Published in : Archives of Osteoporosis (2025), vol. 20, article n°96, p. 1–11
DOI: 10.1007/s11657-025-01570-z
Status : Postprint (Author's version)

REAL-WORLD DATA FROM A NATIONAL SURVEY ON MANAGEMENT OF CKD-ASSOCIATED OSTEOPOROSIS AMONG ITALIAN NEPHROLOGISTS

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Published in : Archives of Osteoporosis (2025), vol. 20, article n°96, p. 1–11
DOI: 10.1007/s11657-025-01570-z
Status : Postprint (Author's version)

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Abstract

Summary Chronic kidney disease (CKD)-associated osteoporosis increases fracture risk, yet clinical guidance remains unclear. A survey of 89 Italian nephrologists revealed heterogeneous biomarker availability and varied treatment approaches. Denosumab was the preferred antiresorptive agent, while anabolic drugs were rarely used. Findings highlight progress in CKD-related bone health management despite existing uncertainties.

CKD-associated osteoporosis comprises the skeletal effects of a complex mineral and bone disorder causing increased risks of fragility fractures (FF), cardiovascular events, and mortality. Existing clinical guidance about CKD-associated osteoporosis is vague, leading us to hypothesize that a treatment gap exists and that clinical practice is dependent on local availability of diagnostic tools.

Purpose and methods The aim of the current survey was to determine current attitudes and practices among Italian nephrologists regarding the evaluation and management of CKD-associated osteoporosis. An online survey was designed, consisting of 9 thematic groups with a set of 16 closed questions regarding the availability of biomarkers and BTMs at reference laboratories and their use for the diagnosis and treatment

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of CKD-associated osteoporosis in patients with different stages of CKD, including CKD stages G4-5 and dialysis patients. Results were compared to a previous survey on the use of BTMs from 2022.

Results Eighty-nine Italian nephrologists participated in the survey, reporting that parathyroid hormone (PTH), alkaline phosphatase, and 25-hydroxy-vitamin D measurements were available in 92–100% of their reference laboratories. Measurements for fibroblast growth factor-23, Klotho, Matrix Gla protein, procollagen type 1 N-terminal propeptide, and tartrateresistant acid phosphatase 5b were available in 64–74% of cases. Regarding PTH cut-off values, 47.2% followed KDOQI and 43.8% followed KDIGO recommendations. Vitamin D was widely used across CKD stages (cholecalciferol 27–37.1%, calcifediol 9–12.4%, calcitriol 47.2–53.9%, and paricalcitol 21.3–30.3). Denosumab was the preferred antiresorptive agent in all CKD stages (22.5%–28.1%), while the use of bisphosphonates was uncommon in advanced CKD. Anabolic drugs were rarely prescribed.

Conclusions The availability of bone biomarkers is heterogeneous, and an uncertainty still exists regarding the clinical use of biomarkers in CKD-associated osteoporosis. Nonetheless, our findings indicate that Italian nephrologists are increasingly taking proactive steps to prevent and treat bone fragility in CKD patients.

Keywords

CKD-MBD · Bone turnover markers · Bone fracture · Vascular calcification

Introduction

Chronic kidney disease-mineral and bone disorders (CKDMBD) is characterized by complex and variable alterations of biochemical determinants of mineral metabolism; bone turnover, mineralization, and volume; and extra-skeletal calcifications. Dependent effects in patients are the high risk of fragility fractures (FF), cardiovascular events, and mortality, that impact severely on disability-free life expectancy and quality of life [1]. These alterations occur early during the course of CKD, resulting from systemic effects of activated renal repair mechanisms and a decrease in the anti-aging factor klotho [2]. With progressive CKD, phosphorus retention stimulates secretion of the phosphaturic hormones fibroblast growth factor 23 (FGF23) and parathyroid hormone (PTH) [1, 2]. Inhibition of vitamin D activation and reduced calcium uptake further stimulate the development of secondary hyperparathyroidism [3]. Nutritional deficits and a dysbiosis of the gut are common findings in CKD and contribute to reduction in vitamin K levels and a decrease in the active forms of vitamin K-dependent proteins such as osteocalcin (OC) and matrix gla protein (MGP), impacting on bone mineralization and vascular calcification.

