Complications of CKD: Current State, Knowledge Gaps and Strategy for Action

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Abstract

Context: The International Society of Nephrology (ISN) has adopted a proactive approach to defining the current state of kidney care and the unmet needs through a multifaceted ‘Closing the Gaps’ initiative. As part of this initiative, the ISN convened a meeting of experts to develop an approach to tackling acute kidney injury (AKI) and chronic kidney disease (CKD). This manuscript expands on the recently published ISN CKD Roadmap and reports on the discussions of the Working Group assigned the task of reviewing the global impact of complication of chronic kidney disease. The Working Group defined the following goals:

Goal 1: Optimise the management of anaemia, endocrine and metabolic abnormalities associated with CKD. The impact of these conditions at a global level is not well understood, particularly in regions where renal replacement therapy is not readily available. Some treatment regimens may be affordable in low to middle income countries (LMICs) and if implemented, could have an impact on the burden of suffering associated with CKD.

Goal 2: Improve prevention and management of cardiovascular complications linked to CKD. Most research into cardiovascular complications of CKD has focused on atherosclerotic disease (myocardial infarction, ischaemic stroke and peripheral gangrene). There has been growing recognition that other forms of cardiovascular disease (CVD) such as heart failure, valvular disease and arrhythmias, have a major

impact on patient outcomes. Much less in known about the mechanisms and treatment of these “non-atherosclerotic” complications.

Goal 3: Improve the diagnosis and management of symptoms associated with CKD.

Symptom management is one of the greatest challenges in the management of CKD with limited knowledge about the mechanisms associated with the development of these common problems, and how best to characterise them into usable clinical phenotypes.

Conclusions: Improved understanding of the complications of CKD may alleviate suffering and may prolong life among the millions of people worldwide both in developed countries and in regions where renal replacement therapy is not widely available.

Key words: CKD, complications, mechanisms, management, knowledge gaps

Introduction

Chronic kidney disease (CKD) is associated with several adverse clinical outcomes such as cardiovascular events, kidney failure requiring renal replacement therapy (RRT), mortality, and for survivors, poor quality of life in general.[1-6] Kidney disease amplifies the enormous burden and the population health impact associated with both communicable and non-communicable diseases (NCDs)[6,7].

CKD has not been included in the major chronic disease control strategies at international, regional and/or national levels. The progressive nature of CKD, the associated cardiovascular morbidity and mortality, and the ensuing end-stage kidney disease (ESKD) place a considerable burden on global healthcare resources[6-8]. A better understanding of the nature of the complications associated with CKD could help to optimise diagnosis, prevention and management.

The International Society of Nephrology (ISN) 'Closing the Gaps' initiative has been set up to define the global needs and current state of kidney care building on some of the AKI initiatives (0by25; www.theisn.org) and focussing on CKD. The goal is to create a 'blueprint' to enhance optimal care globally, through research, education and advocacy. As part of this initiative, the ISN convened the first Global Kidney Health Summit, July 26-28, 2016 in Vancouver, Canada. This article expands on the recently published ISN CKD Roadmap,[9] which is the output from the Summit.

CKD-related complications: Current state

Progressive CKD is linked to several complications with higher prevalence and intensity at lower levels of kidney function and which interact with each other[8,10-11] **(Table 1, Figure 1 & 2)**. These complications contribute to high morbidity, mortality and poor quality of life. Some of these complications can be readily defined and quantified (cardiovascular disease, hypertension, anaemia, mineral bone disorder, volume overload, electrolytes and acid-base abnormalities) and may require a specific management approach, for example the prescription of erythropoiesis stimulating agents to correct anaemia. Other complications are less well defined and may be manifest as the complex symptoms often associated with advanced CKD which have a less distinct pathogenesis such as anorexia, fatigue, cachexia, pruritus, nausea and sexual dysfunction. The work group identified the following complications of CKD as being relevant to the global burden of poor health caused by CKD:

