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ORIGINAL ARTICLE

Renal impairment among postmenopausal women with osteoporosis from a large health plan in Israel

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Abstract
Summary Bisphosphonates are a first-line treatment for osteoporosis but require adequate renal function. We estimated the prevalence of renal impairment among osteoporotic women in Israeli. Approximately 2.3 % of women had renal impairment at a level that makes them inappropriate for bisphosphonate use, demonstrating the need for alternative therapies for osteoporosis treatment.
Purpose The purpose of this study is to estimate the prevalence of renal impairment among postmenopausal osteoporotic women within a large Israeli health plan.
Methods This was a retrospective analysis of Maccabi electronic medical records, including Israeli women aged ≥55 with either an osteoporosis diagnosis or osteoporosis-related fracture between January 1, 2007, and December 31, 2011. The estimated glomerular filtration rate (eGFR), which was calculated from the lowest serum creatinine levels reported during the study period, was used to classify stage 1–5 renal impairment: normal ≥90, mild 60–89, moderate 30–59, severe 15–29, and failure <15 mL/min/1.73 m^2, respectively. Outcomes were distributions of renal impairment across the study population and stratified by age and osteoporosis-defining event.
Results A total of 15,608 patients met all eligibility criteria. Patients with stage 1–5 renal function accounted for 25.2, 54.9, 18.5, 1.2, and 0.3 %, respectively, of all patients. Of osteoporotic patients, 2.3 % had eGFR levels (<35 mL/min/1.73 m^2) that make them inappropriate for bisphosphonate use. This rate was 1.6 % among patients with an osteoporosis diagnosis and 3.8 % among patients with osteoporosis-related fracture. Within the group of renally impaired patients, older patients were overrepresented. Of the fracture group, patients with hip fractures had a higher prevalence of renal dysfunction (9.3 %) than those having vertebral fractures (3.2 %) or other fractures (2.0 %).
Conclusions Among postmenopausal women with osteoporosis, 2.3 % had renal impairment which makes them inappropriate for bisphosphonate use in Israel.

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Keywords Bisphosphonates · Osteoporosis · Postmenopausal · Renal impairment

Introduction

Osteoporosis is estimated to affect 200 million women worldwide [1, 2]. In one 2003 study of osteoporosis in Israel, approximately 25 % of women 60 years or older self-reported having osteoporosis [3]. The prevalence of osteoporosis increases after menopause because estrogen withdrawal accelerates the rate of bone remodeling, during which more bone is resorbed than replaced [4]. The major clinical manifestation of osteoporosis is fracture, particularly of the hip, which has a considerable negative impact on both the quality of life and the economics of osteoporotic individuals [5].

A number of pharmacologic therapies are available to treat osteoporosis, including bisphosphonates, estrogen, selective estrogen receptor modulators (SERMs), and denosumab [6]. Bisphosphonates, which inhibit bone resorption, are the most commonly used agents for the treatment of osteoporosis [7]. However, because bisphosphonates are cleared by the kidneys, their use requires adequate renal function [8]. Treatment options for osteoporotic patients with severe renal impairment are limited, since all bisphosphonates are not recommended in this population; however, there are variations in the lower limit of creatinine clearance below which a therapy is not recommended: alendronate and zoledronic acid <35 mL/min, ibandronate and risedronate <30 mL/min, and zoledronic acid <40 mL/min. Renal function is typically assessed by estimating glomerular filtration rate, which can be accomplished using different equations, such as the Modification of Diet in Renal Disease (MDRD) equation, the Cockcroft-Gault equation, and the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) formula. Regardless of the equation used, renal dysfunction is generally defined by an estimated glomerular filtration rate (eGFR) <60 mL/min/1.73 m^2 [9]. Renal dysfunction of any severity occurs in 23 to 36 % of the general elderly population (age ≥64 years) [9], with increased prevalence among women compared with men, regardless of age [9].

Not only is the prevalence of renal impairment high among older women, but osteoporosis is also a well-known complication of chronic kidney disease [10], a condition common to the aging population. This association between kidney disease and osteoporosis is due to an imbalance between bone formation and resorption in patients with renal impairment [10]. Thus, it is not surprising that renal impairment is a significant issue for a substantial proportion of women with osteoporosis. Data from the National Health and Nutrition Examination Survey (NHANES) 2005–2008 study, which was conducted in the USA, demonstrated that 25 % of the 9914 women surveyed had moderate to severe osteoporosis and 4.3 % of the 693 women with osteoporosis would be inappropriate for bisphosphonate therapy (i.e., glomerular filtration rate <35 mL/min) [11]. These data can be extrapolated to 12.7 million American women with moderate to severe osteoporosis and 439,000 osteoporotic women who would be contraindicated for bisphosphonate therapy [11]. Limited data have been published demonstrating the prevalence of renal impairment among women with osteoporosis in Israel.

