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CKJ REVIEW

The renal patient seen by non-renal physicians: the kidney embedded in the 'milieu intérieur'

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ABSTRACT

Chronic kidney disease is defined as a decrease in renal function or evidence of kidney injury for >3 months. This represents an oversimplification that may confuse physicians. Thus kidney function is equated to glomerular filtration rate, which represents one of multiple kidney functions. Some potentially more important renal functions are lost earlier, such as the production for the anti-ageing factor Klotho. Overall, these changes modify the emergent properties of the body, altering the relationships between different organs and systems, in a manner that is difficult to predict the response to interventions based on normal physiology concepts, as there is a novel steady state of interorgan relations. In this regard we now discuss the impact of CKD on heart failure; osteomuscular and joint pain and bone fragility and fractures; and osteosarcopaenia as seen by a cardiologist, a rheumatologist and a geriatrician.

Keywords: bone fragility, chronic kidney disease, emergence, fracture, heart failure, network disease, osteosarcopaenia

INTRODUCTORY REMARKS: THE KIDNEY AT THE CENTRE OF THE BODY AS AN EMERGENT ENTITY

Physicians and researchers in the renal field are now used to reading in the introductory remarks of many papers dealing with different aspects of renal pathology and associated syndromes what has become the basic information about 'renal patients': (i) chronic kidney disease (CKD) has been defined as 'structural or functional abnormalities of the kidney observed at least two times separated by a 3-month elapsed time' [1]; (ii) the worldwide prevalence of CKD has been estimated with some variability at ~10% of the population [2] and (iii) CKD may evolve to end-stage renal disease (ESRD) requiring renal replacement therapy, with worrying medical consequences for the patients and financial burden for societies [2]. These features have prompted some authors to talk about CKD as an important epidemic with very high societal impact.

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From the renal physician standpoint, it is of interest that CKD patients present a wide range of complications involving many systems, behaving as a disease with multi-organ relationships and consequences. This causes the renal physician to continuously interact with other medical specialists and surgeons. Indeed, we know from the medical literature that CKD is a risk factor for pathology in almost every system: oncological diseases [3], haematology syndromes [4], cardiovascular diseases [5], rheumatological diseases [6] and infectious diseases, including acquired immune deficiency syndrome [7] and coronavirus disease 2019 (COVID-19) [8], among many others. However, we seldom pay attention to how non-renal physicians see the CKD patient. Some may feel fear in treating CKD patients, as they know that these patients have a worse prognosis, some may perceive renal diseases as a complicated medical field that they hesitate to get into in-depth and others may feel a mixture of these sensations. In the European Uraemic Toxin Work Group, we explored the vision of CKD by non-renal physicians following these multi-organ consequences of CKD, which brings us to place the kidneys and kidney diseases in the centre of the medical pathology, recovering the *milieu intérieur* concept proposed in 1855 by Claude Bernard [9]. We present in this article the perceptions of the CKD patient by a cardiologist, a rheumatologist and a geriatrician. However, before that, and based on all the above-mentioned information, we introduce the new vision of uraemic compounds as actors of dynamic and adaptive processes in renal diseases, which involve many different organs, very much in the sense of the *milieu intérieur*. As an extension of this new vision of uraemic compounds, the CKD state integrates the interrelation between different organs and the kidneys. The body, which is constituted of many different compounds, is an emergent element, as it appears with the programmed and physiologically regulated interactions between them. In this case, the concept of emergence implies that an entity (e.g. the body) is observed to have properties its parts do not have separately on their own (e.g. the chemical components of organic molecules or these molecules themselves) (https://en.wikipedia.org/wiki/Emergence). These properties or behaviours appear only when the parts interact in a wider whole. CKD is now viewed as a network disease that disrupts the equilibrium state of the organism viewed as an emergent entity of the body organs and systems. With the altered signalling and responses of the kidneys as well as of the different organs in the new situation of CKD, a new steady state may be reached by compensatory phenomena ensuring adaptation to survival. The interrelations between organs may no longer be perceived with the rules of physiology and sometimes correcting a given alteration linked to CKD may be detrimental for the emergent body, which is now regulated at the new steady state (Trial to Reduce Cardiovascular Events with Aranesp Therapy) [10]. The kidney is at the centre of the network in CKD, with new roles for the network members (Figure 1).

CKD BY THE CARDIOLOGIST: THE KIDNEY IN HEART FAILURE

There are multiple bilateral links between the kidney and cardiovascular disease. However, in day-to-day clinical practice, heart failure (HF) is probably the most common condition in which cardiologists are confronted by the complexity of CKD patients.

Neurohormonal activation in HF

Patients with HF due to systolic dysfunction present an early activation of the sympathetic system and the renin–angiotensin–aldosterone system (RAAS). Renin is an enzyme synthesized by specialized granular cells of the juxtaglomerular apparatus. It is released by the afferent arteriole in response to decreased arterial blood pressure, sensed by baroreceptor cells in the arteriolar vessel wall, and to sympathetic activation. Renin breaks down circulating angiotensinogen secreted by the liver, forming angiotensin I, which is subsequently converted into angiotensin II by endothelial cells, mainly from the pulmonary vasculature. Angiotensin II is the most potent stimulator of aldosterone release by the adrenal glands. This humoral system has been identified as a pivotal player in the pathophysiology of HF. Indeed, persistent and excessive RAAS activation causes