1. ***Hypertension:*** Hypertension remains one of the most damaging complications of CKD and is thought to contribute both to acceleration of progressive decline in kidney function and to CVD and related mortality. Both detection and control of high blood pressure is frequently suboptimal and improvements could directly help patients.[12] The Systolic Blood Pressure Intervention Trial (SPRINT) provided important information about the effects of more stringent lowering of systolic blood pressure to a target of <120 mmHg that may be relevant to CKD patients although this trial excluded high risk subjects with CKD and proteinuria or diabetes.[13] Lifestyle modifications such as weight loss and dietary salt restriction may also improve

blood pressure control. Such interventions can be lower in cost than pharmacological therapy, and have the potential to impact on outcomes such as heart failure and stroke in both developed healthcare systems and low and middle income countries (LMICs). Since many anti-hypertensive agents are available and affordable in LMICs, one feasible goal would be to improve control of high blood pressure complicating CKD aiming to achieve target ranges in a proportion of patients. Such a goal could be attainable globally and the impact easily measurable.

2. ***Cardiovascular complications:*** Cardiovascular diseases represents the leading cause of mortality in patients with CKD and the prevalence and burden of these complications increases with declining kidney function **(Figure 1 & 2)**.[8,14] For example, the risk of mortality from cardiovascular disease is 8.1-fold greater in a patient with CKD stage G5 A3 (eGFR <15 ml/min/1.73msq, urinary albumin:creatinine ratio > 300 mg/g) when compared to a to a reference population without kidney disease.[4] While the risk of conventional atherosclerotic cardiovascular events increases with CKD, the majority of the increase in risk is attributable to "non-atherosclerotic" pathologies such as left ventricular hypertrophy with diastolic and systolic dysfunction, valvular disease and arterial calcification. These pathologies may manifest as atrial and ventricular dysrhythmias, heart failure and sudden death.[15] While it is generally accepted that treatment of traditional cardiovascular risk factors such as cholesterol[16] and blood pressure[17] is efficacious in the CKD population, particularly in patients with stages 1-3 CKD, there are additional risk factors to consider in CKD patients, most of which are considered to be CKD complications. For

example, mineral and endocrine disturbances that characterise the CKD-mineral bone disorder, such as phosphate retention, elevated levels of fibroblast growth factor 23 and disturbances in Klotho metabolism may contribute to cardiomyopathy and vasculopathy.[18] Improvements in our understanding of the factors that contribute to CKD-associated cardiovascular disease and identification of additional therapeutic targets, along with efforts to control blood pressure and increase prescription of lipid-lowering therapies, could ultimately lead a global reduction in the burden of cardiovascular disease attributable to CKD.[19]

3. ***Anaemia:*** Anaemia complicating CKD has been well characterised and is treated in many parts of the world with iron and erythropoiesis-stimulating agents (ESAs). However, the optimal doses of ESAs, and indications and dosage of parenteral iron are not established. While ESAs can provide symptomatic relief, the impact of these medications on survival remains unclear[20] and may increase cardiovascular and cancer risks. The full spectrum of side effects of ESA are not known nor has the role of high hepcidin in CKD been adequately studied.[21] There may be regional differences in resistance to ESA therapy, which renders patient more susceptible to the harmful effects of these high cost agents.[22] The current management of anaemia of CKD in many LMICs where ESAs are variably available and prohibitively expensive is different from developed countries where these agents are widely available. While we still need to learn more about the risks and benefits of ESAs and intravenous iron, efforts to make these therapies (and blood transfusions) more

readily accessible in LMICs may help to reduce the symptom burden associated with anaemia complicating CKD.

4. ***CKD-related mineral bone disorder:*** The syndrome of chronic kidney disease-mineral and bone disorder (CKD-MBD) was defined by KDIGO[23-25] and encompasses traditional mineral biochemical abnormalities, the spectrum of renal osteodystrophy, and soft tissue calcification. Left ventricular hypertrophy may be causally linked to these abnormalities. This complex group of disorders are poorly understood and despite a considerable body of preclinical data, very few developments have been translated to clinical applications.[10] High blood phosphate levels, deficiency of vitamin D and secondary hyperparathyroidism can be monitored and treated although the true benefits of interventions to correct these abnormalities are unproven. The role of low cost calcium-based phosphate binders is controversial because of the potential for these agents to exacerbate tissue calcium deposition.[26,27] A pragmatic approach based on our current level of knowledge would be to increase availability of phosphate binders, nutritional vitamin D and analogues of 1,25 dihydroxy vitamin D to alleviate the recognised symptoms that result from tertiary hyperparathyroidism.