The objective of the current study was to estimate the prevalence of renal impairment among osteoporotic women from a large health plan in Israel overall and by patient characteristics (i.e., age group, fracture occurrence, and body mass index [BMI]).

Methods

Data source

Data for this analysis were obtained from the Maccabi Healthcare Services (MHS) database, which comprises the electronic medical records (EMRs) of all patients from the MHS health maintenance organization (HMO), a large health plan in Israel that currently covers 2.0 million lives (i.e., approximately 25 % of the Israeli population) [12].

Study design

This was a retrospective analysis of the Maccabi EMR database of claims from January 1, 2007, through December 31, 2011. The study population was defined using the following eligibility criteria: (1) any physician diagnosis of osteoporosis (International Classification of Diseases code 9 (ICD-9): 733.0X) or any osteoporosis-related fracture (see Appendix A), (2) female gender, (3) ≥55 years of age at osteoporosis-defining event (osteoporosis diagnosis or fracture), and (4) continuous enrollment in MHS health plan beginning at least 1 year before and continuing at least 1 year after the osteoporosis-defining event. The ICD-9 codes used to identify osteoporosis-related fractures are supported by an algorithm for identifying fractures attributable to osteoporosis in claims databases [13]. To exclude patients with cancer-related pathologic fractures, otherwise-eligible patients who had a fracture but no osteoporosis diagnosis were excluded if they were also present in the Maccabi cancer registry.

The following data were extracted from the records of all eligible patients: the osteoporosis-defining event, age and date of the osteoporosis-defining event, and the minimum serum creatinine level (Scr), assessed as the lowest Scr at any point from 1 year before through 1 year after the osteoporosis-defining event. If there were more than one medical record with osteoporosis diagnosis during the

study period, the first event was used, and if an osteoporosis diagnosis and osteoporosis-related fracture occurred on the same date, the event was classified as a diagnosis.

The estimated glomerular filtration rate (eGFR) was calculated using the CKD-EPI formula [14]:

$$144 \times (\mathrm{Scr}/0.70)^{-0.329} \times (0.993)^{\mathrm{age}} \text{ when } \mathrm{Scr} \le 0.7 \text{ or}$$
$$144 \times (\mathrm{Scr}/0.70)^{-1.209} \times (0.993)^{\mathrm{age}} \text{ when } \mathrm{Scr} > 0.7$$

Renal impairment stage was classified using the CKD-EPI renal impairment staging system [14], as shown below:

Stage 1 (normal)=eGFR ≥90 mL/min/1.73 m^2
Stage 2 (mild)=eGFR 60–89 mL/min/1.73 m^2
Stage 3 (moderate)=eGFR 30–59 mL/min/1.73 m^2
Stage 4 (severe)=eGFR 15–29 mL/min/1.73 m^2
Stage 5 (failure)=eGFR <15 mL/min/1.73 m^2 or dialysis

Outcomes and statistics

The outcomes analyzed were the distributions of renal impairment across the entire study population and by age, osteoporosis-defining event (osteoporosis diagnosis or fracture), and BMI. Confidence intervals were computed for the estimates of the age and event-specific percent prevalence, using WINPEPI software [15].

Results

Patient sample and baseline characteristics

Of the 20,747 female patients aged ≥55 years with an osteoporosis-defining event between January 1, 2007, and December 31, 2011, a total of 15,608 patients met all the eligibility criteria (Fig. 1). Approximately one third (31.9 %) of patients had a fracture as their osteoporosis-defining event. The mean age (± standard deviation [SD]) of those patients with fracture as their osteoporosis-defining event was 66.9± 9.5 and 65.7±7.9 years for those with an osteoporosis diagnosis as their osteoporosis-defining event; approximately one third of the patients in both categories were at least 70 years old (Table 1). Over one third (37.8 %) of the patients with fracture were obese, compared with 28.4 % of the patients with an osteoporosis diagnosis.

