RESEARCH LETTER

Prescription Patterns of Osteoporosis Medications in Patients With Advanced CKD: A Retrospective Cohort Study

To the Editor:

Pharmacologic strategies to prevent fractures in the general population with osteoporosis include calcium, vitamin D, antiresorptive agents, and bone anabolic drugs. In patients with chronic kidney disease (CKD) stages 2-3, post hoc analyses suggest that bisphosphonates, raloxifene, denosumab, or teriparatide may be effective for fracture prevention. However, there is limited published experience with these medications in patients with CKD stages 4-5 (estimated glomerular filtration rate [eGFR] < 30 mL/min/1.73 m²). For these patients, experts suggest evaluating bone turnover by serologic markers and to consider antiresorptive agents for those with evidence of normal- or high-turnover disease. Providers treating patients with CKD stages 4-5 and osteoporosis must balance the potential benefit of available pharmacologic options in fracture prevention against the largely unstudied potential side effects in this patient population.

We aimed to review the current pharmacologic treatment patterns of patients with CKD stages 4-5 diagnosed with osteoporosis by dual-energy x-ray absorptiometry (DXA) scan (T score ≤ 2.5), comparing them with osteoporotic patients with CKD stages 2-3 (eGFRs, 30-90 mL/min/1.73 m²). Our primary outcome was the proportion of patients within each group who were prescribed antiresorptive or bone anabolic medications.

Using the Research Patient Data Registry, a centralized clinical data registry at Mass General Brigham, we screened for all adults 55 years and older treated at Massachusetts General Hospital with at least 1 available DXA scan and diagnosis of CKD by International Classification of Diseases, Tenth Revision codes between January 1, 2000, and January 1, 2019. After limiting the CKD cohort to patients with an osteoporotic T score of ≤ 2.5 or less at 1 or more skeletal site, we defined CKD stage by eGFR within 1 year before the DXA scan result (Fig S1). Patients with CKD stages 4-5 who were then matched to patients with CKD stages 2-3 on a 1:1 basis by age, sex, race, and year of DXA scan. We ascertained the use of osteoporosis medication at 1 year and incidence of fractures at 2 years after DXA by manual chart review. Detailed methods are provided in Item S1. The Institutional Review Board approved this study (2020P003016).

Demographic characteristics were similar between the CKD groups with osteoporosis (Table 1). Despite having lower femoral bone density, patients with CKD stages 4-5 had lower rates of osteoporosis treatment, with 53% prescribed an antiresorptive or anabolic medication compared with 71% of patients with CKD stages 2-3 (P=0.004). Although treatment rates for patients with CKD stages 4-5 not receiving dialysis were statistically similar to those with CKD stages 2-3 (60% vs 71%; P=0.09), treatment rates for dialysis patients with CKD stage 5 were much lower (36% vs 71%; P<0.001). Among the subset of solid-organ transplant recipients, prescription of osteoporosis medications was similar among CKD stages 2-3 and stages 4-5 not receiving dialysis (68% vs 67%; P=0.9; Table S1). Dose-adjusted alendronate (35 mg per week) was the most commonly prescribed medication for patients with CKD stages 4-5 (12%), followed by denosumab (11%), while patients with CKD stages 2-3 were most commonly prescribed 70 mg per week of alendronate (34%), followed by zoledronic acid, ≥4 mg per year (13%; Table 2; Fig S2). The use of either calcium or vitamin D analogues was similar between the CKD stages 2-3 and stages 4-5 (87% vs 89%; P=0.7). Finally, analyses within the full cohort of patients with CKD stages 4-5 (n=154) revealed similar demographic characteristics among patients who were prescribed osteoporosis treatment and those who were untreated (Table S2). Of note, 47% of patients using antiresorptive medications with stages 4-5 CKD had parathyroid hormone (PTH) levels < 100 pg/mL. Fractures at 2 years were more common among patients with CKD stages 4-5 compared with stages 2-3 (11% vs 23%; P=0.02).