In patients with CKD, fracture risk increases progressively as kidney function decreases [4–7]. In addition to traditional risk factors, biochemical determinants of mineral metabolism, including PTH, bone alkaline phosphatase (BALP), vitamin K1, and FGF23, are associated with increased fracture risk in CKD [6, 8, 9]. Besides the considerable disease burden associated with fractures, evidence exists for a link between fractures and cardiovascular disease in CKD [10–12].

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Determination of bone mineral density (BMD) by dual X-ray absorptiometry (DXA) is a well-established risk marker, and risk prediction tools based on clinical risk factors, e.g., the FRAX score, are widely used for screening of populations at risk to identify individuals for further evaluation by DXA. Both FRAX and DXA can also identify patient with increased fracture risk at all stages of CKD, including dialysis patients. While no CKD-specific cut-offs have been determined, the current KDIGO guidelines recommend DXA for assessment of fracture risk if results influence treatment decisions but no specific recommendations for the use of FRAX have been issued.

In the general population, bone turnover markers (BTMs) are suggested for the evaluation of treatment effects in fracture prevention. Several bone turnover markers are renally excreted (e.g., the bone resorption marker C-terminal crosslink of collagen I (β-CTX-I), limiting their use in CKD, but the bone formation markers intact procollagen type 1 amino-terminal propeptide (iPINP) and BALP and the bone resorption marker tartrate resistant acid phosphatase type 5b (TRACPb) are not influenced by kidney function or dialysis and can be used in all CKD stages for the clinical estimation of bone turnover [13–16]. In addition, BTMs predict cardiovascular outcomes and mortality in CKD [12] and BALP may be a stronger predictor of fracture risk than DXA in hemodialysis patients [17].

Bone biopsy (BB) with histomorphometric analysis serves as the gold standard diagnosing various forms of renal osteodystrophy [8, 9, 18, 19], but the invasiveness of the procedure, low accessibility to the histomorphometry method, small studies, and lack of standardized diagnostic criteria may explain a considerable heterogeneity regarding reported prevalences of ROD subtypes [10, 15]. Consequently, the utilization of BB has significantly declined in the last decades [8]. The potential of BTMs to replace BB with histomorphometry has been demonstrated in several studies [14, 15, 20]. The effect of combining BTMs with clinical fracture prediction tools and imaging on the accuracy of fracture risk prediction has not yet been sufficiently studied.

Native and active vitamin D is indicated in CKD for the treatment of hyperparathyroidism [11, 21].

Antiresorptive drugs, i.e., bisphosphonates and denosumab, have a well-documented effect on fracture risk in patients with osteoporosis. While a positive effect on BMD in patients with CKD has been demonstrated in several studies, evidence for fracture prevention from large randomized controlled trials is lacking [12]. The risk of hypocalcemia increases in patients with high bone turnover, especially with denosumab, but can be mitigated by adequate PTH control and substitution of vitamin D and calcium before initiation of antiresorptive treatment. An additional concern is a theoretical risk of vascular calcifications due to the inhibitory effect on bone turnover; however, clinical trials in patients with preserved or impaired kidney function demonstrated no increased cardiovascular risk [22]. Instead, bisphosphonates may even exert a vasculoprotective effect [23–26].

Drugs with anabolic action can induce an osteogenic action at the bone level. Teriparatide is a recombinant human 1–34 N-terminal PTH sequence with a positive effect on bone turnover and BMD in patients with different stages of CKD [27]; however, efficacy regarding fracture risk reduction and safety and tolerability in patients with advanced CKD are not sufficiently studied [27].

Romosozumab is a humanized monoclonal antibody that inhibits sclerostin, promoting osteoblast differentiation and activity. In patients with mild to moderate CKD, administration of romosozumab has

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been shown to increase BMD at the lumbar spine and femoral neck [28, 29]. However, its use is associated with a potentially increased risk of cardiovascular events, necessitating caution in CKD patients who are already at high cardiovascular risk [30]. The aim of the current survey was to determine current attitudes and practices among Italian nephrologists regarding evaluation and management of CKD-associated osteoporosis.

Material and methods

An online survey was designed, consisting of 9 thematic groups with a set of 16 closed questions regarding the availability of biomarkers at reference laboratories and their use for the diagnosis and monitoring of CKD-associated osteoporosis; the frequency of consultation requests to the Italian Medicines Agency (AIFA) regarding Note 79 on osteoporosis therapy for treating skeletal fragility in patients with CKD, and the use of pharmacological agents in the management of CKD-associated osteoporosis in patients with different stages of CKD, including CKD stages G4-5 and dialysis patients.