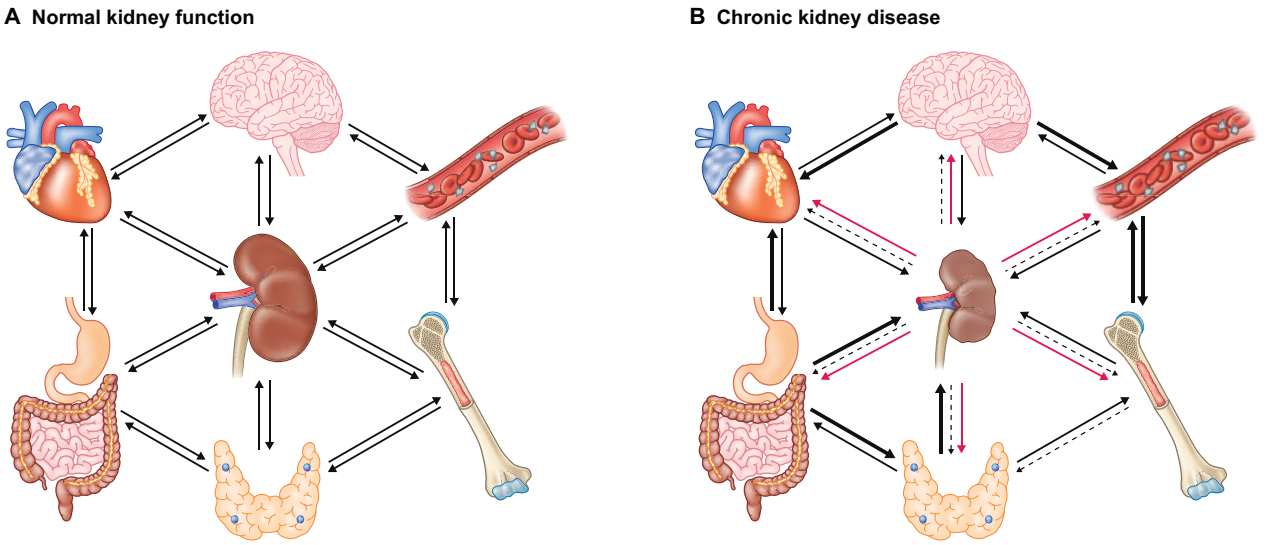

FIGURE 1: CKD as a network disease that disrupts the emergent properties of the body organs and systems. CKD alters the normal interactions between the kidney and different organs and systems, resulting in altered interactions between non-kidney organs. Normal signals emerging from the kidney may become fainter while novel pathological signals replace them. In the disrupted state, the results of any intervention cannot be accurately predicted by applying normal physiology concepts.

adverse cardiac remodelling and contributes to fluid retention with signs and symptoms of congestion. The final result of this neurohormonal activation is an increase in systemic vascular resistance (left ventricle afterload) and an increase in sodium and water retention (left ventricle preload). The increase in preload and, especially in afterload, causes worsening HF, with a decrease in stroke volume and cardiac output that will stimulate even more the neurohormonal activation, producing a vicious cycle.

The pharmacological treatment of HF is based on inhibition of the neurohormonal activation we just described. Therapy with β-blockers, angiotensin-converting enzyme inhibitors (ACEIs), angiotensin II receptor blockers (ARBs) and mineralocorticoid receptor antagonists has consistently demonstrated a significant reduction in mortality and in hospitalizations in HF patients [11]. More recently, the new ARB–neprilysin inhibitor combinations (e.g. sacubitril + valsartan), through inhibition of the enzyme that degrades natriuretic (and other vasoactive) peptides, neprilysin and ARB, have demonstrated an even more intense reduction in cardiovascular death and hospitalization for HF compared with ACEIs (enalapril) [12].

The effects of diuretics on mortality and morbidity have not been studied in patients with HF. However, they relieve dyspnoea and oedema and are recommended for this reason in patients with signs and symptoms of congestion [11]. Ultrafiltration has been proposed as an alternative to intravenous diuretics for patients hospitalized for acute decompensated HF [13]. However, the Cardiorenal Rescue Study [14] found no significant differences between both therapies in weight loss, mortality or rehospitalization.

The importance of renal dysfunction in HF

Renal impairment is common in patients with HF. In a comprehensive meta-analysis [15], 57 studies were reviewed including ~1 million HF patients. CKD was defined most often as an estimated glomerular filtration rate (eGFR) <60 mL/min/1.73 m^2. The overall prevalence of CKD was 32% in the total selected population. Patients with HF and CKD had a higher risk of all-cause mortality {odds ratio [OR] 2.34 [95% confidence interval (CI) 2.20–2.50], P = 0.001}.

Acute kidney injury (AKI), usually defined as >26.5 mmol/L (>0.3 mg/dL) increases in serum creatinine, independently increased mortality risk [OR 1.81 (95% CI 1.55–2.12), P = 0.001] and was observed in 23% of HF patients [15]. This definition is consistent with the Kidney Disease: Improving Global Outcomes (KDIGO) definition of AKI, which uses the same serum creatinine cut-off.

The main pathophysiological mechanisms explaining the relationship between HF and renal dysfunction are a decrease in renal blood flow and an increase in central and renal venous pressure [16]. The importance of venous congestion for AKI in decompensated HF was highlighted by Mullens *et al.* [17]. They identified central venous pressure on admission as the best haemodynamic predictor for the development of AKI.

Clinical significance of AKI in patients with acute HF

AKI in patients with acute HF is not always indicative of increased risk of death. Brisco *et al.* [18] found that an improvement in eGFR was associated with a markedly increased risk of the composite endpoint of death, HF hospitalization or emergency department visit. Breidthardt *et al.* [19] demonstrated that haemoconcentration, an easily assessable pathophysiological signal of adequate decongestion in acute HF, is associated with lower mortality, even in the presence of AKI. Thus AKI, when associated with decongestion, would no longer be a marker of worse prognosis [20].

