REVIEW

Managing Musculoskeletal and Kidney Aging: A Call for Holistic Insights

Pierre-Emmanuel Cailleaux [ID], Martine Cohen-Solal [ID]

Inserm UMR-S 1132 Bioscar, Université Paris Cité - Hôpital Lariboisiere, Paris, F-75010, France

Correspondence: Martine Cohen-Solal, Inserm UMR-S 1132 (Université Paris Cité), Hôpital Lariboisière, 2 rue Ambroise Paré, Paris, F-75010, France, Tel/Fax +33-1-49-95-63-58, Email martine.cohen-solal@inserm.fr

Abstract: Aging represents a major concern, with a two-fold increase in individuals >65 years old by 2040. Older patients experience multiple declines in condition, with overlapping concerns. Fractures, frailty and falls remain underestimated events in routine practice. They are shared by numerous conditions and diseases, such as osteoporosis, sarcopenia and undernutrition, which mostly feature low evolution and are silent. In this review, we focused on musculoskeletal decline in older individuals who also have chronic kidney disease (CKD), which promotes fractures and falls. We aimed to highlight the need for a global approach for musculoskeletal and kidney aging. Although strategies limiting falls remain controversial, the need for an early diagnosis can limit these declines and allow for specific treatment of bone fragility in addition to non-pharmacological approaches. The emergence of senolytic agents offers new hope for preventing musculoskeletal disorders. This scoping review describes these overlapping silent diseases, provides evidence for their global understanding and management, and sheds light on new therapeutic directions.

Keywords: older individuals, osteoporosis, sarcopenia, kidney disease, senolytics

Introduction

Dependence represents the threshold of tertiary prevention that we aim to avoid. Many injuries leading to dependence are affected by aging, and the effects of some could be minimized, if early managed. Early prevention remains a challenge in poorly symptomatic patients with concomitant silent multiple declines. Therefore, the "F-issues" (fragility fractures, falls and frailty), should be considered as red flags in an asymptomatic aging patient. Hip fracture represents a burden, with a yearly 25% mortality rate, especially in the elderly. In Europe, the number of death due to fracture events in 2019 was around 250.000, when the number of new fragility fractures was estimated at 4.3 million, comprising 826,708 hip fractures (19%) and 662,544 vertebral fractures (16%).[1] The majority of fragility fractures are related to osteoporosis after the age of 50. Falls are the main trigger for fracture in older individuals, and a relevant marker shared with musculoskeletal frailty such as muscle loss and undernutrition.

Although kidney function is not systematically assessed in musculoskeletal frailty, chronic kidney disease (CKD) exposes to increased risk of fracture. Age-standardized incidence of hip fracture among patients with non-dialysis-requiring CKD is estimated 1.81/1000 persons, 2-times higher than in normal kidney function patients.[2] In addition, CKD also exposes to increased risk of falling, frailty and sarcopenia, and these increases with age. Here, we addressed the crosstalk between these declining functions in older people and reported the assessment tools and the combined management of musculoskeletal failure in patients with altered renal function. We aimed to highlight the existing gap in this specific field. Although this work was designed as a narrative review, our research methodology is available at the bottom of the text.

State of the Art in Aging of Either Musculoskeletal System or Kidney Function

Aging Muscle: Is This Frailty?

Frailty is defined as a phenotype leading to morbidity and dependence. Frailty is reversible and could be prevented by an early intervention. As dependence increases with age, frailty is found in 10.7% of individuals >65-yo and in 25% to 50%

of those >85-yo. Frailty is associated with increased risk of falls and fractures.[3] The assessment of frailty includes different approaches, such as the Fried's model in which five indicators overlap with the sarcopenia assessment.[4]

Sarcopenia is a global muscle disease that precipitates the loss of muscular mass, altering muscle function (strength and power) and physical performance. The diagnosis of sarcopenia remains a challenge, given the extensive number of tools available for the definition. The expert group of the European Society for Clinical and Economic Aspects of Osteoporosis and Musculoskeletal Diseases advises the use of grip strength to measure muscle strength, and 4-m gait speed or the Short Physical Performance Battery, to measure physical performance in daily practice.[5] In addition, dual energy X-ray absorptiometry (DEXA) provides the distribution of fat mass and appendicular lean mass. However, recent studies demonstrated the lean mass is a poor marker for fracture prediction after adjustment of femoral neck bone mineral density (BMD).[6] Thus, in the more recent definitions of sarcopenia, lean mass has been associated with measures of physical function/performance/strength. The European Group on Sarcopenia in Older People (EWGSOP) definition (with gait speed, DEXA, grip strength, chair stand) seemed the most predictive of all definitions in predicting fracture independent of BMD, falls and Fracture Risk Assessment Tool (FRAX®) in the MrOS cohort study.[7]

The prevalence of sarcopenia increases with age and compromises health in 1% to 29% of older people in community living (10% in acute medicine unit) and in 14% to 33% of those in nursing homes.[8] The decline in muscular strength occurs earlier and is more severe than the loss of muscular mass (3% per decade after age 70 vs 1–2% after 50).[9]

Malnutrition is also common in older people and is a major risk factor for frailty and sarcopenia. The prevalence of protein-uptake malnutrition depends on many factors and differs between acute-care or community patients, although the diagnosis relies on the definition and the tools used to define malnutrition. Prevalence rates of high malnutrition risk across all countries and screening tools ranged from 8.5% in the community setting to 28.0% for people in hospitals, in a recent analysis including 22 malnutrition screening tools validated in adults aged 65 years or older.[10–13] This observation highlights the need for a parallel assessment of both sarcopenia and undernutrition. Although anthropometry indices are used to assess nutritional status in older adults, these are not relevant for muscle mass assessment. Body mass index (BMI) measurement remains the simplest approach, with the 21 kg/m^2 threshold considered for malnutrition in older people. The extent of metabolic undernutrition is assessed with serum albumin level, according to the last recommendations. However, calf circumference remains an alternative in muscle mass evaluation when no other diagnostic methods are available.[14]

