KDIGO CKD-MBD Discussion forum: Brazilian perspective

ABSTRACT
On November 14th, 2009, the Brazilian Society of Nephrology coordinated the Brazilian Discussion Meeting on the new KDIGO (Kidney Disease: Improving Global Outcomes) guidelines. The purpose of this meeting, which was attended by 64 nephrologists, was to discuss these new guidelines from the Brazilian perspective. This meeting was supported by an unrestricted grant of the biotechnology company Genzyme, which did not have access to the meeting room or to the discussion sections. This article brings a summary of the KDIGO guidelines and of the discussions by the attendees.

Keywords: renal osteodystrophy, phosphorus metabolism disorders, parathyroid hormone, metabolic bone diseases, chronic kidney failure.

CRITICAL ANALYSIS FROM THE BRAZILIAN PERSPECTIVE

METHODOLOGY AND DEVELOPMENT OF THE KIDNEY DISEASE: IMPROVING GLOBAL OUTCOME (KDIGO)
In the Brazilian clinical practice guidelines for the management of the mineral and bone disorder due to chronic kidney disease (CKD-MBD) of the Brazilian Society of Nephrology (BSN), the term “Evidence” was used every time the guidelines were based on an article in the literature, independently of its level of evidence, while the term “Opinion” was used every time the recommendation was based on opinions contained in the guidelines consulted, and, sometimes, it expressed the personal experience of the developers of the guideline. On the other hand, in the KDIGO guidelines, the use of the term “Evidence” met the criteria of the “GRADE (Grading of Recommendations Assessment, Development and Evaluation) Working Group”, a group created by KDIGO to assess all studies used in developing the guidelines. The two guidelines also differ in regard to the definition of endpoints: to determine the best treatment options, the KDIGO work group assessed only studies whose outcomes were fractures, cardiovascular events, hospitalizations, decreased quality of life, and mortality. On the other hand, the Brazilian guidelines have also accepted the improvement in biochemical parameters and/or bone lesions (assessed by use of biopsy) as a criterion of successful treatment. Although this can be interpreted as a mere detail, that difference of concepts was a determinant factor for some of the differences found between the guidelines. In the Brazilian guidelines, as in the North-American guidelines (KDOQI), the definition of evidence is more liberal. On the other hand, in the KDIGO guidelines, the criteria were markedly strict, and, by the end of the analysis, only a few clinical studies were considered adequate to be used in developing the body of evidence.

PHOSPHORUS AND CALCIUM LEVELS CONTROL
Hyperphosphatemia is an important and inevitable consequence of advanced CKD, since phosphorus balance is permanently positive in patients with CKD stages 4-5D. The presence of hyperphosphatemia relates to higher mortality and an increased risk for cardiovascular diseases in both the healthy population and patients with CKD. In addition, in those patients, it contributes to the development of vascular calcifications and
secondary hyperparathyroidism, through the stimulation of parathormone (PTH) production and a reduction in calcitriol production.

**Phosphorus control – Therapeutic target: CKD stages 3-5D: to maintain phosphorus within the reference range**

The phosphorus levels recommended by KDIGO are similar for patients with CKD stages 3-5D and should be kept within the reference range of the method used. That recommendation differs from those in the Brazilian and North-American guidelines that recommended normal phosphorus levels for patients with CKD stages 3-4, while, for stage 5, slightly more liberal values were recommended, ranging from 3.5 to 5.5 mg/dL. The rationale of the option for lower phosphorus levels even in more advanced stages of the disease lies in the recent evidence of the relation between higher phosphorus levels, even if in the upper limit of normality, and a higher risk for death and cardiovascular events in individuals with either normal or decreased renal function. It is worth noting the lack of randomized clinical trials determining whether controlling phosphorus levels has an impact on morbidity and mortality of individuals with CKD, and which would be the exact ideal target range. Thus, considering only the current epidemiological evidence, it seems reasonable to maintain serum levels of phosphorus as close to normal as possible.

**Calcium control – Therapeutic target: CKD stages 3-5D: to maintain calcium within the reference range**

Similarly to the recommendation referring to phosphorus, the calcium levels recommended by KDIGO are those within the reference range of the method used for all CKD stages. Again, in this case, the KDIGO orientation differs from that of the Brazilian and North-American guidelines, which recommend maintaining calcium serum levels between 8.4 and 9.5 mg/dL, based on previous studies on the association between calcium levels above those values and mortality in patients with CKD. However, because there are no randomized and prospective studies establishing the ideal level to be kept, until new data from future studies are available, KDIGO chooses a more conservative recommendation.