EVIDENCE FOR THE USE OF HF THERAPY IN CKD PATIENTS

Most evidence-based therapies for HF patients show consistent outcome benefits in patients with moderate renal insufficiency (CKD Stage 3), whereas there are very scarce data on patients with severe (CKD Stages 4–5) renal insufficiency. However, the outcome benefit might be even greater in CKD Stage 3 compared with those with relatively preserved renal function [11].

Increase in serum creatinine levels after RAAS blockade initiation

The interaction between baseline and an early increase in serum creatinine levels and efficacy of RAAS blockade in patients with HF was analysed by Lesogor *et al.* [21] using data from the 5010 patients enrolled in the Valsartan Heart Failure Trial. The composite endpoint of cardiovascular death and HF hospitalization was significantly lower in patients receiving valsartan compared with placebo. In patients with aneGFR <60 mL/min/1.73 m^2 at baseline or early after valsartan initiation, the benefit of receiving valsartan was even greater than in patients with normal renal function [21]. The same effect was demonstrated for enalapril and spironolactone [22]. Actually, an early increase in serum creatinine levels after RAAS blockade initiation identifies a population of patients at higher risk of mortality and with more potential benefit from the therapy. Nevertheless, careful medical surveillance is warranted in these patients to avoid the risk of hyperkalaemia.

CKD and heart transplantation

Heart transplantation remains the best therapy for advanced HF. In this scenario, recipient creatinine has a nearly linear relationship with postoperative mortality, while recipient dialysis is one of the most important risk factors for 1-year mortality after heart transplantation [OR 1.57 (95% CI 1.21–2.04), P < 0.01] [23]. The best option for patients with end-stage heart and kidney disease is combined heart–kidney transplantation. This combined transplant has a survival of >50% at 10 years, non-different from the isolated heart transplantation [24].

CONCLUSION: CKD AND HF

The presence of CKD contributes to and increases the complexity of the management approach to HF. CKD facilitates the development of congestion, while AKI is common. AKI in patients with acute HF is not always indicative of increased risk of death, as it may be present following decongestion or initiation of RAS blockade. In any case, additional biomarkers are needed to improve the interpretation of AKI in daily clinical practice.

CKD AND ISCHAEMIC HEART DISEASE

Several large registries have demonstrated poor outcomes among patients with acute myocardial infarction (MI) and CKD.

In addition to greater comorbidities, lower use of guideline-recommended therapies has been postulated as a reason for worse outcomes among these patients.

Over the past decade, several interventional [primary percutaneous coronary intervention (PCI)] and medical (ticagrelor, prasugrel) strategies have demonstrated improvements in outcomes after MI; however, patients with renal dysfunction have typically been excluded from these studies. Thus the application of this evidence base to patients with renal disease, particularly those with ESRD treated with dialysis, may not be automatically extrapolated.

In a recent evaluation of in-hospital treatment and outcomes of MI patients in the USA [25], CKD remains highly prevalent, with ~25% of ST-elevation MI (STEMI) patients and 40% of non-STEMI patients having CKD. The use of ticagrelor or prasugrel and primary PCI in patients with CKD have increased over the past decade among STEMI patients; however, it still remains significantly lower compared with MI patients with preserved renal function.

CKD BY THE RHEUMATOLOGIST: CKD PATIENTS ACHE AND BREAK

In France, as in other countries in Europe, rheumatologists take care of patients with musculoskeletal disorders, whether they suffer from stiff joints, exhibit walking disabilities or have bone fragility with fractures. Therefore patients with CKD, especially those with advanced stages (CKD Stages 3b–5) may be managed by rheumatologists because the prevalence of these disorders is very high in this population. However, as illustrated in Figure 2, taking care of these patients remains a challenge for rheumatologists because their symptomatology is often complex, their multiple comorbidities are a hurdle for optimal treatments and recommendations are sometimes incomplete due to the lack of solid clinical trials.

Pain of musculoskeletal origin

By looking at a quick MEDLINE search using the key words 'haemodialysis/CKD/chronic renal failure' and 'pain', 'bone' or 'cardiovascular/vascular' (Figure 3) we can see that studying pain is not a research priority in CKD. However, pain is a major symptom that affects 20–70% of CKD patients [26, 27], with muscle cramps and bone/joint pain being most commonly reported. The interest in pain in CKD is illustrated by the 2017 re-edition of one of the most cited papers in *ckj* history on pain management in CKD [28]. The severity of pain increases with a decrease in GFR and is positively correlated with dialysis vintage [29]. Indeed, pain is felt to be inadequately treated by a majority of CKD patients and lasts for significantly longer periods when compared with non-CKD patients [30], resulting in poor quality of life [31, 32]. Therefore we need to pay attention to recurrent chronic pain in CKD patients. This necessitates promoting the collaboration of nurses, nephrologists and the committees fighting against pain ('CLUD' in France) and rheumatologists.

Musculoskeletal pain can come from joints, tendons/bursae/tendon sheaths, muscles or bone. The causes of musculoskeletal pain include peripheral neuropathy and arterial disease, but also osteoarthritis, periarticular calcifications, gout and joint involvement of some of the initial renal diseases such as lupus. In addition, in CKD Stage 5 haemodialysed patients, rapid changes in electrolyte content may cause recurrent pain during dialysis sessions [33].