As far as treatment is concerned in undernutrition, avoiding a restrictive diet in older people is recommended first, as is prescribing a nutritional oral complement when needed. Together, loss in muscle strength, function and performance are associated with severe prevalent adverse health conditions in older people. Frailty, undernutrition and sarcopenia are reliable markers associated with several outcomes such as falls, fractures and death.[15]

Ageing Bone Issues

Most fractures occur after a fall, the risk increasing with age. Bone strength includes both bone density (BMD) and bone quality (microarchitecture and turnover). In post-menopausal women, the association with BMD and the fracture risk easily allows to predict fracture risk. Fractures, especially hip fractures, are a public health challenge because of their cost and mortality. Most patients who experience a hip fracture are older than 80 years.[16] The impact of hip fracture on quality of life and life expectancy in older people is similar to that for other chronic diseases.[17] The advances in Fracture Liaison Service and reeducation therapies can improve the consequences of fracture and re-fracture risk.[18] However, about 75% to 80% of hip fractured patients, whom are mainly older, never received any treatment for their bone fragility within the year after the fracture. In the oldest old individuals, the risk of death competes with the risk of fracture.[19] Thus, life expectancy represents a key factor for decision-making in this population, especially in patients with major disabilities.

Although the mean life expectancy at birth in Europe is 82.6 years for women and 76.7 years for men, residual life expectancy above age 85 and 95 is about 6.97 and 3.19 years, respectively, for both genders. Thus, the question of preventing osteoporotic fractures remains crucial.

When investigating bone fragility in older people, the usual tools for young adults do not reach the same level of validation. Major factors remain the history of fracture or the history of fall. Although the FRAX® now adjusts the result in very old patients for the competing hazard of death, the FRAX® remains a 10-year prediction of fracture risk.

Biological assays are performed for ruling out malignant bone diseases, a metabolic bone disorder and monitoring contraindications to therapy. Bone biomarkers help to determine the levels of bone remodeling and the monitoring/ adherence to therapy (always after a reasonable time delay after a fracture). The International Osteoporosis Foundation (IOF) only recommends serum P1NP and CTX assays because they are modified by therapy.[20]

Measurements of Vitamin-D levels are recommended because Vitamin-D level must be in the normal range to initiate a therapy. Supplementation also had a significant effect on femoral neck BMD,[21] with no major effect on incident fracture prevention after age 70.[22] The last results were confirmed in a meta-analysis that only analyzed vitamin D without calcium supplementation.[23] Vitamin-D supplementation could have numerous positive effects, in particular on muscle and falls, in which the effect appears to be dose-dependent[24] and not found in the same Bolland work.

BMD measurement in this population also has several limitations. BMD does not accurately reflect the situation for patients with prevalent major fracture. Therefore, reference curves and thresholds for the diagnosis are questionable. The low reproducibility in positioning and frequent presence of bilateral hip prosthesis, lumbar spine osteoarthritis, unknown vertebral fracture, spine deformity and aortic calcification[25] are frequent issues limiting BMD interpretation and reproducibility (Figure 1). Lateral imaging of the spine reinforce BMD measurement interpretation, providing information on silent vertebral fracture (Figure 1A), the level of aortic vascular calcification and the presence of osteoarthritis (Figure 1B and C).

Osteoporosis drugs have proved their efficiency in patients with >1 year life expectancy.[26] With age >70 and vascular risk, selective estrogen receptor modulators are a non-relevant option in this population. Therefore, discussion of osteoporosis drugs in older people will involve bisphosphonates, teriparatide and denosumab. Recently, the International Conference on Frailty and Sarcopenia Research Task Force developed targets for research on osteoporosis in frail older adults.[27] According to these recommendations, optimal treatment for osteoporosis in older people may require combined or sequential therapies. Romosozumab followed by denosumab reduced the risk of fracture in postmenopausal women in the recent FRAME phase-2 study. This combination should have been a helpful sequence,[28] although currently not approved in women above 75 with a history of ischemic heart failure.
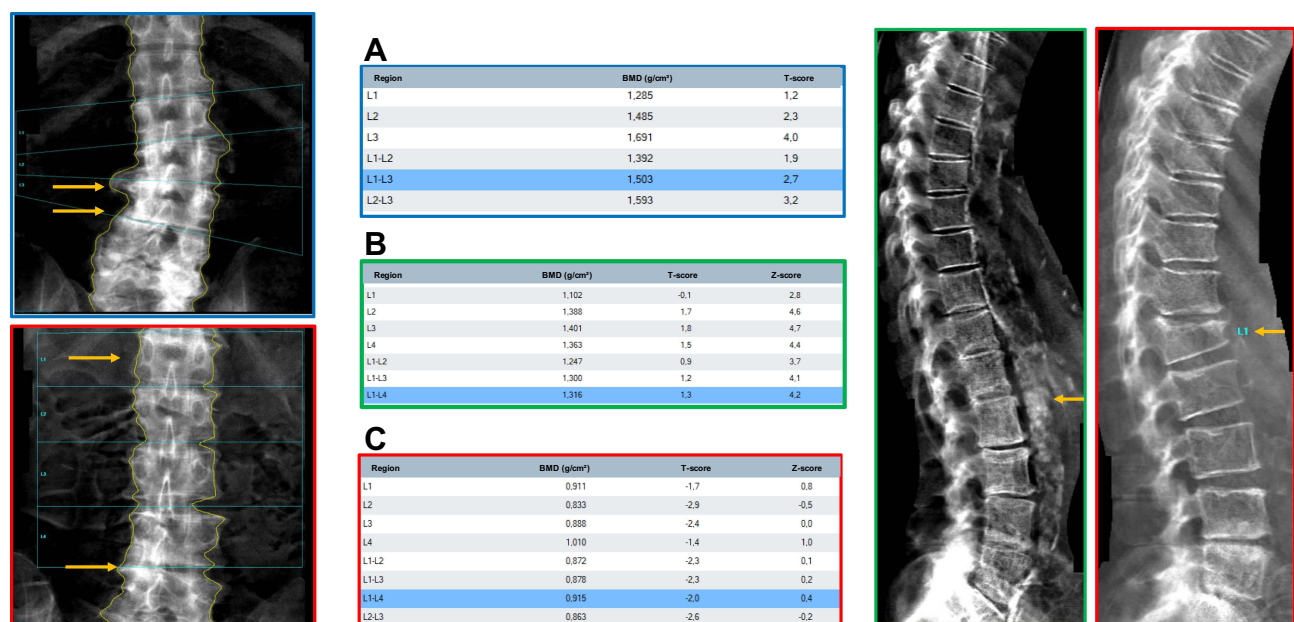