A web platform (Limesurvey) was used to distribute the survey and collect the answers. The survey was sent to all members of the Italian Society of Nephrology (SIN, Società Italiana Nefrologia) from November 2022 to March 2023. Besides the questions, the survey contained an introduction, explaining the aims and purposes, as well as instructions on how to fill out the form.

Most biomarkers considered in the survey are determined using immunochemiluminescent methods on automatized platforms available in the clinical laboratory setting; however, sclerostin is evaluated using manual ELISA assays. The analytical performance for all tests is routinely monitored using procedures adopted by all clinical laboratories for the monitoring of quality performance of all tests in the routine setting.

Statistical analysis

Data were analyzed with STATA software (StataCorp. Stata Statistical Software: Release 16. College Station, TX: StataCorp LLC, USA.). Results were expressed as absolute frequencies and rates, and the confidence interval (95%) was calculated using Mid-P exact method. For medication use, data were presented as median and interquartile range for dose and as frequency in percentage terms for drug utilization.

Results

Out of 2025 (1048 females and 977 males; 61% aged ≤ 50 years) nephrologists registered as members of SIN during the study period, 89 responded, for an overall response rate of about 4%.

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Availability of biomarkers for management of CKD-associated osteoporosis

A high degree of availability at referral laboratories was reported for venous pH, 25-OH-vitamin D, ionized calcium, phosphorus, magnesium, PTH, and ALP, while availability was fair regarding BALP and poor regarding vitamin K, osteocalcin, β-CTX-I, and 1,25-OH-dihydroxyvitamin D (Supplementary Table 1). Most clinicians reported that they could not request total FGF23, intact FGF23 or its c-terminal, soluble Klotho, Matrix Gla protein, PINP, or TRACP5b.

Use of parathyroid hormone

Of the 89 nephrologists interviewed, 53.9% stated that they controlled PTH every 3 months, 17.9% every other month, 11.2% every month, and 15.7% every 6 months. Only 1.1% controlled PTH irregularly, depending on calcium, phosphorus, and vitamin D levels. Most nephrologists used a third-generation (37.1%) or a second-generation (25.8%) PTH assay, while 34.8% did not know which method was used and 2.2% used other methods. Regarding treatment, a majority (62.9%) considered phosphorus and PTH equally important, 34.8% gave priority to hyperphosphatemia, and 2.2% prioritized PTH. Target levels for PTH were 150–300 ng/L (47.2%) or 2–9 × upper limit of normal for the assay used (43.8%), 2.2% treated SHPT if PTH was > 500 ng/ml, and 1.1% if PTH was > 600 ng/ml. Five nephrologists did not use any of these criteria. The reported proportions of patients with hyperparathyroidism are depicted in Supplementary Fig. 1.

Use of alkaline phosphatase

Regular intervals for control of ALP varied from once per month to once per year, while 4.5% reported irregular control, depending on calcium, phosphorus, or PTH levels (Fig. 1). A majority considered ALP of equal importance to PTH as a predictor of fracture risk, 8.9% consider it more important than PTH, while 26.9% did not consider ALP as a predictor of fracture risk.

Use of other biomarkers and determinants of mineral metabolism

Frequencies for control of 25-hydroxy-vitamin D varied from once per month to once per year, while 12.3% controlled it irregularly, depending on calcium, phosphate, or PTH levels (Fig. 2A). The majority of nephrologists never consider FGF23 or Klotho in patients with CKDassociated osteoporosis, but 22.5% consider these markers in patient with fracture or increased cardiovascular risk (Fig. 2B). Determination of the BTMs β-CTX-I, PINP, and TRACP5b was uncommon among the interviewed nephrologist, but approximately 1/3 considered their determination in CKD patients up to stage 5D (Fig. 2C–E). Most of the interviewed nephrologists considered the determination of OC and uremic toxins (such as p-Cresyl sulfate and indoxyl sulfate) relevant for the evaluation of CKD-associated osteoporosis (Supplementary Fig. 2A-B).