5. ***Salt and water retention****:* In CKD stages 4-5 and possibly in stage 3 there is loss of defense against both sodium excess and sodium depletion. In clinical practice, sodium excess with fluid retention is by far the more common, although the exact prevalence has not been determined. While extracellular fluid volume may be expanded, sodium balance appears to be relatively well maintained until ESRD.[28]

Excess sodium and fluid not only contribute to oedema, which may negatively impact on quality of life, but also to hypertension and thereby to cardiovascular disease, (specifically concentric left ventricular hypertrophy which can result in diastolic dysfunction). The mainstay of therapy is adherence to simple fluid balance ("intake vs output") concepts, restriction of dietary salt intake and use of natriuretic agents (which may be less effective in the more advanced stages of CKD). Thiazides and loop diuretics are widely available at low cost and could be used more widely to alleviate symptomatic oedema in CKD patients with the potential to improve cardiovascular outcomes.

6. ***Metabolic acidosis and electrolytes disorders:*** Metabolic acidosis is common in CKD and is caused when acid intake and generation exceed renal acid excretion. In the early stages, it may be manifest as "acid excess with normal bicarbonate" a state of positive acid balance without low plasma bicarbonate due to buffering and renal adaptation.[29] Alkali therapy is effective but limited by the mandatory sodium and/or potassium loads. Chronic metabolic acidosis contributes to skeletal muscle catabolism, insensitivity to endocrine hormones and bone disease[30] and may accelerate progression of CKD.[31] The challenge is early detection which requires identification of potentially harmful acid loading before a fall in serum bicarbonate occurs. Treatment of metabolic acidosis could be implemented on a global basis since the therapies are inexpensive, but the benefits of such intervention are unproven and the sodium or potassium loading that accompanies current alkali therapy may be harmful, particularly in more advanced stages of CKD. Alternative

ways of alkali delivery are needed. Non-sodium and potassium containing alkali are under development but availability and affordability, particularly to LMIC, are likely to be problematic. At the present time, more widespread use of sodium bicarbonate to treat symptomatic metabolic acidosis in advanced CKD seems appropriate in an effort to alleviate suffering.

7. ***Uremic symptoms:*** The syndrome of “uremia” encompasses a variety of symptoms including anorexia, fatigue, cachexia, pruritus, nausea, restless leg syndrome, sleep disturbances, and sexual dysfunction.[32] Pruritus is common and can adversely impact on quality of life. The causes are poorly understood but are likely to include the accumulation of specific “uremic toxins” in the skin. Distinguishing “uremic itching” from itching caused by other conditions is important as management may be different. Topical therapy and antihistamines are accessible to LMIC. Other agents such as gabapentin and opioid receptor modulators are likely to be of more limited availabity.[33] The treatment of hyperparathyroidism and hyperphosphatemia may be effective in relieving pruritus in at least some patients. Restless leg syndrome is a related clinical diagnosis that can be debilitating.[23] Although this problem is recognised in individuals with normal kidney function, it is much more prevalence in CKD and dialysis patients. Both pruritus and restless leg syndrome are associated with sleep disturbance, depression, poor quality of life, higher cardiovascular morbidity and higher mortality. The pathophysiology is unknown but may reflect a state of general poor health. The symptoms of restless leg syndrome can be relieved by exercise as well as by several pharmacologic agents including gabapentin,

dopaminergic modulators, serotonin antidepressants, and lithium. Although data on efficacy of these interventions is limited they are accessible in many LMICs.

Knowledge gaps

Research into CKD complications over the last few decades has been largely focused on the management of endocrinological abnormalities (anaemia and secondary hyperparathyroidism). Despite this effort there have been few clinical advances proven to improve clinical outcomes. This calls for more efforts to improve our understanding of the mechanisms by which these abnormalities impact on patient-related outcomes, the clinical implications of the complications and the development of more effective treatment strategies **(Panel 1)**.