Figure 1 Examples of dual energy X-ray absorptiometry scans illustrating the limitations of the measurement at the lumbar spine. These examples illustrate frequent limitations encountered in the assessment of dual energy X-ray absorptiometry scans in older patients. Yellow arrows point out osteophytes and bone calcification in the blue squared lumbar spine picture. (**A**) Blue frame: The blue table related to the blue frame picture underline the impact in overestimation of BMD with osteoarthritis at lumbar spine. (**B**) Green frame: These figure point out the important aortic calcification in vertebral assessment picture, leading to conclude to normal BMD shown in the green frame table. (**C**) Red squared pictures emphasize the presence of an unseen vertebral fracture at the first lumbar vertebra (Genant II-stage). In the associated dual energy X-ray absorptiometry scan, this fracture was not suspected, so BMD was overestimated in L1 compared to L2.
Abbreviations: BMD, bone mineral density; LS, lumbar spine; VFA, vertebral fracture assessment.

The tolerance of any osteoporosis therapy is good in older individuals, with mild and reversible adverse effects. In older patients, oral drugs should be evaluated in the light of the lower bioavailability of oral treatment, slower metabolic rate, concomitant deficiencies and treatments. The remnant effect of parenteral bisphosphonates calls for their use when life expectancy is reduced and the risk of poor adherence is increased. Reevaluation is relevant within 3 years if no new fracture or risk factor has occurred. Overall, because of the diagnostic tools and treatment available, osteoporosis is one of the best characterized diseases to achieve musculoskeletal prevention in older people, in which osteoporosis is prevalent.

Kidney Function and Assessment in Older Individuals

Kidney function declines with age. The loss of function is the result of kidney aging and lifelong pathologic injuries. A progressive decline of glomerular filtration rate (GFR) of about 1 mL/min/year represents normal ageing of kidney function above age 40. Although the incidence of renal impairment is still increasing,[29] most adults with CKD never reach end-stage renal disease.[30,31] After the age of 80, the incidence of CKD increases by 10-fold as compared with 18 to 50 years. In addition, the longitudinal SCOPE study assessed the profile of comorbidity conditions in 2252 subjects aged above 75 years across Europe. They showed that CKD was the most frequent conditions and was rarely observed without any other co-occurring disease. Besides the cardiovascular diseases that were predominant, CKD was highly associated with osteoporosis and hip fracture.[32] The score of physical performance was reduced in subjects with severe CKD, suggesting that multi-organ decline.

Numerous frequent comorbidities, such as cognitive impairment, probably because it is a vascular component, are related to renal impairment in older people.[33] In a diabetes mellitus cohort, patients aged >80 with dementia had an increased mortality in case of renal impairment.[34] Nonetheless, in patients with CKD stage 3, the 10-year cumulative incidence of dialysis and transplantation (0.04) contrasts with the mortality incidence (0.51, mainly due to cardiovascular diseases).[35] This fact highlights that the phenotype of older CKD patients is not similar to younger patients.

Thus, this observation could be related to a difference in the assessment of renal function in older versus younger people. However, older people with CKD stage 3A without proteinuria have no additional risk of mortality as compared with similar age-class individuals with estimated GFR>60 mL/min/1.73 m^2.[36] This underlined the probable overestimation of CKD stage 3 in older individuals, in which a few CKD stage 3A patients met the 2-parameters assessment recommended by the Kidney Disease: Improving Global Outcomes (KDIGO) guidelines.

Other limitations in the CKD assessment in older individuals are identified. The measurement of GFR using isotopic or iohexol injection is optimal but is limited to dedicated physiology departments. In a routine setting, serum creatinine level remains widely used as a surrogate marker for renal function estimation. To date, no strong evidence is available to prefer other biomarkers (cystatin-C …) in old patients. However, in acute care, creatinine in older patients do not correctly reflect the renal function. Furthermore, creatinine levels are determined by muscular production, which is a major limitation in this population. Moreover, technical conditions also limit the assessment of the 24-hr urinary creatinine level.