Thus, among a population of patients with CKD with osteoporosis, our study found overall lower rates of osteoporosis treatment among patients with more advanced CKD. Hesitancy when prescribing antiresorptive medicines could be due to the perceived risk for worsening adynamic bone disease. Nevertheless, the finding that 47% of patients using antiresorptive medications with stages 4-5 CKD had PTH levels < 100 pg/mL, which can potentially indicate adynamic bone disease in CKD, reveals that some patients with CKD are treated without specific knowledge of the cause of bone abnormalities in this population. Although it has been suggested that osteoanabolic agents might be an effective treatment for adynamic bone disease in CKD, there remains uncertainty about potential cardiovascular effects of PTH/PTH-related peptide analogues and romosozumab in the context of CKD.

Of note, none of our patients had bone biopsy results available and there was very limited use of other serologic markers of bone turnover. Our study is limited by sample size, lack of time-varying eGFR data, and markers of kidney injury such as albuminuria. In summary, this study highlights knowledge gaps and practice variability regarding the use of osteoporosis medications in this high-risk population. Our findings invite researchers to study the use of osteoporosis medications and dosing regimens as they relate to specific CKD stages and serologic markers of bone metabolism.
Table 1. Demographics and Bone Outcomes Among Adults With Osteoporotic T Score and CKD Stages 2-3 Versus CKD Stages 4-5

| Demographics and Outcomes | CKD 2-3 | CKD 4-5 (all) | P vs CKD 2-3 | CKD 4-5 No Dialysis | P vs CKD 2-3 | CKD 5 Dialysis | P vs CKD 2-3 |
|---------------------------|---------|---------------|-------------|---------------------|-------------|----------------|-------------|
| Total patients            | 133 (100%) | 133 (100%)    | 94 (100%)  | 39 (100%)           |             |                |             |
| Age, y                    | 67.6±7.2 | 66.9±7.5      | 0.43        | 67.1±7.9            | 0.62        | 66.4±6.2       | 0.34        |
| Men                       | 28 (21%)  | 28 (21%)      | 0.9         | 21 (22%)            | 0.87        | 7 (18%)        | 0.82        |
| White                     | 104 (78%) | 104 (78%)     | 0.9         | 75 (80%)            | 0.87        | 29 (74%)       | 0.67        |
| Black                     | 14 (11%)  | 14 (11%)      | 0.9         | 9 (10%)             | 0.9         | 5 (13%)        | 0.77        |
| Hispanic                  | 6 (5%)    | 6 (5%)        | 0.9         | 4 (4%)              | 0.9         | 2 (5%)         | 0.9         |
| T score spine             | −2.3±1.1  | −2.3±1.2      | 0.88        | −2.3±1.1            | 0.9         | −2.2±1.5       | 0.69        |
| T score total hip         | −2.0±0.8  | −2.4±0.8      | <0.001      | −2.3±0.8            | 0.003       | −2.6±0.7       | <0.001      |
| T score femoral neck      | −2.5±0.7  | −2.8±0.7      | 0.002       | −2.7±0.7            | 0.01        | −2.9±0.6       | 0.007       |
| Osteoporosis medication   | 94 (71%)  | 70 (53%)      | 0.004       | 56 (60%)            | 0.09        | 14 (36%)       | <0.001      |
| Antiresorptive            | 94 (71%)  | 69 (52%)      | 0.002       | 55 (59%)            | 0.07        | 14 (36%)       | <0.001      |
| Anabolic                  | 0 (0%)    | 1 (1%)        | 1.00        | 1 (1.1%)            | 0.41        | 0 (0%)         | 0.9         |
| Active vitamin D          | 26 (20%)  | 50 (38%)      | 0.002       | 28 (30%)            | 0.08        | 22 (56%)       | <0.001      |
| Nutritional vitamin D     | 90 (68%)  | 94 (71%)      | 0.69        | 69 (73%)            | 0.38        | 25 (64%)       | 0.70        |
| Calcium carbonate or      | 84 (63%)  | 82 (62%)      | 0.9         | 65 (70%)            | 0.40        | 17 (44%)       | 0.04        |
| calcium citrate           |          |              |            |                     |             |                |             |
| Calcium acetate           | 5 (4%)    | 18 (14%)      | 0.008       | 4 (4%)              | 0.9         | 14 (36%)       | <0.001      |
| Calcium or vitamin D      | 115 (87%) | 118 (89%)     | 0.71        | 85 (90%)            | 0.41        | 33 (85%)       | 0.79        |
| Alive at 2 y              | 126 (95%) | 117 (88%)     | 0.08        | 84 (90%)            | 0.20        | 33 (85%)       | 0.08        |
| Fracture within 2 y after DXA | 15 (11%) | 30 (23%) | 0.02 | 19 (20%) | 0.08 | 11 (28%) | 0.08        |
| Hip fracture              | 1 (1%)    | 9 (7%)        | 0.01        | 6 (6%)              | 0.02        | 3 (8%)         | 0.03        |
| Vertebral fracture        | 6 (5%)    | 3 (2%)        | 0.5         | 3 (3%)              | 0.73        | 0 (0%)         | 0.33        |
| Calcium, mg/dL            | 9.5±0.5   | 9.4±0.7       | 0.39        | 9.5±0.6             | 0.7         | 9.2±0.8        | 0.01        |
| Phosphorus, mg/dL         | 3.1±0.7   | 3.5±1.2       | 0.001       | 3.3±0.8             | 0.04        | 4.1±1.6        | <0.001      |
| PTH, pg/mL                | 65 [42, 104] | 116 [69, 212] | <0.001 | 92 [55, 155] | 0.003 | 212 [149, 351] | <0.001 |
| B AlkPhos, %              | 30.6±16.3 | 29.4±17.4     | 0.94        | 29.4±17.4           | 0.94        | NA             | NA          |
| 25-Hydroxyvitamin D, ng/mL | 35.3±17.3 | 33.3±18.9  | 0.45 | 35±19.4 | 0.91 | 29.3±170 | 0.09 |