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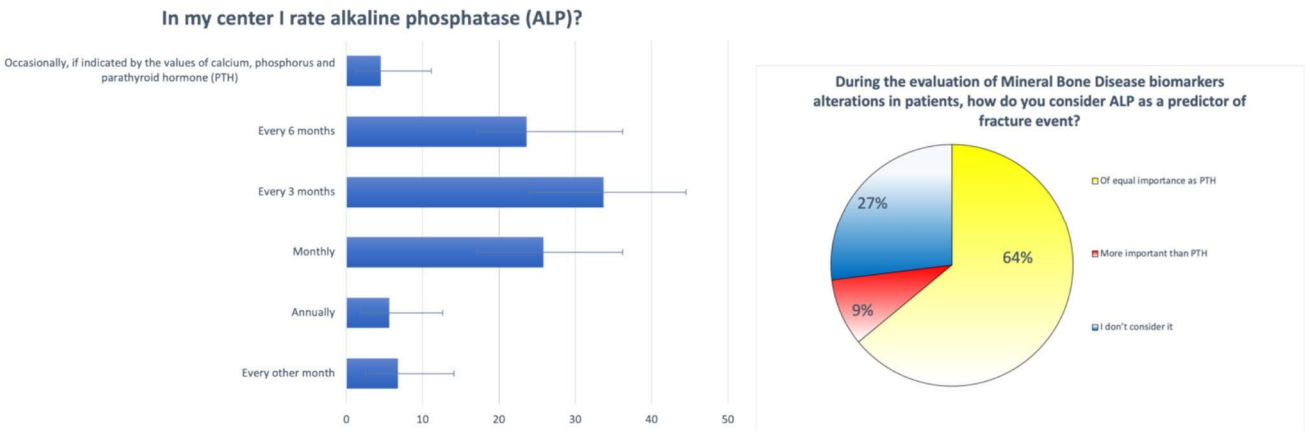