**Calcium concentration in the dialysate: Recommended calcium concentration in the dialysate is 2.5 to 3.0 mEq/L**

Calcium balance during the dialysis session depends on the total body content of calcium, on serum levels of calcium, and also on serum levels of PTH. In patients undergoing hemodialysis, that balance is influenced by the ultrafiltration rate and ionic calcium. A few studies have assessed the effect of calcium concentration in the dialysate on calcium balance, but neutrality seems to occur in most patients when calcium concentration in the dialysate equals 2.5-3.0 mEq/L. In peritoneal dialysis, the use of reduced calcium concentrations is recommended, because exposure to the dialysate is longer and there is a greater prevalence of adynamic bone disease in that population. Such recommendations are similar to those of the Brazilian guidelines. In our case, the use of a calcium concentration of 2.5 mEq/L is recommended for patients with serum PTH levels lower than 150 pg/ml, and of 3.0 mEq/L for patients with serum PTH levels above 500 pg/ml. The North-American guideline recommends a calcium concentration in the dialysate of 2.5 mEq/L for most patients. In reality, once again this is controversial because of the lack of prospective and randomized studies assessing the effect of different concentrations of calcium in the dialysate on PTH levels, development of vascular calcifications, and endpoints, such as fractures, hospitalizations, and mortality.

**Use of phosphorus binders: Phosphorus binders are recommended in all stages of CKD in the presence of hyperphosphatemia.**

The use of calcium-containing phosphorus binders should be avoided in the presence of hypercalcemia, adynamic bone disease, low levels of PTH, or evidence of arterial calcification.

The KDIGO guidelines, as well as the Brazilian and North-American guidelines, recommend the use of phosphorus binders in the presence of hyperphosphatemia in all stages of CKD. All phosphorus binders available are effective in reducing serum levels of phosphorus. However, the evidence about the effects of each class of binder on other endpoints, such as morbidity and mortality, vascular calcification, and bone disease, remains inconclusive. Thus, the choice of the binder should be individualized. Regarding the impact of the use of different classes of binders on clinical endpoints, only two randomized studies compared morbidity and mortality in patients with CKD stage 5D using sevelamer and calcium-containing binders. Both have severe methodological limitations, and their results were conflicting. None of them assessed endpoints, such as fractures, cardiovascular events, or the need for parathyroidectomy. Regarding the benefit of the use of binders on the progression of vascular calcifications, there are five prospective studies already concluded, one of them in patients with CKD stages 3-5, and the others in patients with CKD.
stage 5D. Once again the evidence is conflicting. In two of the studies, the use of sevelamer hydrochloride attenuated the progression of the arterial calcification when compared with the use of calcium-containing binders. Two other studies showed no difference between the groups. The prevalence of vascular calcification is an intermediary endpoint and there is no evidence that delaying its progression leads to a reduction in cardiovascular events or mortality. The impact of the use of lanthanum as a binder on clinical endpoints and vascular calcification was not assessed.

The alterations in bone remodeling due to the use of different binders were heterogeneous and seem to depend on the underlying bone histology. The biochemical parameters seem to differ with the use of calcium-containing binders when compared with other binders, because elevated calcium levels and PTH suppression were more frequent in the first group considering the set of studies assessed. The KDIGO guidelines maintained the previous recommendations regarding the calcium restriction in situations of hypercalcemia, reduced PTH, adynamic bone disease, and arterial calcifications, although evidence in the last two cases is inconclusive.

**Restriction to the use of aluminum-containing binders:**

The long-term use of aluminum-containing binders should be avoided.

KDIGO recommends avoiding the use of aluminum-containing binders because of the risk of aluminum intoxication and the existence of a large number of binders that do not contain the metal. To date, we do not know for how long the use of aluminum binders would be safe. That recommendation is similar to that of the Brazilian guidelines.

**Dietary phosphorus restriction:**

Dietary phosphorus restriction alone or in association with the use of binders is recommended.