The most widely used tools for estimating GFR remains creatinine-based equations (4-variable Modification of Diet in Renal Disease [MDRD], CKD Epidemiology Collaboration [CKD-EPI] and Cockcroft and Gault [CG] equations). Values for patients above age 90 years are not correctly represented in each of these reference populations, which raises concerns about their validity. Of all methods, MDRD equations produce the most accurate results for an association with the gold-standard.[37]

Besides kidney failure, older patients are exposed to iatrogenic issues. We will not get into it here. In the musculoskeletal approach, attention should either be paid to drugs with a negative impact on bone long-term corticosteroid, heparin, vitamin K antagonist[38] or with a positive impact (bisphosphonates, teriparatide, thiazide diuretics, statins, etc.). Also, it is important to balance the individual risk on drugs that expose to falls such as antihypertensive therapy, especially for renin-angiotensin antagonists, which protect kidney function.[39]

Need for Novel Comprehensive Approach in Concomitant Declines of Musculoskeletal and Kidney Function

Frailty and Sarcopenia in CKD

Musculoskeletal frailty involves several interacting systems that converge toward fracture occurrence (Figure 2), including kidney failure that increased with aging. The prevalence of frailty in CKD patients is estimated at about 14%, which increases their mortality risk by 2.5 points. Sarcopenia is mostly prevalent in late CKD stages, whatever the definition,[40] and with an altered handgrip,[41] as confirmed by results from the NHANES study.[42] Although sarcopenia progressively increases with renal impairment in CKD, only some evidence links muscular function to fracture risk in CKD,[43] with numerous hypotheses studied for their potential role in change in myostatin metabolism.

One of the aims in care for sarcopenia remains to limit falls. The increase in risk of fall is well documented in CKD,[44,45] in particular in end-stage renal disease[46,47] and in patients >65 years old. Above age 65, falls are more frequent and often generate complications, especially when GFR is <45 mL/min, with the incidence of falls about 38.3 vs 21.7/ 1000 person-years with GFR>60. Risk of falls is also increased with GFR<60mL/min associated with osteoporosis, especially corticosteroid-induced osteoporosis.[48]

Whether specific causes of falls in CKD have not been elucidated; some studies considered that diabetes or uremic-related neuropathy could be good candidates.[43] In older individuals, in whom falls are multifactorial, risk of falls is increased by two-fold with polymedication, BMI <18.5 and low GFR. Dementia also increases this risk by 1.21 points.[49]

Some specific quantitative gait abnormalities have been identified in CKD patients (slower gait speed, shorter stride length, reduced time in the swing phase and increased time in the double support stance phase), adjusted for age and sex associated with fall risk.[50] Although no specific program is available for these patients, the objective of limiting falls should focus on detecting frailty, improving modifiable factors (visual acuity, multiple medications, and home environment) and focusing on strengthening, gait, and balance in exercise programs. Nutrition management could appear as a realistic way of improving sarcopenia, but no drug or no specific biomarker are yet recommended. However, IGF-1 level, which are low in undernutrition, may have a positive impact on both bone and muscle. Such as serum myostatin, in which level increases along with CKD and inhibits muscular mass.[51]
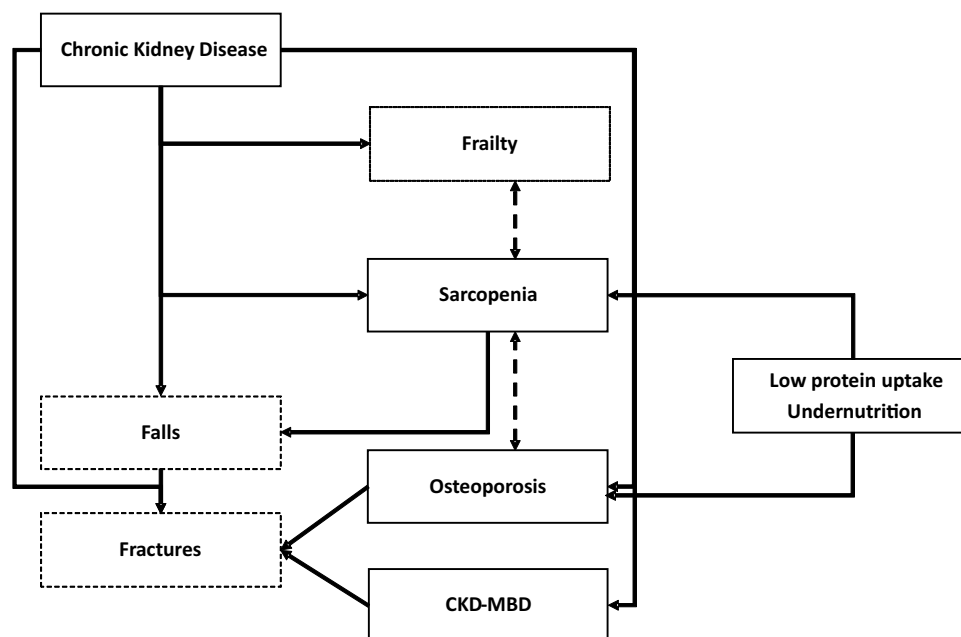

Figure 2 Interactions between musculoskeletal settings in older patients with chronic kidney disease. Plain frame represents diseases, and the other frames are parameters clinically assessed. This figure represents connections and interactions between phenotypes, diseases whatever the severity of each condition, in order to emphasize the key feature that fracture is, and therefore that falls and frailty must be prevented with an integrative management of all these diseases.
Abbreviation: CKD-MBD, chronic kidney disease-bone mineral disorders.