Overall renal impairment

Within the entire study population with eGFR levels or on dialysis, most patients (80.1 %) had either normal (stage 1) eGFR levels or mild (stage 2) renal impairment (Fig. 2). Within the 18.5 % of patients with stage 3 (moderate) disease, most had eGFR levels that are considered appropriate for bisphosphonate use (40–59 mL/min/1.73 m^2) [6], whereas 1.3 % of the total population had borderline levels that may not be considered acceptable for bisphosphonate use (35–39 mL/min/1.73 m^2) and 0.8 % had levels that contraindicated bisphosphonate use (Table 2). An additional 1.5 % of patients had stage 4 (severe) renal impairment, had stage 5 renal

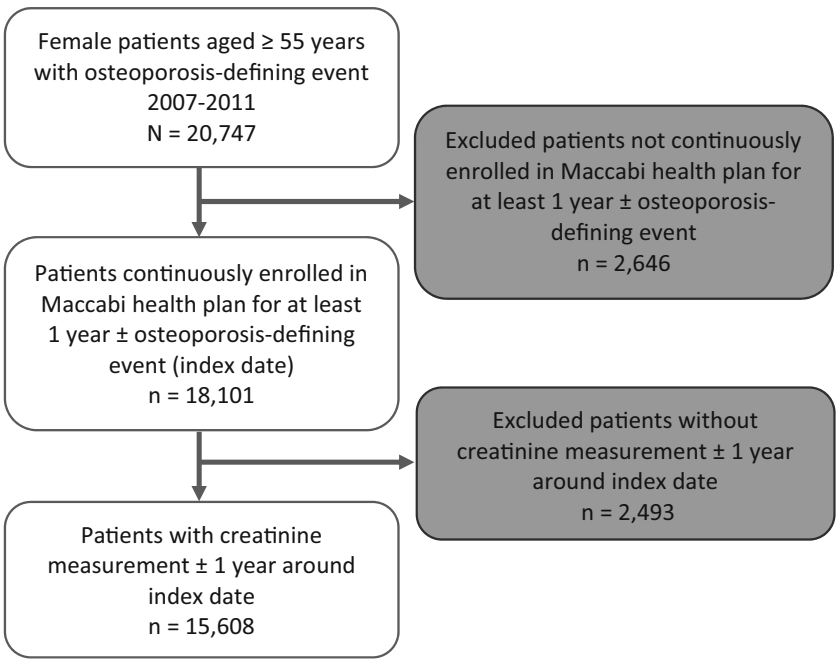

Fig. 1 Patient disposition

Table 1 Baseline characteristics of study population

Baseline characteristics	Fracture at index date (n=4980)	OP diagnosis at index date (n=10,628)
Age, mean±SD	66.9±9.5 years	65.7±7.9 years
55–69 years, *n* (%)	3169 (63.6 %)	7396 (69.6 %)
≥70 years, *n* (%)	1811 (36.4 %)	3232 (30.4 %)
BMI, mean±SD	27.8±8.2 kg/m^2	26.9±7.0 kg/m^2
<18.5 kg/m^2, *n* (%)	280 (5.6 %)	412 (3.9 %)
18.5–24.9 kg/m^2, *n* (%)	1061 (21.3 %)	3308 (31.1 %)
25.0–29.9 kg/m^2, *n* (%)	1706 (34.3 %)	3814 (35.9 %)
30.0–34.9 kg/m^2, *n* (%)	1188 (23.9 %)	2068 (19.5 %)
≥35.0 kg/m^2, *n* (%)	694 (13.9 %)	947 (8.9 %)
Missing BMI, *n* (%)	51 (1 %)	79 (0.7 %)

BMI body mass index, *OP* osteoporosis, *SD* standard deviation

failure, or were already on dialysis. Taken together, 2.3 % of osteoporotic patients who had eGFR levels recorded in their EMRs were contraindicated from taking bisphosphonates (Fig. 2).

Renal impairment by age and osteoporosis-defining event

Among the 10,628 patients with osteoporosis diagnosis as their defining event, 1.6 % were contraindicated for bisphosphonate use. Within that group of 173 renally impaired patients, older patients outnumbered younger patients by more than 4:1 (139 vs 34 patients) (Table 2). Among the 4980 patients with fracture as their osteoporosis-defining event, 3.8 % were contraindicated for bisphosphonate use. Within that group of 187 renally impaired patients, older patients outnumbered younger patients by more than 3:1 (144 vs 43 patients). Of the fracture group, 15.1 % had hip fractures, 8.7 % had vertebral fractures, and the remaining 76.3 % had other fractures. Among those with hip fractures, 9.3 % were contraindicated for bisphosphonates, as were 3.2 % of those with vertebral fractures and 2.0 % of those with other fractures.