Note: Data are presented as number (percentage), mean ± standard deviation, or median [IQ1, IQ3]. CKD stages were defined based on estimated glomerular filtration rate within 1 year before DXA result and therefore variations in CKD stage at the time of prescription of a new medication are possible. Use of medications was ascertained at 1 year after the corresponding DXA result. Calcium or vitamin D category was considered separately from osteoporosis medications and includes at least 1 form of calcium carbonate, calcium citrate, calcium acetate, or any vitamin D analogue; calcium carbonate and/or calcium citrate are also listed as a separate variable (without calcium acetate). Fractures include any fracture within 2 years after DXA, documented in the electronic medical record as a new fracture, after excluding facial, pathologic, or traumatic fractures. Death was ascertained by electronic medical record review. Abbreviations and Definitions: B AlkPhos, bone-specific alkaline phosphatase; CKD, chronic kidney disease; dialysis includes hemodialysis and peritoneal dialysis; DXA, dual-energy x-ray absorptiometry; IQ, interquartile; NA, not available; PTH, parathyroid hormone. *Only 4 patients with CKD 4-5 (and none receiving dialysis) and 3 with CKD 2-3 had a B AlkPhos result available within 1 year before or after the DXA scan. For the rest of missing values see Supplemental Methods (Item S1). Antiresorptive medications include bisphosphonates, denosumab, raloxifene, and estrogen/progesterone. Anabolic medications: teriparatide. No patient was receiving abaloparatide or romosozumab.

Supplementary File (PDF)

Figure S1: Identification of study patients.

Figure S2: Use of osteoporosis medications in patients with CKD 2-3 versus CKD 4-5, with and without RRT.

SUPPLEMENTARY MATERIAL

Ignacio A. Portales-Castillo, MD, Cagri Aksu, MD, Sophia Zhao, MD, PhD, Ian Strohbehn, BA, Meghan Sise, MD, Elaine W. Yu, MD, and Sagar U. Nigwekar, MD, MMSc.

Kidney Med Vol 3 | Iss 6 | November/December 2021 1113
Table 2. Type of Osteoporosis Medications Used in Adults With Osteoporotic T Score and CKD Stages 2-3 Versus CKD Stages 4-5