Clinical Assessment of Bone Disorders in CKD

In CKD patients, a high prevalence of fracture is reported along with a high mortality rate related to the fracture.[52] Osteoporosis in CKD patients is related to diabetes mellitus and hypertension, whose incidence increases with age. However, a recent meta-analysis reported that even about 24% of CKD cases could be related to diabetes mellitus, the condition increasing the fracture risk independent of kidney function.[53] Different entities have been identified in bone mineral and metabolism disorders related to CKD (CKD-mineral and bone disorders [CKD-MBD]) to better understand the participation of renal impairment. The KDIGO work-group defined CKD-MBD as one or a combination of three manifestations. Manifestations can be disorders of bone and mineral metabolism and/or extra-skeletal calcification, and/or renal osteodystrophy defined as altered bone morphology associated with CKD (turnover, mineralization, volume), assessed by histology.

The risk of hip fracture increases by 2- to 14-fold in CKD patients as compared with the general population. This risk appears at the early stages versus non-CKD and increases with the CKD severity.[54] Hip fracture incidence increase in parallel with CKD progression.[55] Fracture risk is increased among older individuals with CKD,[48] which illustrates that age is a major risk factor for fracture,[17] although renal impairment and osteoporosis have an independent or additive impact on fracture risk.[56] In contrast, older people with osteoporosis frequently have renal impairment with age.[57]

However, these progressions differ by sex. With menopause, bone mass declines faster in women between age 50 to 70 than men,[58] whereas in general, decline in renal function is fastest in men. Nonetheless, CKD seems to remain more common among women, with an estimated prevalence of 11–13%. Regardless, Big data analyses do not individualize a homogenous male: female distribution of CKD across the world, according to countries with different economic states.[59] GFR increase its decline after age 70 in osteoporosis women, as seen in the post-hoc analysis of the Horizon-PFT study.[60] The overlap between CKD and osteoporosis can be illustrated with the NHANES-III cohort, in which 60% of women with osteoporosis also had CKD stage 3 and 23% stage 4.

In patients with CKD stage 1–2 with osteoporosis and/or high risk of fracture or in those with CKD stage 3 with PTH concentration in the normal range, the KDIGO recommends managing osteoporosis as for the general population. However, CKD does not systematically imply associated CKD-MBD, whereas 85% of women with osteoporosis show altered renal function.

The FRAX® is used for assessment in CKD especially when enhanced with BMD and trabecular bone score results.[61] Nevertheless, the FRAX® does not include key factors for CKD-MBD or GFR evaluation, number of fractures and falls.[62]

Low BMD correctly predicts risk of hip fracture in older people with CKD.[63] With CKD stages 1 to 3, BMD can predict risk of fracture, which confirms that people at early stages of CKD with no evidence of CKD-MBD can be considered as having osteoporosis. Conversely, a CKD stage 3–4 was discovered in 84% of older women with osteoporosis. However, BMD in late stages remains controversial in estimating risk of fracture. Thus, the 2009 KDIGO recommendations were updated in 2017 to favor assessing BMD in patients with CKD stage 3a-5 if the result would affect treatment decisions but also to identify patients at high risk of fracture. With longitudinal follow-up in patients with CKD stage 3–5 and with measured GFR and BMD follow-up, a slight bone loss occurs at the radius only, a cortical bone.[64] However, because the levels of bone loss remain unknown, the frequency of serial BMD assessments remains to be determined. Therefore, the European Dialysis and Transplant Association and the IOF integrate the evaluation of fracture risk as a target in the management of CKD-MBD.[65] In older patients with 11 years of follow-up, a 1-SD change at the femoral neck increased by two-fold the risk of fracture in CKD as compared with no CKD. In end-stage renal disease, BMD is lower, especially at cortical bone sites,[66] so this site may be more relevant in CKD patients in whom aortic calcifications are more prevalent, thus possibly distorting lumbar spine BMD.

Investigating Bone Biochemical Parameters in CKD

The last KDIGO recommendations highlighted that other priorities are competing with CKD-MBD management in people aged 75 to 78 with a 2.5-year follow-up, thus justifying the need for screening older people with a global assessment.[67] CKD patients have numerous comorbidities and there is a trend to not test patients beyond age 85.

The most frequent conditions in CKD-MBD are: secondary hyperparathyroidism, hyperphosphatemia, hypocalcemia and low calcitriol level.

- In CKD patients with hyperparathyroidism, serum PTH level increases in parallel with CKD progression.[68] Other causes such as vitamin D deficiency hyperparathyroidism should be explored to avoid concluding renal secondary hyperparathyroidism. KDIGO guidelines also recommend managing hypocalcemia, hyperphosphatemia and vitamin D deficiency in CKD stage 3 to 5 with hyperparathyroidism.[69] BMD should be interpreted with those bone parameters: low BMD in CKD seems to predict fracture better if associated with normal-range PTH level.[70]

- Although serum phosphate levels are expected to be normal in osteoporosis, they could remain useful to assess bone fragility in older CKD individuals. According to the MrOS and the Rotterdam cohorts, increased phosphate levels could be related to fracture risk along with CKD,[71] even after adjustment for PTH and FGF-23.