The limitations in our knowledge reflect the variety and complexity of the underlying pathophysiology processes that lead to CKD complications and the heterogeneity in their presentation. This is reflected in the limited therapeutic options available. Unfortunately, the “uremic symptoms” described above, which matter most to patients are the most poorly understood of all CKD complications.[32]

Of the other CKD complications, cardiovascular disease is the perhaps the most important because of the potential to limit length and quality of life. However, as discussed above, the pathogenetic mechanisms may be somewhat different in CKD as compared to the general population, with pathways that are complex involve and may involve other CKD-related complications. While the pathophysiology of cardiovascular

disease remains incompletely understood, it will be challenging to develop effective treatment strategies with a high degree of specificity.

The work group defined the following specific goals to focus future efforts to alleviate morbidity and mortality resulting from CKD complications at a global level.

Goal 1: Optimise the management of anaemia and other endocrine abnormalities associated with CKD. Clinical practice guidelines such as those developed by Kidney Disease: Improving Global Outcomes (KDIGO) provide recommendations on the approach to the management of these common complications associated with CKD.[24,25] The clinical consequences of these complications in LMICs, particularly in regions where renal replacement therapy programmes are not available, needs to be defined. Dissemination and implementation of KDIGO guidelines in LMICs has been limited and could be improved.[34]

To achieve this goal and close these gaps the following activities were suggested:

Activity 1: Promote research into understanding the links between laboratory abnormalities (low hemoglobin, mineral disorders such as calcium and phosphate and elevated PTH) and clinically relevant outcomes (CVD outcomes, progression of CKD, and uremic symptoms.

Activity 2: Promote consistent assessment and documentation of laboratory abnormalities in CKD populations as recommended in KDIGO guidelines in both developing and developed nations of the world.

Activity 3: Promote research and education into region-specific causes of abnormalities in CKD patients. Most publications focussed on the management of laboratory abnormalities in CKD populations are based on studies conducted in developed countries.[11,35-37] However, it is likely that the underlying causes of these abnormalities differ by health system characteristics and are influenced by socio-cultural factors. For example, in LMICs, parasitic infection or nutritional deficiency may be more common causes of anemia than erythropoietin deficiency and are not appropriately treated with ESAs.

Activity 4: Promote availability of affordable point-of-care measurement devices and treatments for endocrine, abnormalities. The key challenge is the lack of adequate laboratory capacity and/or trained workforce to measure the common biochemical abnormalities (e.g. PTH) due to issues with cost and available of reagents. Effort should be targeted towards development affordable point-of-care testing instruments for these common laboratory abnormalities. Point-of-care devices with acceptable performance at affordable prices should be a high priority for future research and perhaps public-private partnerships. Data from a variety of settings that document the current availability of affordable assays (or lack thereof) would help to make the

case that these innovations are worthwhile, and should be included in future global CKD surveys.

Goal 2: Improve prevention and management of cardiovascular complications linked to CKD. Most cardiovascular research in CKD has focused on atherosclerotic disease. Non-atherosclerotic diseases that may, for example, lead to heart failure and sudden death through arrhythmia have been less well studied. Understanding regional variations in CVD phenotype among CKD populations may offer new insights into how outcomes can be improved. In addition, much remains to be learned about fundamental aspects of cardiovascular risk reduction in CKD populations (e.g., optimal target blood pressure or benefits of aspirin in dialysis patients). Finally, continued work is needed to develop novel therapies for CKD-related cardiovascular disease.

Activity 1: Develop an integrated research program to better understand non-traditional cardiovascular risk factors and impact on patients' outcomes in terms mechanism, treatment and prognosis. The current approach to CVD management largely involves extrapolation of evidence from the general population. There is an pressing need for focused research programs that evaluate the benefits of standard treatment approaches (e.g., ARB for heart failure, implantable defibrillators to prevent sudden cardiac death) in CKD populations, as well as investigate novel interventions that might reduce the risk of cardiovascular events in people with kidney disease (e.g., intradialytic potassium profiling).