THE ROLE OF THE RHEUMATOLOGIST

The rheumatologist aims at identifying the aetiology of pain to propose an adequate therapeutic strategy. The clinical evaluation includes a thorough anamnesis [assessing pain severity, history, time course, triggering factors, localization and type (neuropathic versus nociceptive), efficacy/tolerance of previous treatments, disability, walking distance, quality of life and psychological factors] and physical examination (including joint and bone palpation, joint amplitude evaluation, gait and limp analysis, followed by neurological examination). Difficulties

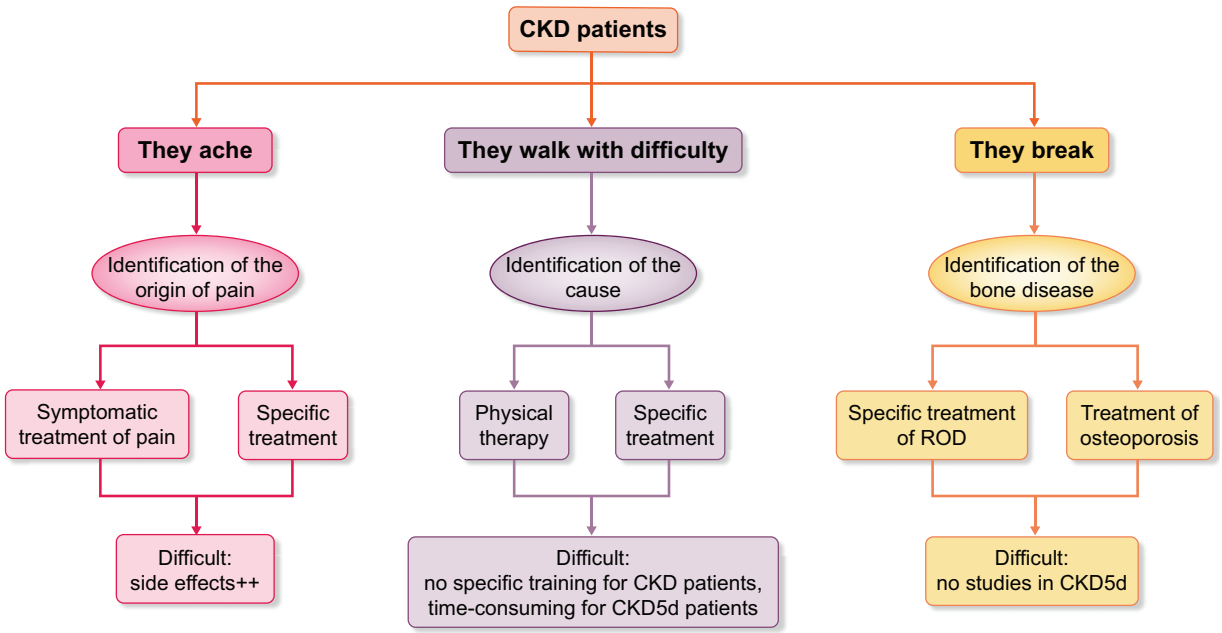

FIGURE 2: CKD patients ACHE and BREAK: the multiple challenges to manage diagnosis and treatment of pain in CKD patients (ROD).

often come with multiple comorbidities that may all generate pain: a haemodialysis patient with long vintage complaining of a reduction in walking distance may suffer from knee or hip joint disease, peripheral artery disease, spinal stenosis, destructive cervical spondyloarthropathy or dialysis-related amyloidosis and these disorders may be combined to various degrees in a single patient.

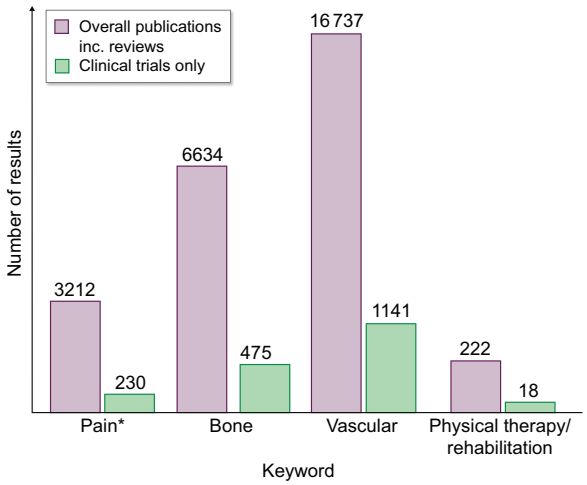

FIGURE 3: MEDLINE survey for evaluation and treatment of pain in CKD patients: key words 'haemodialysis/CKD/chronic renal failure' AND 'pain', 'bone' or 'cardio-vascular/vascular'. Dark grey bars: overall number of publications including reviews; light grey bars: number of clinical trials only.

Imaging is needed to confirm the clinical diagnosis when the localization of pain is established. Plain X-rays (Figure 4A–D) and technetium bone scan coupled to tomodensitometry or magnetic resonance imaging (MRI) allow a precise diagnosis (Figure 4E–H). However, false-negative results can be observed with delayed images or in case of very low bone turnover. Joint ultrasounds, although highly operator-dependent, are quick, cheap and as reliable as MRI to assess peripheral joint diseases or tendon disorders. They detect subchondral erosions and calcifications or crystals in joints and, when coupled with Doppler, allow estimation of inflammation severity. Pain treatment includes systemic and locally administrated pharmacological agents and physical therapy. Pharmacological treatment of pain in CKD is well summarized in Davison *et al.* [31].

Joint/tendon-related pain may be treated with local injections of glucocorticoids in the absence of contraindications (uncontrolled diabetes, recent infection and coagulation disorders). For CKD Stage 5d patients, the injection must be performed the day after dialysis. This procedure may be ultrasound- or tomodensitometry-guided to increase accuracy and thereby success. For instance, injecting the omo-humeral cavity to relieve a shoulder pain may be of low efficacy if the acromioclavicular joint is at the origin of the pain. Also, the risk of bacterial infection increased in CKD, especially in diabetics.

