health Survey (SF-36) and EuroQol 5 Dimension (EQ-5D) are candidate tools for PRO. In the field of rheumatology, PRO is frequently used to evaluate the efficacy of new drugs. Moreover, multidimensional measure of dialysis was proposed [55]. In dialysis patients, there are a lot of clinical measures including PRO. Then, we will see the relationship between these measures and dialysis strategies and with QOL and survival of dialysis patients. This process has been practiced by experienced practitioners with frequent patient contact.

RCTs provide the most reliable evidence about the safety and effectiveness of interventions to improve health care and patient outcomes. Unfortunately, the potential for trials to inform treatment decisions remains limited because the outcomes reported often do not resonate with what is directly meaningful and relevant to patients and their clinicians. Recently, initiative for standardized outcomes in Nephrology (SONG) was proposed [56]. Outcome reporting bias exists as it is not uniformly defined. They report on the basis of favorable results. Such problems may undermine the reliability of published trials, leading to inefficient use of scarce research and health care resources and unintended harm to patients.

Muscle and fat wasting may develop in CKD, in particular elderly, and exacerbated by decreasing kidney function, coexisting conditions and frailty. Protein-energy wasting (PEW) is common in dialysis patients, and dietary management is difficult in such patients. Dietary habits and lifestyle vary widely by cultural, socio-economic, and racial background. Diagnostic criteria of PEW were proposed in 2008 [57]. Additional studies that are patient centered and cost-effective are needed to ensure a more robust, evidence-based approach to the nutritional management of CKD [58].

Conclusions

Due to the small number of RCT in Nephrology, CPG is largely based on expert opinion and observational studies. In this regard, more research on PRO and socio-economic factors is required to prevent the incidence and progression of CKD and improve the life expectancy. Currently, there are several cohort studies from nationwide general screening program [59, 60], CKD cohort [61], and dialysis patients [62, 63] in Japan. CKD-MBD Asia summit by KDIGO was the first to discuss such issues. Management for CKD-MBD is rapidly changing as new drugs appear in the market [64].

KDIGO is currently working to response to the proposal from SONG with the glomerulonephritis (GN) guideline. GN is still the leading cause of ESRD in some Asian countries [65, 66]. Stakeholders such as patients, clinicians, and policymakers need to be involved for the decision-making.

Abbreviations

APSN: Asian Pacific Society of Nephrology; ASN: American Society of Nephrology; CC: Controversy conference; CKD: Chronic kidney disease; CPC: Clinical practice conference; CPG: Clinical practice guideline; CVD: Cardiovascular disease; DM: Diabetes mellitus; DOPPS: Dialysis Outcomes and Practice Patterns Study; EQ-5D: EuroQol 5 Dimension; ESRD: End-stage renal disease; ISN: International Society of Nephrology; JSDT: Japanese Society for Dialysis Therapy; JSN: Japanese Society of Nephrology; KDIGO: Kidney Disease: Improving Global Outcomes; MBD: Mineral bone disorder; PEW: Protein-energy wasting; PRO: Patient-reported outcomes; QOL: Quality of life; RCT: Randomized control trial; SF-36: 36-Item Short-Form Health Survey; SONG: Standardized outcomes in Nephrology; USRDS: United States Renal Data System

Author's contributions

The author read and approved the final manuscript.

Author's information

The author is an executive committee member of the KDIGO (2017–2019).

Ethics approval and consent to participate

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Consent for publication

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Competing interests

The author declare that he has no competing interests.

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