Activity 2: Improve understanding of global variation in cardiovascular diseases associated with CKD. The phenotype of cardiovascular diseases in people with CKD exhibits potentially important regional variation. For example, Japanese haemodialysis patients appear to have a lower risk of sudden death than those in other countries. Whether this is due to patient characteristics, environmental factors or treatment practices is unknown. If this observation is confirmed, further study of between-country variations in risk and outcomes might lead to new insights into pathophysiology or optimal management. Careful observational studies that use common definitions to compare the epidemiology of these conditions across countries should be a high priority. There is also paucity of data from LMICs on cardiovascular disease outcomes in patients with CKD, and there are pertinent geographic and racial characteristics that define these disorders in the populations from those countries.

Activity 3: Determine barriers to dissemination and implementation of existing guidelines on dyslipidemia and hypertension management to reduce cardiovascular risk in CKD, and implement strategies to overcome those barriers. Although new research is certainly needed, knowledge translation (rather than knowledge generation) should be the key priority in other areas. For instance, there is little controversy about the merits of controlling blood pressure, blood sugar and dyslipidemia in people with less advanced CKD, yet many people worldwide do not have access to these treatments. Knowledge transfer and advocacy efforts should focus on the implementation of global guidelines in CKD populations, especially in LMIC.

Activity 4: Develop new therapeutic approaches to reduce cardiovascular disease risk in CKD patients. In addition to a high burden of traditional risk factors, cardiovascular disease in CKD appears to also be driven by novel (CKD-specific) risk factors. For example, abnormalities in phosphate, fibroblast growth factor 23 and Klotho all appear to contribute to cardiovascular in CKD populations. Continued work is needed to translate discoveries from biomedical science into novel therapies that address these risk factors and mitigate the burden of CVD.

Activity 5: Promote further research into optimal therapeutic targets for cardiovascular risk factor management (e.g., blood pressure control) and how best to achieve them. Key knowledge gaps exist in fundamental aspects of cardiovascular management and prevention in CKD populations, especially in dialysis patients. Clinical trials are needed to examine the risks and benefits of treatments like aspirin, renin/angiotensin system interruption and spironolactone in patients with advanced kidney disease and kidney failure. Since these trials are unlikely to be funded by industry partners, their success likely depends on cooperation between public research funders from different countries.

Goal 3: Improve the diagnosis and management of symptoms associated with CKD.

These present the greatest challenge in the management of CKD related complications stemming from limited knowledge about the mechanisms associated with the

development of these common problems and how best to characterise them into usable clinical phenotypes. The Nephrology research community should focus on understanding these common but often neglected complications that may matter most to CKD patients.

Activity 1: Develop a taxonomy of symptoms (clinical phenotypes) associated with CKD and their impact on quality of life and functional status. The clinical and epidemiologic characteristics associated with the presence, severity, onset, and remission of CKD-related symptoms are poorly described. How symptoms (individually and collectively) impact on quality of life and other patient-important outcomes such as employability and functional status has not been completely studied. In addition, the relative importance of each symptom to the total symptom burden is not quantified. This information is required to characterize the impact of symptoms on patient well-being (thus building the case for action) and to identify the symptoms and patient populations that should be the highest priority for immediate study.

Activity 2: Enhance understanding of the pathophysiology and mechanistic pathways of the key symptoms to guide diagnostic, prognostic and therapeutic decisions. Because the mechanisms underlying uremic symptoms are poorly understood, no specific treatments are available. Multidisciplinary research efforts should capitalize on new technologies such as metabolomics and proteomics to link uremic toxins with symptoms and to identify the pathophysiology that causes or exacerbates symptom burden. Consideration should be given to study of potentially

related symptoms (e.g., pain and pruritus, which have similar neurobiology). Collaboration of scientists from multiple disciplines, communication with patients and communication with industry partners may help to ensure maximum potential for clinical impact and facilitate commercialization.

Activity 3: Building and enhancing effective symptoms management strategies. Regulatory authorities have approved few if any drugs for the treatment of uremic symptoms and there often is very little evidence to support off-label use of therapies although this is common. Summarizing what is known about available therapies and evaluating the best candidates in well-designed clinical trials should be a high priority. This could include therapies for similar symptoms associated with other conditions (e.g., chemotherapy-associated nausea) as well as therapies targeted at uremic-specific conditions (e.g., phototherapy for pruritus). Depending on the findings of Activity 2, new candidate treatments could undergo clinical trials.