Joint pain and fractures result in immobilization and muscle wasting that worsen disability. Therefore, although physical therapy and rehabilitation are needed, they have not been frequently evaluated in CKD patients (see Figure 2, where only 222 studies were displayed with <16 clinical trials). The National Kidney Foundation Kidney Disease Outcomes Quality Initiative

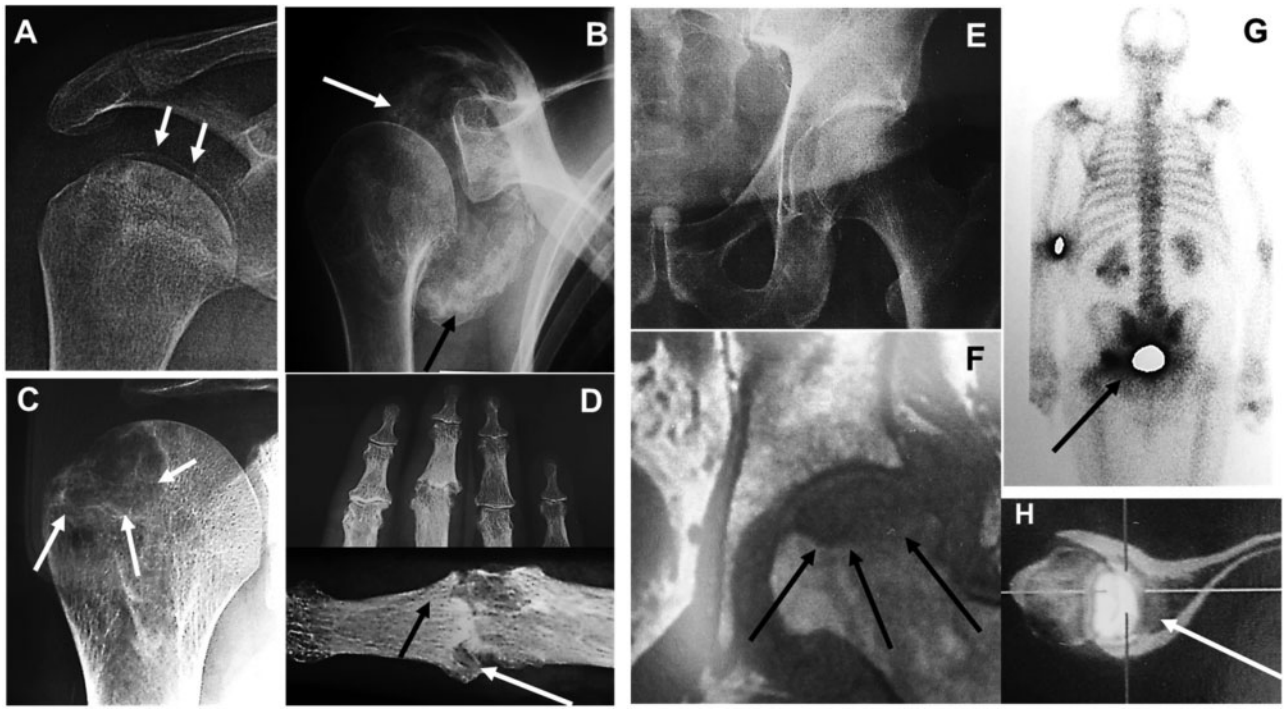

FIGURE 4: The use of imaging for the diagnosis of skeletal pain in CKD patients. (**A–D**) Plain X-rays. (A) Shoulder with osteonecrosis (ON) of the humerus head. (**B**) Periarticular calcifications of the shoulder. (**C**) Massive joint bone cysts observed in a patient with amyloidosis. (**D**) Digital severe joint erosions in a CKD patient with severe osteoarthritis combined with microcrystals arthritis. (**E–H**) Patient with ON of the hip 3 years after kidney transplant failure. (**E**) Plain X-ray: no sign of ON. (**F**) Coronal T1-weighted MRI of the hip showing the necrotic quadrant in the femoral head. (**G**) Technetium bone scan coupled to (H) tomodensitometryshowing high technetium uptake at the hip.

guidelines recommend that CKD Stage 5d patients 'should be counseled and regularly encouraged by nephrology and dialysis staff to increase their level of physical activity'. However, its implementation is difficult in CKD Stage 5d patients because of the renal replacement therapy time commitment and the lack of specific training for physiotherapists to treat CKD patients and thus has seldom been evaluated.

Recently Manfredini *et al.* [34] observed a 12% walking test improvement and better cognitive function scores and quality of social interaction in the exercise group in their randomized trial including 300 dialysis patients. Pre-dialysis exercise programmes [35] and neuromuscular electrical stimulation for patients with poorer physical conditions [36] could be proposed to dialysis patients.

MANAGEMENT OF BONE FRAGILITY

CKD severely affects calcium and phosphate metabolism and bone health. As renal function declines, vitamin D deficiency, increased fibroblast growth factor 23 levels, hyperphosphataemia, hypocalcaemia and secondary hyperparathyroidism develop together with an increased risk for fracture and vascular calcifications, which both have a pronounced impact on morbidity and mortality. The increased risk of fracture has been partly controlled by improving steroid use in CKD, dialysed and transplanted patients.

Risk fracture evaluation is particularly important in CKD patients (Figure 5). A meta-analysis gathering 13 cross-sectional studies including 1785 patients (Stages 3–5d) showed that bone mineral density (BMD) at the lumbar and femoral sites is significantly lower in patients with fracture [37]. CKD does not change the association of low BMD/fracture risk: 587 CKD patients (Stages 3a–b) had the same association level as 2167 normal renal function patients, both followed up for 11 years [38]. Similar conclusions were drawn in a prospective study related to dialysed patients [39]. Thus the latest KDIGO guidelines, in 2018, recommend the use of the highly specific dual-energy X-ray absorptiometry (DXA) in CKD patients [40] despite its low sensitivity.