Renal impairment by BMI

A total of 1.7 % of patients in the normal weight range had renal impairment severe enough to contraindicate them for bisphosphonate use, followed by those who were overweight (1.9 %), those who were obese (2.9 %), and those who were underweight (3.1 %) (Fig. 3). The most severe renal impairment (stage 5 or dialysis) occurred in 0.2 to 0.5 % of patients across weight categories.

Discussion

These results demonstrated that nearly 75 % of the postmenopausal, Israeli women in the study had some level of renal dysfunction; moreover, 2.3 % of the women with recorded eGFR levels were inappropriate for bisphosphonate use based on renal impairment (<35 mL/min/1.73 m^2) and another 1.3 % of osteoporotic women had borderline levels that may contraindicate them for bisphosphonates (35–39 mL/min/1.73 m^2). When these patients were divided by type of osteoporosis-defining event, it was revealed that the fracture group had more than double the proportion of patients with renal impairment contraindicating bisphosphonate use than the diagnosis group (3.8 vs 1.6 %). This is consistent with the

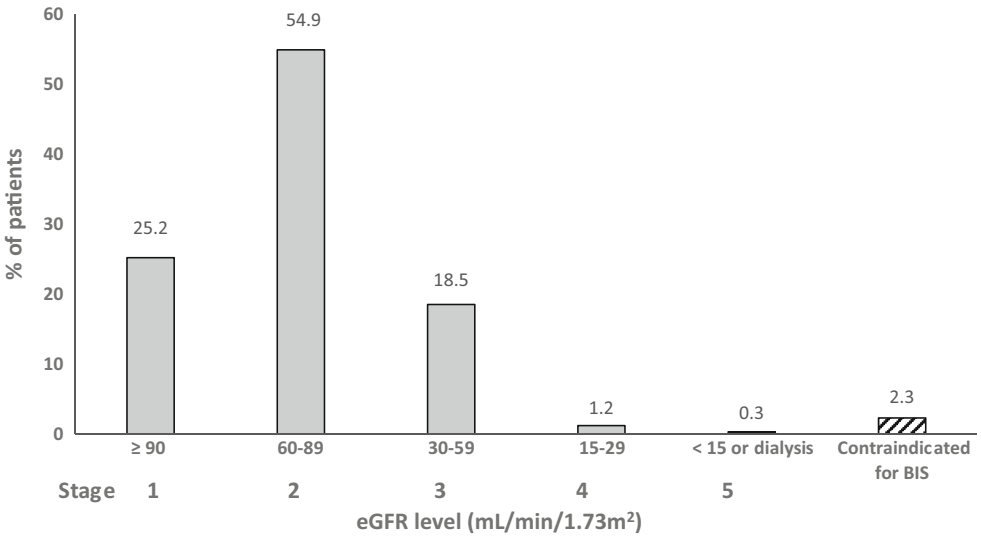

Fig. 2 Patient distribution by renal impairment stages defined with eGFR levels. *BIS* bisphosphonates, *eGFR* estimated glomerular filtration rate

BIS = bisphosphonates; eGFR = estimated glomerular filtration rate

Table 2 Renal impairment by age and osteoporosis-defining event in patients with recorded creatinine levels or on dialysis

Minimum eGFR level 1 year ±osteoporosis-defining event (mL/min/1.73 m^2)	All patients n=15,608	Osteoporosis diagnosis n=10,628			Osteoporosis fracture n=4980		
		Age 55–69	Age ≥70	Total	Age 55–69	Age ≥70	Total
Stage 1 ≥90	3926 (25.2 %)	2543 (34.4 %)	182 (5.6 %)	2725 (25.6 %)	1124 (35.5 %)	77 (4.3 %)	1201 (24.1 %)
Stage 2 60–89	8570 (54.9 %)	4154 (56.2 %)	1828 (56.6 %)	5985 (56.3 %)	1703 (53.7 %)	885 (48.9 %)	2588 (52.0 %)
Stage 3	2553 (16.4 %)	639 (8.6 %)	990 (30.6 %)	1629 (15.3 %)	283 (8.9 %)	641 (35.4 %)	924 (18.6 %)
40–59	199 (1.3 %)	16 (0.5 %)	93 (2.9 %)	119 (1.1 %)	16 (0.5 %)	64 (3.5 %)	80 (1.6 %)
35–39	122 (0.8 %)	5 (0.2 %)	57 (1.8 %)	63 (0.6 %)	5 (0.2 %)	54 (3.0 %)	59 (1.2 %)
30–34							
Stage 4 15–29	185 (1.2 %)	23 (0.7 %)	72 (2.2 %)	89 (0.8 %)	23 (0.7 %)	73 (4.0 %)	96 (1.9 %)
Stage 5 <15 or dialysis	53 (0.3 %)	15 (0.5 %)	10 (0.3 %)	21 (0.2 %)	15 (0.5 %)	17 (0.9 %)	32 (0.6 %)
Bisphosphonate contraindication due to renal impairment <35 or dialysis	360 (2.3 %) 2.1–2.8 %[a]	43 (1.4 %) 1.0–1.8 %[a]	139 (4.3 %) 3.6–5.1 %[a]	173 (1.6 %) 1.4–1.9 %[a]	43 (1.4 %) 1.0–1.8 %[a]	144 (8.0 %) 6.8–9.3 %[a]	187 (3.8 %) 3.2–4.3 %[a]