Conclusion

Progressive CKD is linked to several complications with higher frequency and greater severity in the advancing stages of the disease. These complications lead to high morbidity, mortality and poor quality of life. We have outlined three key goals (underpinning a set of activities) targeted at reducing the population health impact of CKD-related complications. Although there has been considerable progress in defining CKD-related complications across regions and countries, significant gaps in knowledge still exist and optimal ways to specifically close these gaps remained undefined. This is

the first attempt to develop a blueprint for a concerted approach to better understand these disorders. This involves improving our understanding of the spectrum of pathophysiology and mechanistic pathways, clinical presentations and phenotypes, as well as the development of practice and policy guidelines to guide optimal care. Under this ISN initiative, we have developed an action plan to enhance our understanding of which uremic symptoms impact most on quality of life in CKD, the cause of these symptoms and the best management strategies to alleviate them.

We endeavoured to identify the CKD-related complications with the greatest impact on population and/or individual patient survival and quality of life. We identified seven systemic complications of CKD, how they evolve and interact with each other in the whole CKD spectrum **(Table 1, Figure 1 & 2)**. We then defined the current state of knowledge and existing gaps and developed a set of goals, with activities and deliverables relevant to each goal. We also defined potential threats and opportunities towards achieving such goals **(Panel 1)**. We deliberately focused on three key goals that have immediate deliverables and potential for impact at the global level.

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Table 1. Systematic complications of CKD and cross-links

System	Common manifestations	Cardiovascular	Endo/metabolic	Gastrointestinal	Hematologic	Neurologic	Muscuskeletal	Intergument
Cardiovascular	Atherosclerosis, HTN, cardiomyopathy		X		X	X		
Endo/metabolic	Menstrual disorders, sexual dysfunction, infertility, pregnancy disorders, electrolytes, and MBD	X		X	X	X		X
Gastrointestinal	Anorexia, nausea, emesis, weight loss		X					
Hematologic	Anaemia, platelets disorders, coagulopathy, low cell count and infection risk	X		X				X
Neurologic	Neuropathy, seizures (with severe uremia), strokes	X	X					X
Musculoskeletal	MBD, fractures, myopathy	x	x			x		x
Intergument	Dry skin, dermatitis, pruritus		X		X	X		
Complex symptoms*	Fatigue, insomnia, impotence, cachexia	X	X	X	X	X		X

X denotes crosslink across systems, e.g. MBD contributing to cardiovascular, anaemia contributing to cardiovascular, and interplay of all systemic features causing complex symptoms phenotypes. HTN =hypertension. MBD=mineral bone disorder.

Panel 1. Action plan towards reducing the global impact of CKD-related complications[9]

Goal and related activities	Opportunities	Threats
Goal 1: Optimize the management of anaemia, endocrine and metabolic abnormalities associated with CKD • Activity 1: Promote research to understand links between laboratory abnormalities (low hemoglobin, mineral disorders such as calcium and phosphate and elevated PTH) and clinically outcomes. • Activity 2: Promote consistent assessment and documentation of laboratory abnormalities in CKD populations per KDIGO guidelines in both developing and developed nations of the world. • Activity 3: Promote research and education into region-specific causes of abnormalities in CKD patients. • Activity 4: Promote availability of affordable point-of-care measurement devices.	Availability of globally accepted KDIGO guidelines. International collaborative networks of clinicians and researchers. International advocacy support such as the ISN, and other regional and national nephrology associations. Patient advocacy groups and kidney foundations Willing and supportive industry partners	Lack of proven efficacy of the current management arsenals (e.g. Erythropoietin, vitamin D) to impact positively on patient outcomes beyond changes in laboratory metrics. Limited access and affordability issues of the available medications in the developing nations. Limited and unavailable diagnostic tools across all settings. Language barriers in guidelines disseminations (though KDIGO making significant efforts to eliminate this barrier but remains a challenge due to multiplicity of languages across countries)
Goal 2: Improve prevention and management of CVD-related complications linked to CKD • Activity 1: Integrated research program to better understand non-traditional CVD risk factors and impact on patients' outcomes. • Activity 2: Improve understanding of global variation in CVD in CKD population. • Activity 3: Determine	As above CVD recognition as the most common adverse endpoint in CKD	As above Very limited evidence as care approach remains an extrapolation based on studies in general population