- Vitamin-D insufficiency must be managed with a targeted level for 25OH-vitamin D above 75 nmol/mL whatever is the aim (osteoporosis, CKD, or falls). In CKD stage 3–4, a normal gait speed is associated with the highest level of 25 (OH)-vitamin D.[72] When associated with hypocalcemia, calcitriol level can also be assessed to adapt therapy. Some evidence suggests that in inhibiting the Wnt signaling pathway, vitamin D could limit vascular calcification, one of the components of CKD-MBD.[73] Because of the effect on muscle via the vitamin D receptor, as for the mitochondrial or non-genomic pathway, vitamin D remain a good candidate for intervention in sarcopenia.[74] Vitamin D is also known to lower myostatin level[75] and increase levels of insulin-like growth factor 1, sclerostin, osteocalcin and FGF-23 and therefore muscular mass.[76]

- In addition, serum FGF-23 is a hormone produced by osteocytes that stimulates renal phosphate excretion. FGF-23 level increases from the early stages of CKD and plays a role in the decrease in calcitriol level. FGF-23 is not associated with fracture or with lower BMD after adjustment on GFR.[77] Klotho allows for contact between FGF-23 and its receptor. Decreased levels along with CKD lead to a lower number of osteoclasts with higher activity.[78]

- Finally, urinary calcium levels can also be helpful because fractures seem to occur more frequently in CKD stages 3 and 4 in patients with a history of kidney stone (5.56/100 pa).[79]

Several other bone biomarkers are available, but their renal elimination limits their interpretation. Among bone remodeling biomarkers, only bone-specific alkaline phosphatase (bs-ALP), TRAPc5b and the trimeric form of P1NP are not impacted by kidney elimination. Bs-ALP is a bone formation biomarker associated with both low[80] and high levels of bone turnover. TRAPc5b & P1NP are poorly reported in the aging CKD population.

Therapeutic Approaches in Old CKD Patients

Non-Pharmacological Approaches

Also here, several types of intervention in fall prevention have been developed with poor results.[81] However, the need for care in fall prevention remains a key element for patients at high risk of fracture. Muscle stretching and strengthening, especially the pelvic belt and lamb triceps, could be advised. Physical activities such as Tai-Chi should have a positive effect on osteoporosis prevention.[82] Specific gait abnormalities in old CKD patients could be targeted with specific interventions, as long as no program is recommended. Other risk factors for falls must be corrected according to the evaluation. Malnutrition is one of them. The recommended protein uptake (1–2g/kg/d) is in competition with nephrology guidelines, stating that uptake must be maintained from 0.8 to 1mg/kg/day. In osteoporotic patients too, nutritional recommendations do not systematically match with CKD-MBD, for which avoiding a high phosphate diet is recommended.

In older people, the targeted 25(OH)-vitamin D is >75 nmol/L. In the DOPPS cohort of CKD patients, all those taking vitamin D were healthier than those who did not.[83] Supplementation also affects other aspects (osteoporosis, sarcopenia, falls[84]) especially in CKD patients for whom supplementation could improve global mobility and muscular function.[85] In

older people, improving calcium uptake assessment is useful although some evidence suggests increased vascular risk in patients without any calcium insufficiency.[86]

Pharmacological Approach

In older people, drug prescription is challenged by the prevalence of numerous treatments for their comorbidities, by cognitive impairment limiting drug observance, and by the risk itself. CKD stages 1–3a should be treated like osteoporosis.[87] In CKD stage 3b-5, the needs for priority settings on treatment must be discussed with multidisciplinary global insight. The management of confirmed biochemical abnormalities (hyperphosphatemia, hyperparathyroidism and vitamin D deficiency) should be considered before specific fracture prevention therapeutics. Table 1 summarizes data on CKD and age provided by pivotal studies. Although the older individual is the targeted population, Table 1 also illustrates that a global approach with renal function and geriatric musculoskeletal parameter outcomes remain poorly reported. Here, we discuss the main limitations of drugs in CKD patients.

According to a post-hoc analysis of pivotal studies, CKD-MBD can be treated like osteoporosis until stage 3, including if biochemical parameters remain in the normal range; however, the use of bisphosphonates as any anti-resorptive drug therapy in CKD can paradoxically increase fracture risk by increasing failure in mineralization, but not bone volume. This limitation is related to the prevalence of adynamic bone disease (ABD) in CKD.

Thus, if levels of bone turnover biomarker remain low as in ABD, the use of bisphosphonates can worsen the condition.[88] Long-term use of bisphosphonates in CKD can also lead to ABD.[89] The kidney excretes bisphosphonates hours after ingestion by passive glomerular filtration or a proximal tubular way, whereby about 27% to 62% of the drug is set on bone. A threshold of 30 mL/min is considered for drug prescription. This threshold resulted from pivotal studies and nephrotoxicity studies of animals.[90]

- The more the GFR decreases, the more the drug accumulation increases, with verified nephrotoxicity in rapid intravenous infusion of zoledronate or pamidronate,[91,92] which justifies the spacing between delivery.[93] Nonetheless, the use of oral bisphosphonates such as 5mg risedronate remains safe on the kidney and efficient for BMD[94] and has been tested specifically in older individuals.[95] Alendronate also increases BMD even with CKD stage 3 and 4, and also increases PTH level at 18 months.[96] Alendronate has also been tested on vascular calcifications.

- Teriparatide is a PTH analog. Actually, data are missing in CKD patients with GFR <30 mL/min other than the post-hoc analysis of the 2014 pivotal study.[97] Teriparatide could be useful in ABD or parathyroidectomy.

- Denosumab is a monoclonal anti-Rank-ligand antibody whose specificity was tested in patients with 15 to 30 mL/min GFR. Denosumab remains an antiresorptive therapy with the same bone complications as for bisphosphonates. In addition, because of a lack of residual effect when stopped, denosumab must be relayed by another antiresorptive therapy to avoid a cascade of vertebral fractures, which limits the prescription in the same range as for other drugs. Post-hoc analysis of the FREEDOM study of dialysis showed an increase in BMD at 6 months but also in PTH level and prevalence of hypocalcemia.[98] In CKD stage 4 with high risk of fracture in younger adults, Hampson suggested considering denosumab or off-label prescription of bisphosphonate.[99]

Bone turnover must be explored (bone biopsy, biomarkers) to validate the absence of ABD when antiresorptive drugs have no effect. If this option is retained, the recommendation for patients with low BMD and reduced life expectancy is to keep the therapy to the end, making it suitable also in older CKD patients.