Dietary phosphorus restriction is feasible with no damage to the patient’s nutritional status. However, there is no unequivocal evidence of the isolated usefulness of that measure as a primary intervention. One single study assessed the use of a phosphorus-poor diet alone or in association with the use of binders, and no benefit was observed in the progression of vascular calcifications. As already noted for most topics commented so far, new evidence is required to prove the impact of the intervention on clinical endpoints. The KDIGO guidelines do not recommend specific values for the daily phosphorus intake. On the other hand, the North-American guidelines recommend a daily phosphorus intake of 800 mg, while the Brazilian guidelines recommend that value for patients on dialysis, and up to 700 mg daily for those with CKD stages 3-4.

**Dialysis removal of phosphorus in persistent hyperphosphatemia:**

An increase in dialysis removal of phosphorus is recommended in cases of persistent hyperphosphatemia.

KDIGO recommends, as previous guidelines do, that dialysis removal of phosphorus be incremented, although the best strategy is yet to be defined. One single study has compared a group of patients on conventional hemodialysis with patients on daily long nocturnal hemodialysis and observed, after six months, a better control of phosphorus and PTH, as well as a reduction in the need for phosphorus binders. This is the only evidence available. New studies are urgently required to define the impact of alternative dialysis regimens, such as short daily dialysis, for controlling serum phosphorus.

**Treatment of abnormal levels of PTH**

Patients with CKD frequently have abnormal serum levels of PTH related to bone diseases and increased cardiovascular mortality. Thus, adequate control of the serum levels of PTH, in the several degrees of kidney lesion, is fundamental to prevent such complications.

According to the KDOQI and Brazilian guidelines, the adequate level of PTH in patients with CKD in the pre-dialysis phase varies according to the degree of kidney failure, and should be maintained as follows: between 35 and 70 pg/mL, for CKD stage 3; between 70 and 110 pg/mL, for CKD stage 4; and between 150 and 300 pg/mL, for CKD stage 5. According to KDIGO, the adequate level of PTH for those patients remains undetermined. However, the guidelines suggest that it should be maintained up to the upper limit of the reference range of the method. The PTH elevation in those patients can correspond to a compensatory mechanism to maintain mineral homeostasis of calcium and phosphorus. However, the continuous and sustained elevation of that hormone leads to deleterious alterations, and, thus, should be corrected. The therapeutic approach of those patients should be initiated by controlling the serum levels of calcium and phosphorus, and by correcting vitamin D deficiency. Only after controlling those factors, treatment with calcitriol or vitamin D analogs should be indicated.
For patients on dialysis, the North-American and Brazilian guidelines recommend the maintenance of serum levels of PTH between 150 and 300 pg/mL. However, determining the ideal levels of PTH is still a challenge. Factors, such as the methodology for measuring PTH and the lack of correlation between bone histology and intermediate values of PTH, hinder the determination of ideal levels. Thus, KDIGO suggests that extreme values of PTH should be avoided, aiming at maintaining them between two and nine times the upper limit of the reference range of the method used. Longitudinal follow-up of the patient is fundamental for therapeutic approach. In face of a tendency of PTH levels to not follow the recommended range, immediate measures should be adopted to return to the suggested levels. This implies the use of calcitriol or vitamin D analogs and/or calcimimetics. It is reasonable that the selection of the first-choice drug for treating secondary hyperparathyroidism depends on the serum levels of calcium and phosphorus. Patients who develop hypercalcemia and/or hyperphosphatemia should avoid the use of calcitriol or vitamin D analogs. Those already using those drugs should have their doses reduced. On the other hand, those with hypocalcemia should interrupt the use of calcimimetics depending on the severity of the condition, symptomatology, and concomitant medications. In individuals with a PTH reduction below two times the upper limit of the method, calcitriol, vitamin D analogs, and calcimimetics should be suspended or have their doses reduced. The use of phosphorus binders (with or without calcium) should be adjusted so as to not jeopardize the treatment with modifications in the serum levels of calcium and phosphorus. The lack of studies with appropriate methodology and showing favorable clinical endpoints with the use of a certain class of drug, prevent us from pointing to the best therapeutic alternative for controlling high levels of PTH. For patients not responding satisfactorily to clinical therapy, parathyroidectomy is indicated. The definition of refractory hyperparathyroidism is very difficult. Increasing levels of PTH are usually associated with a lower chance of response to clinical treatment. However, the exact level of PTH determining resistance to treatment is yet to be defined. Usually, the surgical techniques are equivalent, and have similar frequencies of hyperparathyroidism relapse and hypoparathyroidism development. However, candidates to kidney transplantation should not undergo total parathyroidectomy without autotransplantation.