Fig. 1 Alkaline phosphatase (ALP) use

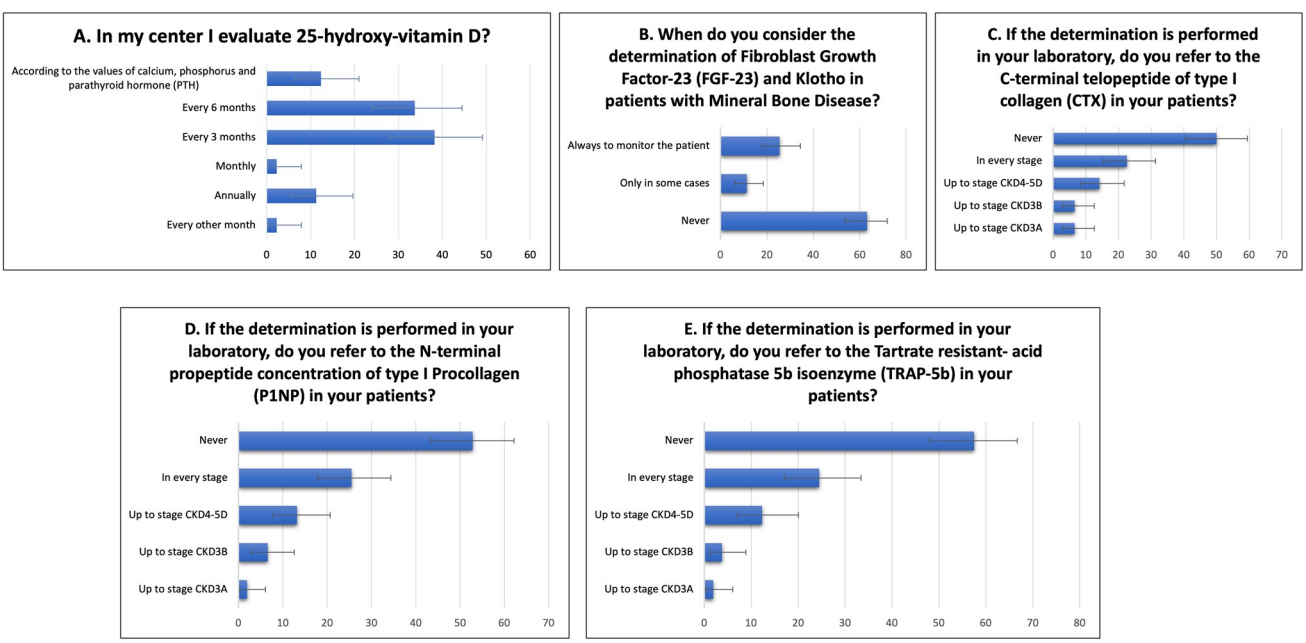

Fig. 2 Other biomarkers use

Treatment with calcium and vitamin D

Oral calcium supplementation increased from 21.3% in CKD stage G3 to 28.1% In hemodialysis patients (Fig. 3). Median daily dose was consistently 500 mg. Calcitriol was the most common vitamin D preparation used, followed by cholecalciferol and paricalcitol (Fig. 3). For calcitriol and cholecalciferol, median daily doses increased in higher CKD stages, while the median daily dose of paricalcitol was 1 µg in all CKD stages. Intravenous (iv) administration of calcitriol and paricalcitol was restricted to dialysis patients and was relatively rare, but more common for paricalcitol (median weekly dose 5 µg) than for calcitriol (median weekly dose 5 µg).

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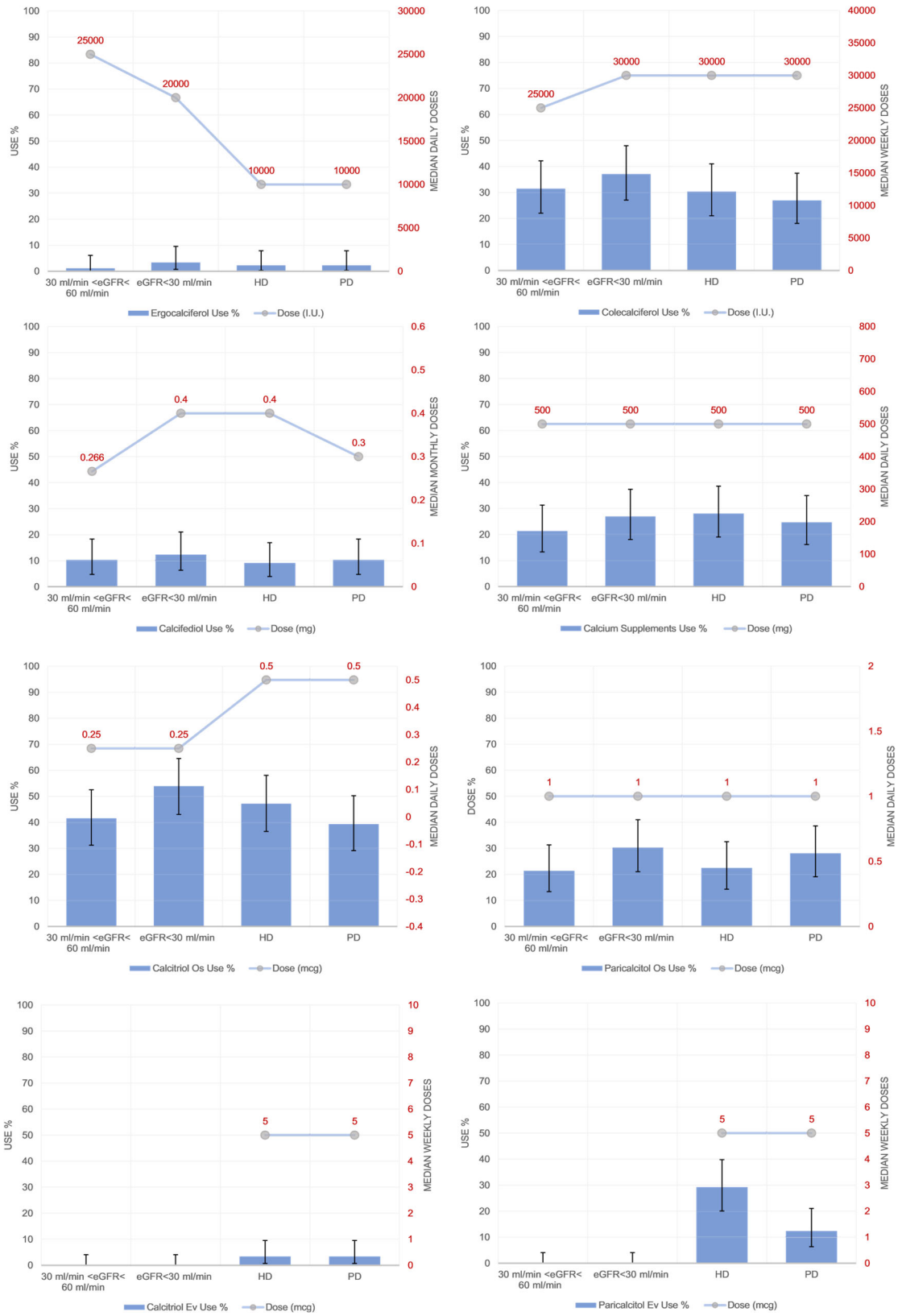