Future Directions

Although aging is a common notion, its mechanisms remain incompletely known. In cell biology, aging could be characterized by programmed senescence or an accumulation of lifelong injuries. Cellular senescence is a cell fate involving extensive changes in gene expression and proliferation arrest. Pathways involved are genetic instability, telomere attrition, hormonal cycle influence or immune system decline. This senescence also involves cell cycle deregulation (via $p21^{CDKN1\alpha}$ or $p16^{INK4\alpha}$), an increase in lysosomal β-galactosidase activity, and apoptosis resistance. Many other pathways have been described, such as oxidative stress pathways and non-enzymatic protein glycation and accumulation of advanced glycation endproducts altering protein function. Moreover, a dynamic process is involved, whereby the senescence phenotype spreads to the surrounding tissue by a specific secretion of senescent cells. Such cells

Table 1 Age and Chronic Kidney Disease (CKD) Assessment from Pivotal Studies or Among Them, for Drugs Used in Osteoporosis in Older People

References	Drug	Study Name	No. of Treated Patients	No. of Older Participants	Mean Age, Years (Intervention Group)	CKD	Relevant Age-Related Outcome
(Black et al, 1996)[103] (PS)	**Alendronate (ALN)**	FIT	1022 ALN (50.4%)	263 (25.8%) in the 75–81 group	70.7 ± 5.6	-	
(Black et al, 2000)[105] (PH)			819+1022 ALN (50%)	-	70.8 (VF group) 68.8 (OP group)	-	History of falls: > 25% Regular exercise: > 44%
(McClung et al, 2001)[95] (PS)	**Risedronate (RSN)**	HIP	6197 RSN (66%)	2573 (66%) RSN ≥ 80 years 3624 (66%) RSN 70–79 years	83 ± 3 (RSN ≥ 80 group) 74 ± 3 (RSN 70–79 group)	-	RSN decreased the number of hip fractures over age 80
(Harris, 1999)[108] (PS) (Boonen et al, 2004)[107] (PH)		VERT HIP VERT-NA VERT-MN	1624 RSN (66%) 6126 RSN (pooled studies)	- 704 (50.5%) RSN patients (all ≥ 80 years)	69 ± 7.1 83.1 ± 3.1	- -	Relevance of RSN in VF prevention in the oldest patients
(Black et al, 2007)[104] (PS) (Boonen et al, 2010)[106] (PH)	**Zoledronate (ZOL)**	HORIZON	3875 ZOL (50%) 4692 ZOL (50%)	1497 (38.6%) ≥ 75 years 1961 (41.7%) ZOL ≥ 75 years	73.1 ± 5.3	CKD 4–5: 160 (4.1%) ZOL and aged group • mean GFR 55.6 ± 15.0 • CKD stage at baseline CKD 1–2: 671 (34.2%) CKD 3:1285 (65.7%) CKD 4–5:1 (0.1%) • Follow-up: 180 (10.4%) GFR< 30 mL/min	• Relevance of ZOL in fracture prevention in older people • No difference in risk of falls in the < 75 and ≥ 75 age groups vs placebo.

Table 1 (Continued).

References	Drug	Study Name	No. of Treated Patients	No. of Older Participants	Mean Age, Years (Intervention Group)	CKD	Relevant Age-Related Outcome
(Neer et al, 2001)[110] (PS)	**Teriparatide (TPD)**	-	544 +552 (50%) TPD		TPD 20 µg with or without X-ray: 69 ± 7 and 71 ± 8	-	Serum creatinine level and creatinine clearance were unaffected by TPD (exclusion creatinine > 177 µM)
		EFOS (PH)	1581 TPD	589 (37.3%) ≥ 75 years	• In the ≥ 75 years group: 79.2 ± 3.6 • < 75 year group: 66.1 ± 6.4		• Better results on quality of life with TPD • Significant difference between age groups in assistance with arms when standing up from chair (p<0.001) and more dementia (p= 0.008)
(Orwoll et al, 2003)[111] (PS men)		GHAJ	290 (66%)	-	59 ± 13	-	White men
(Kendler et al, 2018)[109] (PH)		VERO	680 TPD 680 RSN	147 TPD (22%) ≥ 80 years 111 RSN (16%) ≥ 80 years	TPD arm: 72.6 (8–77) RSN arm: 71.6 (8–58)	Exclusion Cockcroft < 30 mL/min	Comparison between 2 treatments. No more falls with Risedronate or Teriparatide TPD.
(Cummings et al, 2009)[98] (PS)	**Denosumab (DNS)**	FREEDOM	3902 (50%)	1236 (31.6%) DNS ≥ 75 years	72.3 ± 5.2	-	

Notes: All studies included in this table were selected among pivotal studies for each treatment. We chose to provide post-hoc analysis data or studies from multicentric controlled studies involving older people. Number of patients are those in the intervention group. Age: mean age at inclusion. Drugs are always taken without association. A minus sign represents no data are available after reading and specific research with the following key words: creatinine, renal, kidney, CKD, glomerular filtration rate.
Abbreviations: PS, pivotal study; PH, post-hoc study involving older or very old CKD patients; GFR, glomerular filtration rate; NA, not applicable; VF, vertebral fracture; OP, osteoporosis.