| Medications | CKD 2-3 | CKD 4-5 (all) | P vs CKD 2-3 | CKD 4-5 No Dialysis | P vs CKD 2-3 | CKD 5 Dialysis | P vs CKD 2-3 |
|-------------|---------|--------------|--------------|---------------------|--------------|----------------|--------------|
| Total on osteoporosis medication | 94 (71%) | 70 (53%) | 0.004 | 56 (60%) | 0.09 | 14 (36%) | <0.001 |
| Alendronate, 35 mg/wk | 12 (9%) | 16 (12%) | 0.55 | 11 (12%) | 0.51 | 5 (13%) | 0.54 |
| Alendronate, 70 mg/wk | 45 (34%) | 8 (6%) | <0.001 | 8 (9%) | <0.001 | 0 (0%) | <0.001 |
| Zoledronic acid, >4 mg/y | 17 (13%) | 4 (3%) | 0.01 | 4 (4%) | 0.04 | 0 (0%) | 0.01 |
| Zoledronic acid, <3.9 mg/y | 5 (4%) | 9 (7%) | 0.41 | 9 (10%) | 0.09 | 0 (0%) | 0.59 |
| Ibandronate, 150 mg/mo | 2 (2%) | 2 (2%) | 0.9 | 1 (1%) | 0.9 | 1 (3%) | 0.54 |
| Pamidronate, 30 mg/mo | 1 (1%) | 8 (6%) | 0.04 | 5 (5%) | 0.08 | 3 (8%) | 0.04 |
| Risedronate, 35 mg/wk | 3 (2%) | 2 (2%) | 0.9 | 2 (2%) | 0.9 | 0 (0%) | 0.9 |
| Denosumab, 60 mg/6 mo | 4 (3%) | 14 (11%) | 0.03 | 10 (11%) | 0.02 | 4 (10%) | 0.08 |
| Teriparatide, 20 μg/d | 0 (0%) | 1 (1%) | 0.9 | 1 (1%) | 0.41 | 0 (0%) | 0.9 |
| Hormonal | 2 (2%) | 2 (2%) | 0.9 | 2 (2%) | 0.9 | 0 (0%) | 0.9 |
| No dose available | 3 (2%) | 4 (3%) | 0.9 | 3 (3%) | 0.69 | 1 (3%) | 0.9 |
| Untreat | 39 (29%) | 63 (47%) | 0.004 | 38 (40%) | 0.09 | 25 (64%) | <0.001 |

Note: The number (percentage) of patients receiving the corresponding medicine doses or less are presented. Hormonal therapy includes selective estrogen modulators and estrogen/progestrone compounds. Patients for whom specific doses were not available (eg, only medication name was available) and those who had no medication prescribed are also noted. Of note, 9% of patients with CKD stages 2-3 were receiving dose-adjusted alendronate; this could be due to variations in estimated glomerular filtration rates after dual-energy x-ray absorptiometry or other aspects of provider preference not captured.

Abbreviations and Definitions: CKD, chronic kidney disease; dialysis, includes hemodialysis and peritoneal dialysis.

ARTICLE INFORMATION

Authors’ Affiliations: Division of Nephrology (IAP-C, SZ, IS, MS, SUN) and Endocrine Unit (CA, EWY), Department of Medicine, Massachusetts General Hospital, Harvard Medical School, Boston, MA.

Address for Correspondence: Ignacio A. Portales-Castillo, MD, 185 Cambridge St, Ste 302, Boston, MA 02114. Email: iportalescastillo@mgh.harvard.edu

Authors’ Contributions: Research idea and study design: IAP-C, SUN, EWY; data acquisition: IAP-C, CA; data analysis/interpretation: IAP-C, SUN, EWY, CA; SZ, IS, MS; statistical analysis: IAP-C, SZ; supervision or mentorship: SUN, EWY, MS. SUN and EWY contributed equally to research project oversight and thus serve as co-senior authors. Each author contributed important intellectual content during manuscript drafting or revision and accepts accountability for the overall work by ensuring that questions pertaining to the accuracy or integrity of any portion of the work are appropriately investigated and resolved.

Support: None.

Financial Disclosure: Dr Nigwekar reports grant support from Hope Pharmaceuticals, Laboratories Sanifit, and Inozyme Pharma to his institute and honoraria from Fresenius Renal Therapies, Epizin Pharma, and Laboratoris Sanifit. Ms Sise reports no relevant disclosures. Dr Yu reports grant support from Amgen, Inc and Seres Therapeutics.

Peer Review: Received May 21, 2021, as a submission to the expedited consideration track with 2 external peer reviews. Direct editorial input from the Statistical Editor and the Editor-in-Chief. Accepted in revised form July 11, 2021.

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