The FRAX score, combining BMD and clinical data, was designed to improve fracture prediction. However, it performs no better than BMD alone in CKD patients [41], probably because CKD was not included as a risk factor. High-resolution peripheral computerized microtomography, which is able to measure BMD and structural parameters in both the trabecular and cortical compartments at the tibia and the wrist, has also been proposed to help predict fracture in the CKD population [42]. However, this device is not widely available.

Evaluation of the underlying renal osteodystrophy (ROD) (Figure 5), more recently termed CKD–mineral and bone disorder, is of the utmost importance. Evaluating bone turnover and mineralization is critical for the management of ROD, particularly when we consider giving an anti-osteoporotic drug to a CKD patient. Kinetics of intact parathyroid hormone along with bone alkaline phosphatase (BAP) must be evaluated. BAP remains the only marker used when GFR is <30 mL/min/1.73 m^2, as the others are influenced by GFR. BAP provides a rather reliable evaluation of bone turnover, however, it is increased in post-fracture modelling for several weeks and thus becomes useless at a time when it is critically needed [43]. Furthermore, BAP is a marker of bone formation also influenced by bone mineralization, making it less informative in mixed uraemic bone disease. Thus histomorphometric analysis of an anterior iliac crest biopsy remains the ultimate tool for the diagnosis of ROD.

'Bone biopsy' is still recommended by the KDIGO guidelines, but only when its results are used to determine the therapeutic strategy. This procedure had been gradually abandoned because

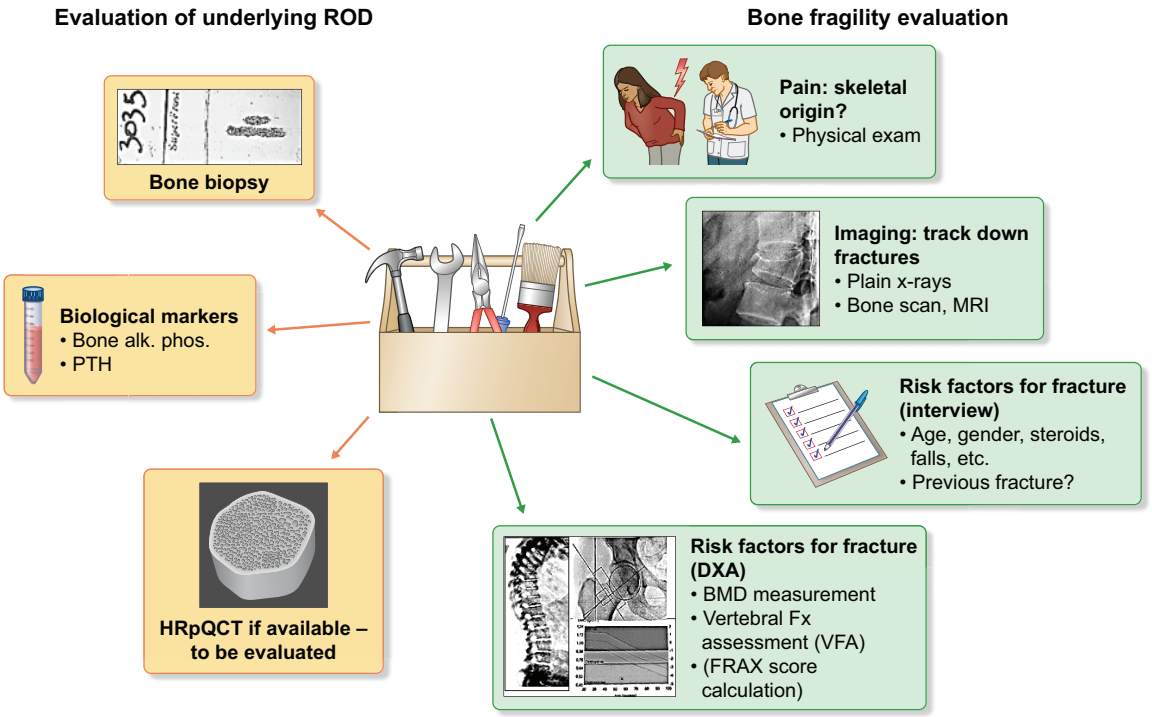

FIGURE 5: Diagnosis strategy to evaluate bone fragility and underlying renal osteodystrophy in CKD patients.

its invasiveness and the lack of experts to perform and interpret it. Reduced-diameter trephines with 3.5-mm-wide bone samples are under evaluation for accuracy and side effects.

Treatment of bone fragility in CKD patients

Management of the disorders of calcium and phosphate metabolism is mainly carried out by nephrologists. Preventing both excessive bone remodelling due to hyperparathyroidism and low bone turnover undoubtedly contribute to better bone health in CKD patients. Calcium- or iron-containing phosphate binders, sevelamer, lanthanum, cinacalcet, vitamin D derivatives and calcimimetics (cinacalcet, etelcalcetide) are currently used by nephrologists, whereas help is generally requested from the rheumatologist when fractures occur.

Bone fragility in CKD patients is the result of combined lesions of ROD and age, menopause or glucocorticoid-related osteoporosis. For patients with a GFR >30 mL/min/1.73 m^2, all the molecules used in non-uraemic patients for osteoporosis treatment, including bisphosphonates [44, 45], raloxifene [46], teriparatide [47] and denosumab [48], are thought to be safe and efficacious in reducing the fracture rate, although no trial dedicated to patients with true renal disease has been conducted. Only *post hoc* studies, derived from pivotal trials, sorting patients according to calculated GFR (mostly with Cockroft–Gault or Modification of Diet in Renal Disease formula) are available [49]. There is not enough information from evidence-based results to recommend any treatment.