Fig. 3 Use of vitamins D and analogues

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Interestingly, approximately 15% of peritoneal dialysis (PD) patients were treated with iv preparations, despite a lack of blood access through the dialysis machines. The use of ergocalciferol and calcifediol was uncommon (Fig. 3).

Treatment with antiresorptive and anabolic drugs

Denosumab was the most commonly used antiresorptive drug in all stages of CKD, with reported proportions of 27% in patients with CKD stage G3 and 28.1% in hemodialysis patients (Fig. 4). The use was least common in peritoneal dialysis patients. The median dose was 60 mg every 6 months in all patients. Oral bisphosphonates were mostly administered in CKD stage G3, while their use was rare in more advanced CKD. Most patients were prescribed alendronate, followed by risedronate and clodronate. The use of intravenous preparations was rare in all CKD stages. Median doses were consistent in all CKD stages for alendronate, risedronate, and ranelate, while doses were decreased in advanced CKD for ibandronate and zoledronate and increased for clodronate (Fig. 4). Teriparatide was only used in a few patients with CKD 3 and in CKD 5D with a daily dose of 20 mg (Fig. 4).

Discussion

The current survey is the largest investigation to date of attitudes and practices among nephrologists regarding the management of CKD-associated osteoporosis across all stages of CKD, including CKD G4-5 and dialysis patients.

The survey confirms our recent report of insufficient availability of BTMs at clinical reference laboratories, based on a survey performed in 2021 [31], despite their superiority for the evaluation of bone turnover compared to PTH, which currently is the most commonly used parameter to evaluate bone turnover in CKD patients [14, 15, 22]. In addition, we demonstrate a novel positive attitude among nephrologists towards an active approach to pharmacological fracture prevention in patients with advanced CKD, indicating a possible paradigm shift in the management of skeletal fragility in CKD patients.

Compared to our previous survey, we observed a similar clinical availability of ionized calcium, magnesium, PTH, ALP, and 25-OH-vitamin D (92–100% vs. 94–99% previously) as well as osteocalcin, β-CTX-I, and 1,25-OHdihydroxyvitamin D (28–58% vs. 32–54% previously). In contrast, the availability of parameters previously considered mostly experimental—FGF23, Klotho, MGP, PINP, and TRACP5b—increased significantly (24–36% vs. 3–11% previously). Among bone turnover markers, BALP had the highest availability (75%), aligning with current KDIGO guidelines, which recommend BALP as an alternative to PTH for assessing low bone turnover in CKD patients. [32]. However, combining several bone turnover markers improves the predictive power; therefore, the increased availability of non-renally excreted bone turnover markers in this report is a positive development.

In the current survey, a majority determines PTH levels every 3 months (53.9%) in a laboratory that generally uses second- (25.8%) or third-generation (37.1%) kits, which is in line with our previous survey [28] and KDIGO recommendations [32]. Approximately half of the respondents favored the KDOQI target

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of 150–300 ng/ml and the other half favored the KDIGO target of 2–9 × ULN for the assay. Only a minority determines ALP less than every 3 months (23.6%) while KDIGO recommends an annual control or more frequently in the presence of hyperparathyroidism. PTH and ALP were by most respondents considered equally important predictors of fracture risk. Most nephrologists control 25-hydroxy-vitamin D every 3–6 months, while only 34.8% of the cohort was convinced of the clinical relevance of OC. Attitudes towards other parameters of mineral metabolism have not changed substantially from our previous study, where they were widely discussed [31].