**Diagnosis of Vascular Calcification**

For the KDIGO and Brazilian guidelines, the diagnosis of CKD-MBD includes the detection of extraossseous calcification. This is due to the fact that in patients with CKD, vascular calcification is premature, severe, prevalent, and accelerated when compared with that of the general population. The presence and severity of the calcification have been associated with a higher incidence of cardiovascular events and are strong predictors of morbidity and mortality. The association between the presence of calcification and mortality has been identified in nine of ten studies with patients with CKD, most of them on dialysis. The vascular calcification is an active process, highly regulated, occurring in two distinct sites, the tunica intima and tunica media, with different clinical presentation, treatment, and prognosis. The prevalence of calcification increases as kidney function decreases. The review by the KDIGO group has identified 25 studies reporting the prevalence of extraosseous calcification in approximately 4,000 patients, most of whom with CKD stage 5. Those studies have evidenced coronary calcification in 51% to 93% of the patients, valvular calcification in 20% to 47%, and, in other sites, the prevalence of calcification varied greatly, depending on the sensitivity of the method used. Progression of calcification was assessed in eight studies, most of which with patients with CKD stage 5, in periods ranging from one to three years, and with several methods. Those studies have concluded that the rate of progression in one year depends on the presence of previous vascular calcification. The following factors have been associated with the development and progression of calcification: clinical factors (age, male sex, diabetes, dialysis time, calcium intake); and biochemical factors (PTH, alkaline phosphatase, phosphorus, calcium x phosphorus product, C reactive protein). However, such findings have not been uniformly reproduced in the different studies assessed.

While the Brazilian guidelines recommend investigating the presence of vascular calcification in every patient with CKD and annual reassessment, the KDIGO group, non-unanimously, does not recommend indiscriminate investigation of calcification in all patients. That recommendation was based on inconsistencies regarding treatment indication due to a positive test, in addition to the existence of limited evidence about the impact of the interventions on mortality. However, the group agreed that knowing about the presence of vascular calcification and its
magnitude helps identifying patients at high risk. The presence of calcification should be considered a complementary component to be incorporated into the decision of CKD-MBD individualized treatment.

For KDIGO, the test recommended for the diagnosis of calcification is computed tomography, because it is a quantitative test, in addition to being the most sensitive. The Brazilian guidelines, however, recommend that vascular calcification can be investigated through quantitative (computed tomography) or semi-quantitative methods. However, the sensitivity and specificity of other methods used for identifying calcification are still controversial. Only one study evidenced that lateral radiography of the abdomen and Doppler echocardiography can be useful for assessing the presence of calcification, because of their reasonable sensitivity and specificity.

**OTHER OPTIONS FOR TREATING BONE DISEASE**

The presence of bone lesions is a common consequence of CKD, and patients with that pathology have an increased risk of fracture compared with that of the general population. Fracture risk relates to bone mineral density and bone quality, together with risk for falling and trauma, factors present in CKD. Contrary to that observed in the general population, analysis of bone mineral density does not predict fracture risk in patients with CKD-MBD, evidencing the importance of bone quality in such patients. In addition, the analysis of bone mineral density does not distinguish the different types of renal osteodystrophy. The studies assessing the medications for treating postmenopausal osteoporosis, such as risendronate, alendronate, teriparatide, and raloxifene, have excluded patients with increased levels of serum creatinine, PTH, and alkaline phosphatase. However, post-hoc analyses of those studies have identified, by use of the Cockcroft-Gault formula, that individuals with a moderate reduction in renal function (CKD stage 3) were included in the study and benefited from the treatment used for the general population. Nevertheless, no evidence-based study has assessed those therapies in CKD stages 3-5D. Finally, growth deficit is one of the cardinal features of progressive CKD in children, and is also one of the components of CKD-MBD. Based on that rationale, KDIGO has proposed that mineral bone density should not be routinely assessed in patients with CKD stages 3-5D. On the other hand, the North-American guidelines have proposed that bone mineral density should be assessed in every patient at risk for osteoporosis, without specifying the patients.