For those patients with GFR <30 mL/min/1.73 m^2, there is no randomized clinical trial testing the efficacy and safety of anti-osteoporotic drugs in preventing bone fractures. Close follow-up of calcium serum levels is recommended in patients on denosumab [50], due to the high risk of hypocalcaemia (median time of 71 days after the injection).

CONCLUSIONS: OSTEOMUSCULAR PAIN AND BONE FRAGILITY

For the rheumatologist, identifying the anatomic structure involved in the pain is the key to providing an accurate diagnosis and appropriate treatment. The evaluation and management of bone fragility in CKD remains a challenge. Due to the major difficulties encountered when we take care of dialysed patients with fractures, it is necessary to detect bone fragility as early as possible, i.e. before CKD Stages 4–5d, to be able to prevent fractures in an efficient and safe manner.

CKD BY THE GERIATRICIAN

Osteosarcopaenia, sarco-osteopaenia and sarco-osteoporosis

Osteoporosis (increased bone fragility due to decreased BMD and altered bone architecture) and sarcopaenia (age-related loss of muscle mass and strength) are two chronic conditions highly prevalent in older age that, as a result of falls and fractures, have major consequences in terms of morbidity, mortality and socio-economic cost [51]. The terms sarco-osteopaenia and sarco-osteoporosis were introduced in 2009. Sarco-osteopaenia was proposed for persons with sarcopaenia and osteopaenia and sarco-osteoporosis for persons with sarcopaenia and the clinical diagnosis of osteoporosis or osteoporosis on DXA [52]. Nowadays the term osteosarcopaenia is used [51]. The concept of osteosarcopaenia will become increasingly relevant, also for nephrologists, not only because of the ageing of the population with increasing prevalence of osteosarcopaenia, but also because of the specific risk of bone and muscle loss that occurs in patients with CKD.

Pathophysiology of osteosarcopaenia

Previous trials have shown a positive correlation between bone mass and muscle mass, with a higher muscle mass being associated with a higher bone mass and vice versa. In 679 men with a mean age of 59.6 years in the European Male Aging Study, sarcopaenia was associated with a low BMD and subjects with low muscle mass had a 3.8 higher risk of osteoporosis [53]. Likewise, a recent meta-analysis of nine studies concluded that, as compared with non-sarcopaenic individuals, sarcopaenia was associated with a 34% higher risk of fractures [54].

Thus there is an association between muscle and bone. Bone and muscle not only interact mechanically [55], but also communicate with each other by the secretion of the so-called myokines and osteokines [51, 55]. In addition, bone and muscle share several pathophysiological pathways (endocrine, nutrition and genetics). Alterations in these pathways that are associated with or are very prevalent in CKD, such as hypogonadism, vitamin D deficiency, increased levels of cortisol and resistance to insulin/insulin-like growth factor in ESRD, contribute to the bone and muscle loss observed in this population [56]. Thus bone and muscle are more than two anatomically nearby entities, they form a real unit, the 'bone–muscle unit' [57].

Diagnosis of osteosarcopaenia

To diagnose osteosarcopaenia, no criteria other than the combination of osteopaenia or osteoporosis and sarcopaenia are required [58].

Osteopaenia/osteoporosis. DXA is the gold standard for the diagnosis of osteoporosis and, as indicated before, is included in the latest KDIGO guidelines. According to the World Health Organization, osteoporosis is defined as a BMD at the vertebrae (L2–L4) or the hip of >2.5 standard devaitions below the average BMD at a young adult age (*t*-score ≤ -2.5) [59]. Although low BMD explains at least part of the osteoporotic fracture risk, it should be noted that DXA is very specific but lacks sensitivity. More than 50% of patients may have a hip fracture and lack a *t*-score ≤ 2.5 on DXA [60], suggesting that there are other risk factors in addition to BMD. Algorithms including clinical factors along with BMD have been developed, such as FRAX, which was discussed above [61]. However, relevant clinical parameters may have been omitted in FRAX. This is the case for CKD, as has been mentioned before, but also for falling. Nevertheless, both falls and sarcopaenia predict fracture risk, independent of FRAX and BMD [62].

Sarcopaenia. To correctly estimate a person's fracture risk, sarcopaenia should be taken into account. To date, there is no consensus on the operational definition of sarcopaenia. Originally sarcopaenia was defined as a loss of muscle mass. Later it was expanded to a loss of muscle mass and strength.

Since 2009, various expert groups have tried to incorporate the concept of sarcopaenia into an operational definition, such as the consensus definition of the European Working Group on Sarcopaenia in Older People (EWGSOP) [63] and the definition of the Asian Working Group on Sarcopaenia (AWGS) [64]. Common

to these definitions is that they contain a component of low muscle mass and a component of low muscle function, which can be low physical performance or low muscle strength. The problem is that these definitions differ in the chosen reference population, measurement method and cut-off values for muscle mass, muscle strength and physical performance [65]. Recently the EWGSOP proposed a revision of their consensus definition, with low muscle strength as the key characteristic of sarcopaenia. Low muscle quantity or quality is used to confirm the diagnosis of sarcopaenia and low physical performance to indicate the severity of the disease [66].