Calcitriol was the most frequently used administered agent with higher doses in dialysis patients than in earlier CKD stages. Cholecalciferol was more common in patients not on dialysis, while the use of paricalcitol was similar in all CKD stages. Calcium supplements are used in all patient categories by approximately 1/3 of the surveyed population at a stable median dose of 500 mg. According to KDIGO guidelines, nutritional vitamin D substitution is recommended for the treatment of hyperparathyroidism in CKD patients not requiring dialysis, while calcitriol, or vitamin D analogues, or calcimimetics, or a combination of calcimimetics and calcitriol or vitamin D analogues are recommended to lower PTH in dialysis patients [17]. Calcitriol may also exert a protective function against vertebral fractures in CKD [33].

The use of *bisphosphonates* decreased with increasing CKD stages in line with a recent observational study [34]. The median dose for alendronate and risedronate, which were most used, remains stable in all CKD stages, while ibandronate and zoledronate dosing was reduced in patients with GFR below 30 ml/min/1.73 m^2. Doses of clodronate were higher in dialysis patients than in patients not on dialysis. The efficacy of bisphosphonates to improve BMD in dialysis patients [35–37] and in CKD patients not on dialysis has been demonstrated repeatedly [32, 38]. While an observational study indicated a dosedependent 14% increased risk of CKD progression [39], a recent study in kidney transplant patients treated with alendronate, risedronate, or ibandronate demonstrated no decrease in GFR [40]. Bisphosphonates appear to reduce the risk of cardiovascular events and cardiovascular mortality [23–25].

Denosumab was the most frequently used antiresorptive drug by the clinicians we interviewed, with the percentage of nephrologists who use it remaining stable in all CKD stages. Numerous observational studies and post hoc analyses of clinical trials in all CKD stages demonstrate the efficacy of denosumab to increase BMD and reduce fracture risk [41, 42]. The risk of hypocalcemia is higher with denosumab than with bisphosphonates [43] and can be predicted by TRACP5b and BALP [42, 44]. Supplementation with calcium and vitamin D can largely prevent severe hypocalcemia [26, 45]. After discontinuation of denosumab, an increase in the BTMs β-CTX-I and PINP and a decrease in BMD to baseline levels after 1 year have been demonstrated [46, 47]. A recent observational study in CKD patients for a period of up to 5 years found increases in BMD, cortical thickness, and strength indices for the first 3.5 years, then reaching a plateau [48], contrasting findings of continued BMD increase in postmenopausal osteoporosis [49]. Data from the current survey has highlighted Italian nephrologists' confidence in using denosumab for fracture prevention in all CKD stages, including dialysis, contrary to that published recently in the literature [43].

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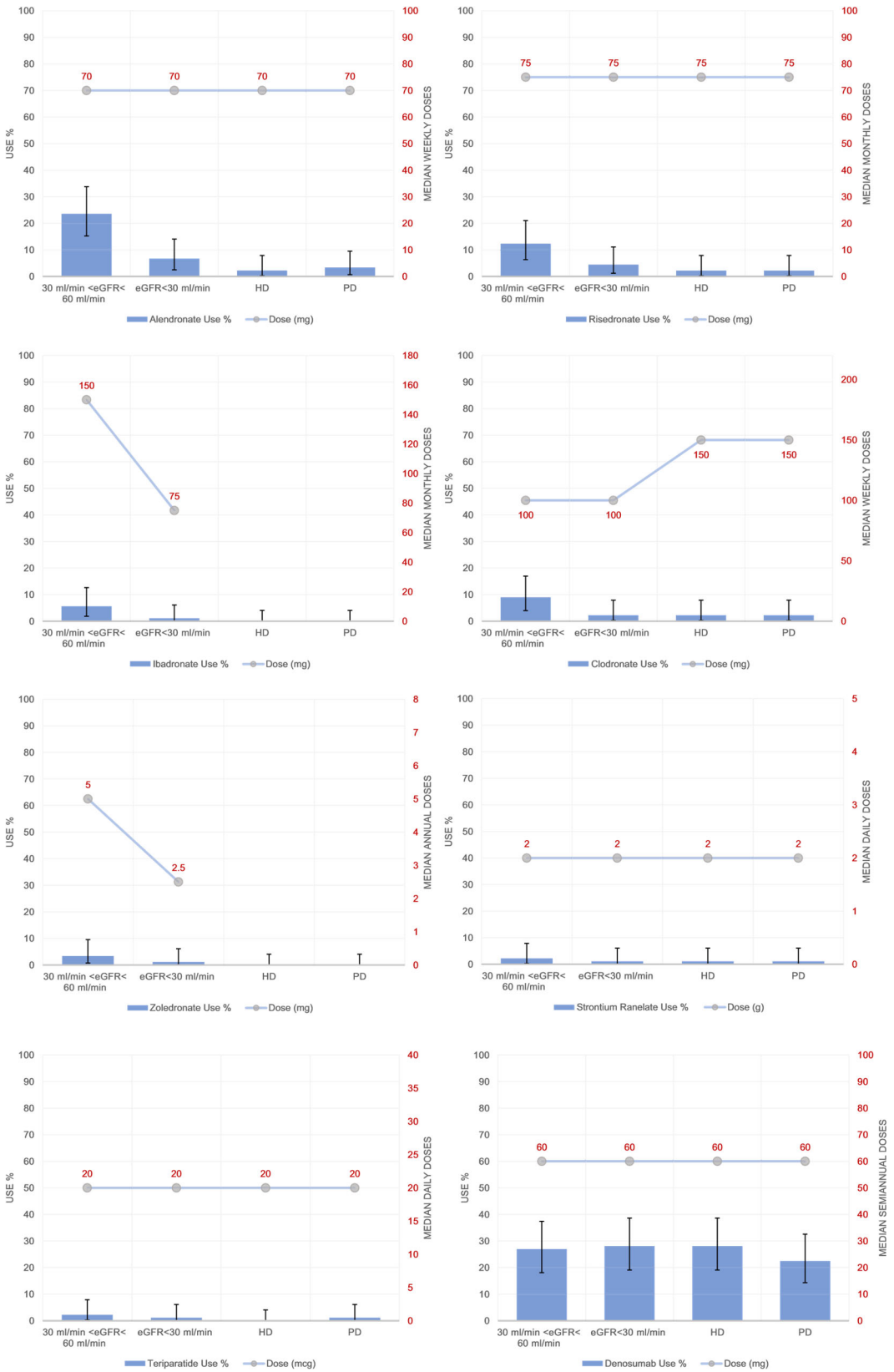