The Brazilian guidelines do not approach that topic. KDIGO has also recommended that, in patients with CKD stage 1-3, osteoporosis and/or high risk for fracture, in accordance with the WHO criteria, the treatment be similar to that of the general population. However, for patients with CKD stage 3, biochemical abnormalities of CKD-MBD, and low bone mineral density and/or pathological fractures, the choices of treatment should consider the magnitude and reversibility of the biochemical abnormalities, as well as CKD progression. Bone biopsy should be considered. For patients with CKD stages 4-5D, CKD-MBD biochemical abnormalities, and low bone mineral density and/or pathological fractures, further investigation with bone biopsy is recommended prior to initiating therapy with anti-osteoporotic agents, and systematic treatment is not recommended. For children and adolescents with CKD stages 2-5D and associated growth failure, treatment with recombinant growth hormone is recommended, and should be initiated after investigation and treatment of malnutrition and biochemical abnormalities of CKD-MBD.

**ASSESSMENT AND TREATMENT OF BONE DISEASE AFTER KIDNEY TRANSPLANTATION**

With the increase in number and survival of kidney-transplanted patients, new challenges for their treatment appear. Persistence of bone disease after transplantation is frequent, worsens the quality of life, and increases morbidity. Successful kidney transplantation usually corrects or improves CKD-MBD. However, several patients persist with bone alterations, which result from a complex interposition of different factors, such as the partial resolution of CKD-MBD, due to deficient graft function and the effect of immunosuppressive drugs. In the early period after kidney transplantation, a significant fluctuation of CKD-MBD biochemical markers occur, the most frequent alterations being hypophosphatemia, hypercalcemia, and a reduction in PTH. In the late period, normalization of the serum level of phosphorus occurs, and calcium and PTH tend to stabilize in the upper limits of normality. Calcitriol levels will depend on graft function. In addition to those factors, kidney transplanted individuals are also subjected to the same risk factors for bone mass loss, which is the development of osteoporosis, observed in the general population as follows: age; sex; race; hypogonadism; nutritional status; and physical activity. The major consequences of the decrease in bone mass are a greater risk for fractures and a greater incidence of cardiovascular
diseases, which, although being traditionally seen as distinct entities, have common physiopathological mechanisms. Most studies have shown a rapid and intense bone loss in the first 6 to 12 months after kidney transplantation, justifying the high prevalence of fractures in those patients. A normal bone mineral density in transplanted patients does not eliminate the risk for fracture, because alterations in bone integrity, not detected on densitometry, may occur. In that population, the correlation between bone mineral density and fracture risk has not been established. Bone histological abnormalities have been uniformly reported in the studies, but etiology and pathology are variable. Bone disease existing in the dialysis period tends to slowly resolve depending on the presence of good graft function, reduced doses of immunosuppressive drugs, and CKD-MBD resolution. There are no randomized, controlled trials assessing the impact of a certain therapeutic intervention on clinical endpoints, such as mortality, hospitalizations, bone fracture, and the need for parathyroidectomy in those patients. The use of calcium, vitamin D analogs, and bisphosphonates seems to improve bone mineral density of kidney-transplanted patients. However, studies using bone biopsy for that assessment are scarce. There is no clear definition of which patients could really benefit from those treatments. Thus, the therapeutic strategy for those patients cannot be generalized.

The Brazilian guidelines have not approached that topic, while the North-American guidelines were the first to admit that bone disorder is frequent after kidney transplantation. Thus, the North-American and KDIGO guidelines recommend frequent calcium and phosphorus measurements in the immediate period following kidney transplantation, until stabilization of their levels. After that immediate period, monitoring of calcium, phosphorus, and PTH is recommended, depending on the magnitude of the alterations and progression of CKD: the more advanced the CKD, the more frequent that monitoring should be. KDIGO has also suggested that calcidiol be measured in all transplanted patients, and both vitamin D deficiency and insufficiency be corrected. Regarding measuring bone mineral density, while the North-American guidelines suggest that the exam be performed in all patients undergoing kidney transplantation, KDIGO suggests that it be performed only in those receiving high doses of corticoids or having risk factors for osteoporosis. Treatment can include vitamin D, calcitriol or bisphosphonates, depending on the calcium, phosphorus, alkaline phosphatase, PTH, and calcidiol levels. KDIGO has also recommended bone biopsy whenever possible, prior to the use of bisphosphonates. In addition, bone densitometry should not be performed in transplanted individuals with CKD stages 4-5T, because that exam can predict neither fracture risk nor the bone disease type. The suggestion is that those patients be treated as patients with CKD stages 4-5 in conservative treatment, as it had already been recommended by the North-American guidelines.