Some specific issues need to be taken into account when making the diagnosis of sarcopaenia in the population with CKD. First, DXA is seen as the gold standard to estimate skeletal muscle mass in clinical practice. In fact, DXA determines bone, fat and lean mass, in which the component lean mass is a surrogate for muscle mass. However, body water is part of the lean component and DXA cannot differentiate between water and bone-free lean tissue ('muscle'). This may be a problem in persons with extracelluar fluid accumulation, as in patients with CKD [67]. Second, no specific cut-offs for low muscle mass, low muscle strength and low physical performance have been validated longitudinally in patients with CKD. It is clear, however, that declining trends in these parameters are associated with poor health outcomes [56, 68]. Thus, despite the lack of validated cut-offs for low muscle mass and function in patients with CKD, it remains relevant to monitor changes in these parameters.

Osteosarcopaenia. A consensus on the definition of osteosarcopaenia is lacking. Most authors retain the term osteosarcopaenia for persons with osteoporosis and sarcopaenia, while others also use the term for persons with osteopaenia and sarcopaenia. Furthermore, the component sarcopaenia varies from low muscle mass only to low muscle mass plus low muscle function.

Prevalence of osteosarcopaenia

A systematic review reported that the prevalence of osteosarcopaenia ranges from 5 to 37% in the general population, depending on the definition of sarcopaenia and the parameter to define low bone mass (osteoporosis or osteopaenia) [69]. For example, in Chinese community-dwelling men and women ≥65 years of age, the prevalence of osteosarcopaenia [defined by the presence of both osteoporosis (*t*-score <−2.5) and sarcopaenia according to the definition of the AWGS] was 10.4% in men and 15.1% in women [70].

To our knowledge, there are almost no data on the prevalence of osteosarcopaenia in the population with CKD. However, this prevalence is likely to be even higher than in the general population, especially in advanced CKD, as the prevalence of both sarcopaenia and osteoporosis increases when CKD progresses to higher stages. In patients with CKD who had undergone kidney transplantation and with a mean age of 46.6 years, the prevalence of osteosarcopaenia was 17.2%, with osteosarcopaenia defined by the presence of osteoporosis and AWGS-defined sarcopaenia [71].

Consequences of osteosarcopaenia

Individuals with osteosarcopaenia experience the negative effects of both sarcopaenia and osteoporosis. They are a subset of very frail elderly who have a significantly higher risk of falls and fractures, more comorbidities and a significantly higher mortality rate than patients with osteoporosis or sarcopaenia alone [58].

As far as we know, there is no research on the outcomes of osteosarcopaenia as a construct in patients with CKD. However, previous research has shown that, as in the general population, sarcopaenia in CKD is associated with negative health outcomes such as impaired performance in ADL (activities of daily living) and increased mortality [72, 73]. In addition, as mentioned before, CKD does not change the association between low BMD and fracture risk, indicating that patients with osteoporosis and with or without CKD have the same risk of fractures [36].

Treatment of osteosarcopaenia

Fractures cannot be completely prevented with anti-resorptive or even anabolic medication. This medication does not completely restore bone strength and has no effect on fall risk or underlying sarcopaenia or frailty. In order to prevent fractures, more powerful anabolic treatment is needed that targets bone and muscle as a whole [57]. Currently most evidence exists for exercise therapy (progressive resistance training) and protein supplementation in the range of 1.0–1.2 g/kg body weight (BW)/day for healthy older adults and up to 1.2–1.5 g/kg BW/day for older adults with an acute or chronic disease [74]. Also, in CKD Stages 3–5, a recent systematic review and meta-analysis showed a beneficial effect of progressive resistance training on muscle mass, muscle strength and health-related quality of life [75]. With respect to protein supplementation, older people with severe CKD who are not on dialysis (eGFR <30 mL/min/1.73 m^2) are an exception to the high-protein rule, as they need to limit protein intake to 0.8 g/kg BW/day. On the other hand, in persons on haemodialysis or peritoneal dialysis, a protein intake >1.2 g/kg BW/day is recommended to compensate for dialysis-induced catabolism [76].

Pharmacotherapy for sarcopaenia is currently under development, such as bimagrumab, a human monoclonal antibody that binds and inhibits the activin receptor IIB. Whether this medication also has a beneficial effect on bone should be investigated in clinical studies in humans [74]. In a Phase 2 proof-of-concept study, bimagrumab for >16 weeks increased muscle mass and strength in older adults with sarcopaenia [77]. Unfortunately, patients with a GFR <30 mL/min/1.73 m^2 were excluded.

CONCLUSIONS: OSTEOSARCOPAENIA

Bone and muscle form a 'muscle–bone unit' in which bone and muscle are not only mechanically connected, but also share common risk factors and communicate with each other by releasing osteokines and myokines. Osteosarcopaenia is a new geriatric syndrome that will become increasingly prevalent in the ageing population. Osteosarcopaenia leads to reduced functionality and bone strength and increases the risk of falls and fractures.

In order to prevent fractures, osteosarcopaenia must be tackled as a whole. Therefore, in clinical practice, not only osteoporosis, but also sarcopaenia should be diagnosed and treated. Current pharmacological treatments for osteoporosis have no effect on sarcopaenia, but progressive resistance training and adequate intake of proteins have a beneficial effect on both bone and muscle and contribute to a reduction of the risk of falls and fractures in osteosarcopaenic patients.

All these considerations are particularly relevant in the CKD setting with an ageing population with increased osteosarcopaenia-linked risks. Currently there is no specific research on diagnosis (e.g. specific cut-off levels for muscle mass, muscle strength and physical performance), prevalence and consequences of osteosarcopaenia in patients with CKD. Given the high frequency of CKD in the elderly, the interaction with CKD merits further studies. This includes assessing the impact of osteosarcopaenia on serum creatinine, falsely resulting in normal eGFR for patients who do have CKD.

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CONFLICT OF INTEREST STATEMENT

The authors report no conflicts of interest.

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