secrete a range of pro-inflammatory cytokines, chemokines and proteases (interleukin 6, CXCL-12, matrix metallopro-teinase, etc.), termed the senescence-associated secretory phenotype (SASP), which contributes to local and systemic dysfunction with aging. To date, three types of senotherapies are described: senolytics, senomorphics, and senosuppres-sors (Figure 3). They inhibit apoptosis resistance and the activation of survival pathways and decrease autophagy, SASP and metabolic aberrations. The use of senotherapeutic agents prevented tissue degeneration and improved longevity in mice models.[100] Senotherapeutic agents also provide new perspectives for musculoskeletal aging. Different approaches are efficient for targeting cellular senescence in age-related bone loss in mice, with a transgene or a pharmacological approach. The use of Janus kinase inhibitors on the SASP also provides efficient results with lower bone resorption and maintained or higher bone formation in trabecular and cortical bone, respectively.[101] In another SASP model of senescence with senescent cell transplant impairing functional parameters used in clinical practice (maximal walking speed, muscle strength, physical endurance, body weight), the use of senolytics such as dasatinib+quercetin reduced senescent cell burden and decreased pro-inflammatory cytokine secretion, even in human adipose tissue explants. Senolytics prevent and alleviate the senescent cell transplantation-induced physical dysfunction. Clearing senescent cells alleviates physical dysfunction and increases the remaining lifespan in older mice.[102] These promising approaches could be a relevant perspective in frailty and dependence prevention in older people.

Conclusions

In the multi-approach course that represent the understanding of aging, this review emphasizes that common clinical concerns (CKD, fall and fractures …) need more than ever a multidisciplinary approach in order to get the big picture. We should remain as simple as possible, and we first recommend assessing residual life expectancy as a major key factor for decision-making. Osteoporosis remains a good model with efficient drugs even on CKD older individuals. It seems important to have in mind the limits of all the assays and measures that could be performed, to limit misinterpretation and excessive inflation of risk of error.
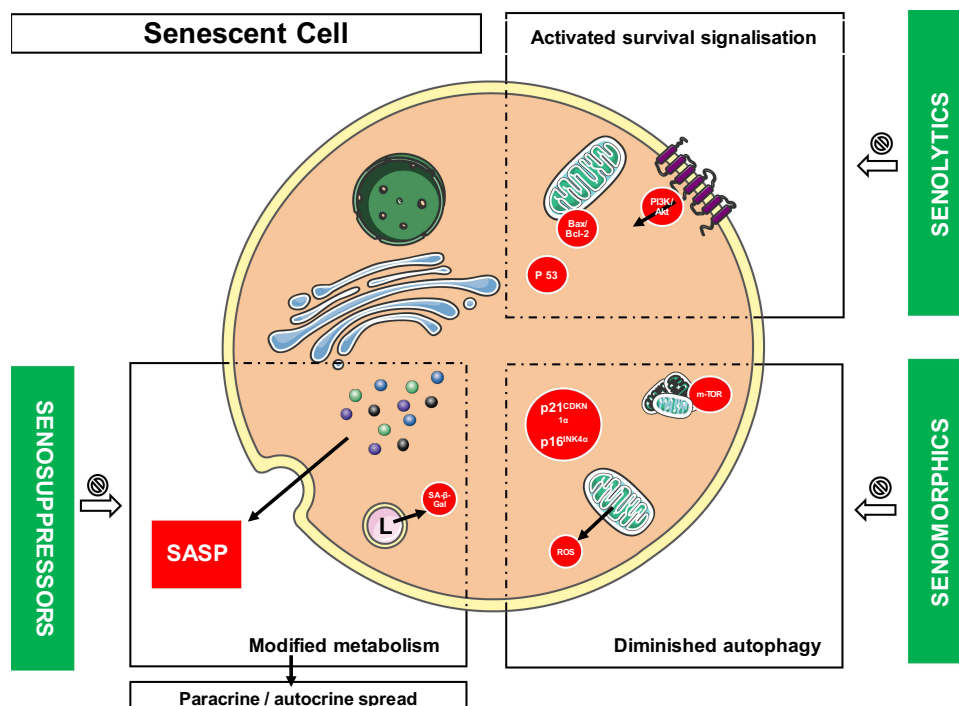

Figure 3 Current approaches in research on senolytics. This figure illustrates different pathways currently known as involved in cellular senescence. Modified metabolism in senescent cells can be identified with the SASP production. Senosuppressors mostly target the SASP secretion, whereas senomorphics limit cell cycle deregulation and oxidative stress. Senolytics also target the apoptosis resistance dysregulation.
Abbreviation: SASP, senescence-associated secretory phenotype.

Concise Methodology

In this review, we first performed an electronic search from January 1980 to February 2020 using MEDLINE (PubMed) for original works and expert report. An iterative approach included 2 equations with the following MeSH terms: "Fracture" + "Chronic kidney disease"; "Bone" +" Elderly" +"Chronic Kidney Disease". The first reviewer (PEC) screened the titles and abstracts according to these keywords criteria. Then, the selection was transferred to the second reviewer (MCS) who refined and confirmed the selection. The two reviewers then performed a more careful reading of the manuscripts and selected the most relevant papers to their aim. We also added guidelines of international and national societies as well as relevant review articles in order to illustrate positions in case scientific data are not available. A narrative synthesis of each organ failure was conducted, aiming to describe the evidence and limitations for the diagnosis for each tissue insufficiency. We then analyzed the literature in the light of concomitant diseases and identify the needs for further research.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

Disclosure

Pierre-Emmanuel Cailleaux declares that he has no competing interest.

Martine Cohen-Solal declares that she has no competing interest.

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