RESEARCH RECOMMENDATIONS

Despite all the information contained in the KDIGO document, the work group emphasizes the need for high quality research in the field, because most recommendations are based on level 2 (weak) and grade C (low) evidence. The need for further studies in this field, as well as in nephrology as a whole, is evidenced when comparing high-quality scientific production between our specialty and other internal medicine specialties. From 1966 to 2002, nephrology produced 2,779 prospective, controlled and randomized clinical studies as compared with 27,109 in cardiology. On the other hand, considering the high incidence and prevalence of CKD worldwide, the scientific production in nephrology may increase. In Brazil, the prevalence of CKD increases every year, and currently 77,589 patients undergo dialysis. That significant population size indicates the possibility of performing high-quality clinical studies.

The research recommendations contained in KDIGO encompass mainly issues relating to clinical endpoints. Research that allow the following is required: risk stratification based on bone and mineral metabolism components; definition of the role of the sequential use of bone densitometry for predicting bone fractures; assessment of the ideal level of phosphorus and of the efficiency of phosphorus binders in CKD at different stages; impact on patient’s survival; impact of drugs, such as bisphosphonates, teriparatide, and raloxifene, on the risk of fractures and vascular calcification; and determining the role of vitamin D and analogs in the progression of CKD and mortality.

In conclusion, most current therapeutic decisions in CKD-MBD are based on scientific data with low evidence grade and on the opinion of specialists. The nephrological scientific community needs to change that reality through prospective, controlled, randomized studies with an adequate number of patients, follow-up longer than six months, and an adequate design for assessing clinical endpoints, such as mortality and CKD progression.
After exposing all topics, discussion with the forum participants was opened. They exposed their opinions regarding the KDIGO guidelines and their potential use by Brazilian nephrologists. The greatest concern of the participants was the non-adoption of the Brazilian guidelines by the Brazilian government authorities. The clinical protocols currently implemented by the federal government are unclear, leading to different interpretations by the different Health Secretariats of each state. Thus, the provision of drugs for the treatment of CKD varies throughout Brazil, and not all patients with CKD have access to adequate treatment.

In face of that concerning situation, the participants of the forum decided to send the letter below to the Health Ministry.

Finally, the participants also decided that a review of the Brazilian guidelines for CKD-MBD treatment is necessary, and suggested that the Brazilian Society of Nephrology organize a new work group for that purpose.

São Paulo, November 19th, 2009

To the Brazilian Society of Nephrology
Prof. Emmanuel A Burdmann, MD

Ref. Urgent change in the ordinance of the Health Ministry regarding care provided to patients with CKD

Dear Professor,

On November 14th, 2009, the National Forum for Discussing the KDIGO Guidelines for the CKD-MBD was held, with the support of the Brazilian Society of Nephrology. More than 60 nephrologists from all over the country attended.

On the occasion, all recently published KDIGO guidelines for chronic kidney disease-mineral and bone disorder were carefully discussed from the Brazilian perspective. The attendees concluded for the need of urgent changes in some topics of the ongoing ordinance of the Health Ministry regarding care provided to patients with CKD as follows:

1. Change the frequency of intact PTH measurement to every three months.
2. Measure 25-hydroxyvitamin D every 12 months.
3. Perform simple lateral radiography of the abdomen annually for patients still not diagnosed with vascular or valvular calcification.
4. Suspend the annual measurement of serum aluminum.
5. Institute Desferal test (2 measurements of serum aluminum + 1 ampoule of Desferal 500 mg), according to medical indication.
6. Provide non-calcium-containing binders for specific situations defined in the guidelines of the Brazilian Society of Nephrology (hypercalcemia; iPTH < 150 pg/mL in two consecutive measurements; Ca x P product > 55 mg²/dL²; presence of extraosseous calcification).
7. Determine that the manufacturer of the concentrated dialysis solution specify the aluminum concentration of the product.

Thank you for your attention,

National Discussion Forum of the KDIGO Guidelines for the CKD-MBD

Other participants of the National Forum:
REFERENCES