barriers to dissemination and implementation of existing guidelines on CVD management. • Activity 4: Develop new therapeutic approaches to reduce CVD risk in CKD patients. • Activity 5: Promote further research into optimal therapeutic targets for CV risk factor management.		
Goal 3: Improve the diagnosis and management of symptoms associated with CKD • Activity 1: Develop a taxonomy of symptoms (clinical phenotypes) associated with CKD and their impact on quality of life and functional status. • Activity 2: Enhance understanding of the pathophysiology and mechanistic pathways of the key symptoms to guide diagnostic, prognostic and therapeutic decisions. • Activity 3: Building and enhancing effective symptoms management strategies	Growing interests in the nephrology community to focus research in this area. Important area of patients' priority with increasing attention that gives voice to both researchers and their funders to develop interest in this area.	Lack of standard taxonomy to define disorders. Significant heterogeneity in manifestation of these disorders. Limited fundamental knowledge of the disorders in terms of pathophysiologic mechanisms. Change management from what the practitioners and researchers are accustomed to.

CKD=chronic kidney disease. CVD= Cardiovascular disease. KDIGO=Kidney Disease Improving Global Outcomes. PTH=parathyroid hormone

Figure 1. Progressive CKD and related complications by disease stage

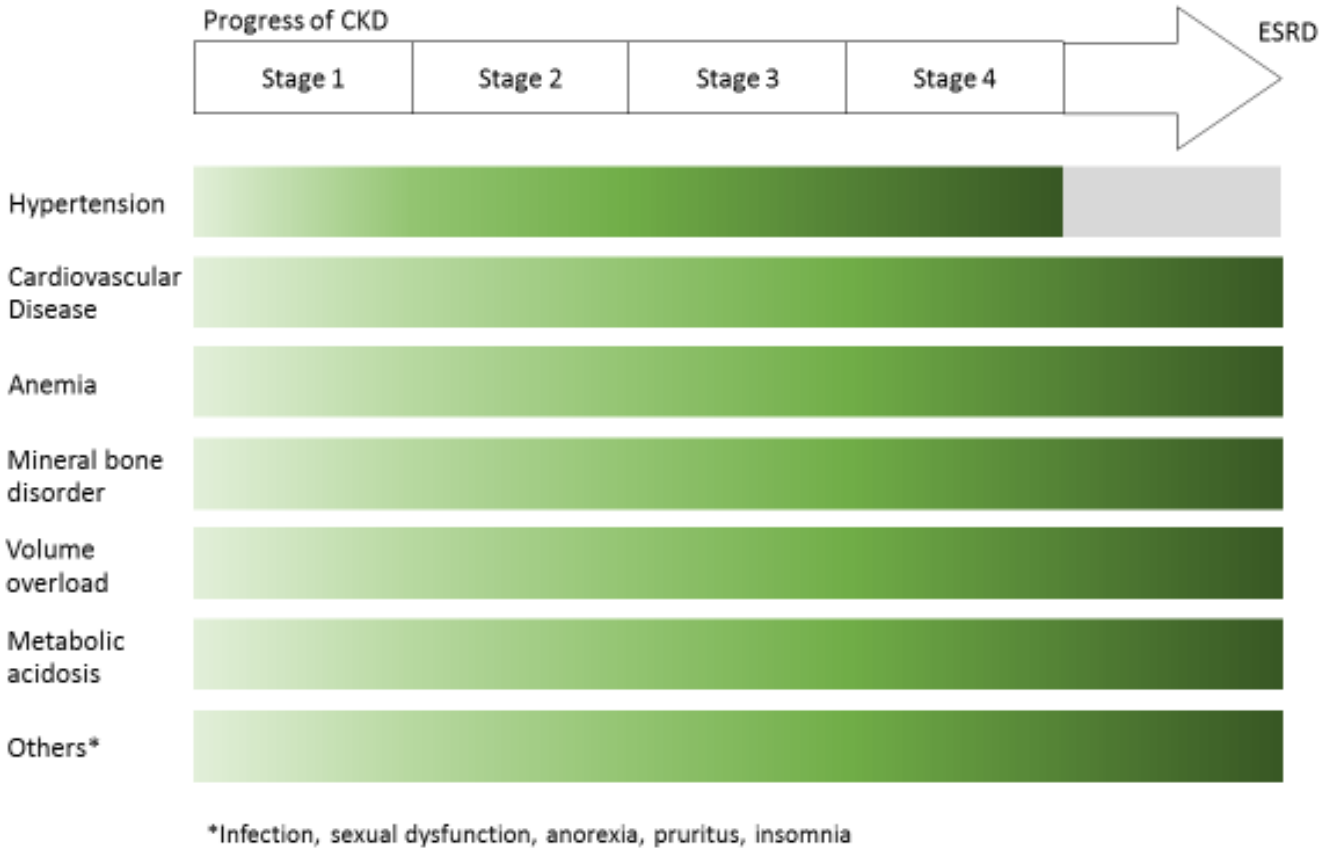
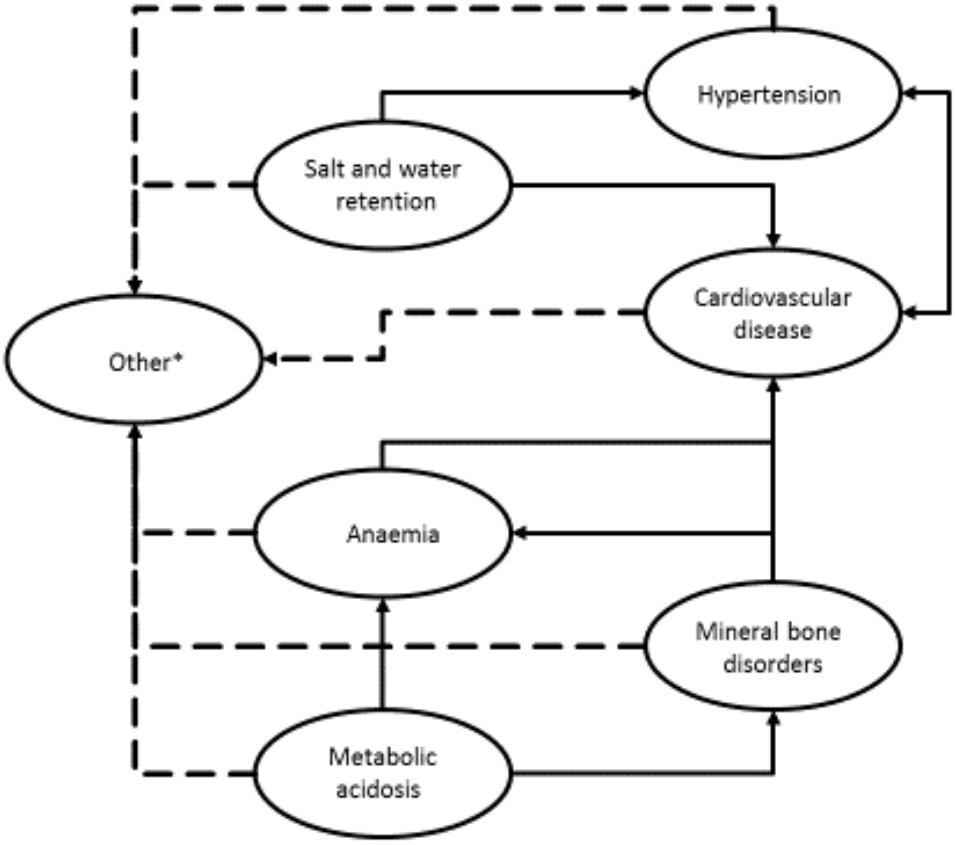


Figure 2. CKD-related complications: Cross-links and interactions



*Infection, sexual dysfunction, anorexia, pruritus, insomnia