Fig. 4 Use of antiresorptive and anabolic drugs

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Teriparatide was not frequently used in the current survey, and none of the nephrologists we interviewed administer this drug to hemodialysis patients. Several studies have demonstrated an increase in BMD by different teriparatide dosing regimens in CKD [50–52]. Both daily and weekly administration led to an increase in the serum levels of BTMs; however, daily administration increased both formation and resorption markers, while weekly administration increase formation markers and reduced resorption markers [50, 52]. In addition, daily administration increased BMD at the femoral and lumbar levels, while in weekly administration, the increase occurred only at the lumbar skeleton. Patients with low bone turnover and parathyroidectomy may benefit particularly from the administration of this drug [30]. However, there are still numerous uncertainties about the use of teriparatide related to dosing, long-term use, and discontinuation [53].

While this study is the largest survey on attitudes and practices regarding fracture prevention in CKD, the low response rate is a limitation, which is unavoidable in national online surveys like ours. Thus, results represent a minority of Italian nephrologists. The lack of demographic data, inability to verify responses, and risk of multiple responses are additional limitations.

Conclusions

This national survey demonstrates an active approach of Italian nephrologists to treat CKD-associated osteoporosis with remarkable confidence, especially regarding the administration of denosumab in all CKD stages. However, it also emerges that access to BTMs, for fracture risk evaluation, treatment choice, and treatment evaluation is still limited. In the absence of guidelines, based on evidence from large clinical trials, better expert opinion-based guidance is needed to reduce the exceptionally high fracture risk of patients with CKD. The search for treatment strategies in this population must therefore be a priority. It may require an increased interaction with pharmaceutical companies to encourage the development of specific treatments for skeletal fragility at various stages of CKD.

Supplementary Information The online version contains supplementary material available at https://d oi.org/1 0 .1007 /s 11657-025-0 1570- z.

Author contribution Conceptualization: MF, GT, MCM, MG, and MH; methodology: MF, GT, AG, AC, and GR; writing: MF, MH, GT, AC, AA, and GR; review and editing: LC, AB, CA, DC, EM, EC, NH, TNL, MLB, SF, CM, SG, SS, GPA, PS, MP, MZ, LDN, CM, MDB, MR, BF, PE, MHLP, JYR, and FB.

Data availability The data that support the findings of this study are available from the corresponding author upon reasonable request.

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DOI: 10.1007/s11657-025-01570-z
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