eGFR estimated glomerular filtration rate

[a] 95 % confidence interval

characterization of patients with fractures as having a poorer health-related quality of life than those with a diagnosis of osteoporosis in the absence of a fracture [16]. Moreover, patients with hip fractures had a threefold to fourfold greater proportion of patients who were contraindicated for bisphosphonates due to renal impairment compared with patients with vertebral or other fractures. This serves to illustrate the need for an alternative for bisphosphonate therapy among this patient group.

In the current study, age was correlated with renal impairment; in both the diagnosis group and the fracture group, patients ≥70 years of age had more than triple the patients contraindicated for bisphosphonates than did the younger patients. This is consistent with a known decline in renal function with age [17]. In comparison of the percentage of patients who were contraindicated for bisphosphonates among the different BMI categories, the normal weight range had the lowest percentage (1.7 %), whereas those categories at the extremes (obese and underweight) had the highest percentages (2.9 and 3.1 %, respectively). This is consistent with previous studies reporting that obesity is associated with increased renal dysfunction [18, 19]. Although obesity has long been believed to provide protection against osteoporosis, recent evidence shows that obesity is associated with an increased fracture risk

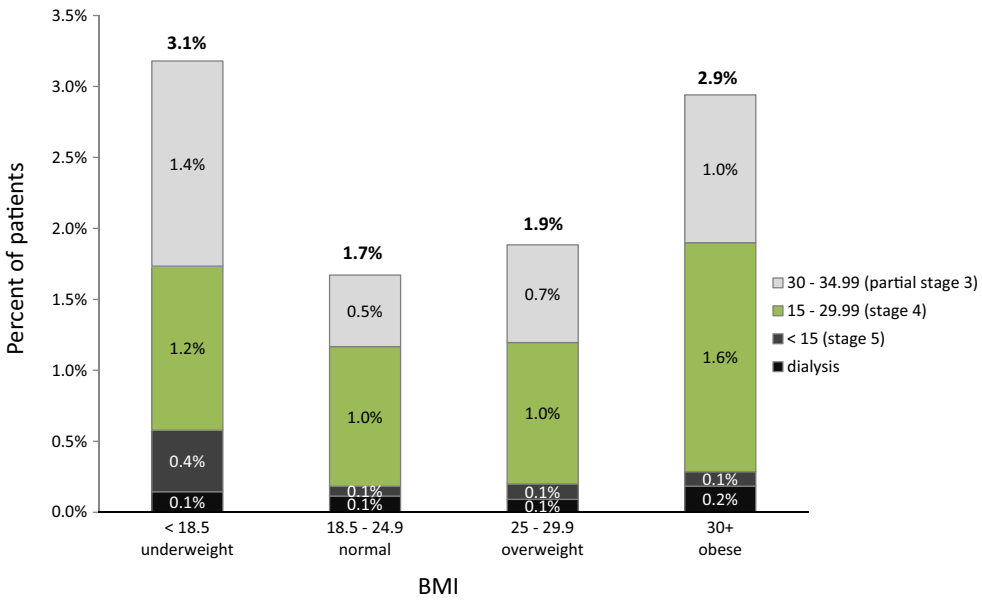

Fig. 3 Percentage of patients with renal impairment by BMI

at certain skeletal sites [20]. Thus, there may be an interaction among obesity, renal function, and osteoporosis that could not be fully examined in this descriptive study.

The NHANES 2005–2008 study, a representative sample of the US population, assessed renal impairment based on 693 women with osteoporosis [21]; the estimates in the current study are based on a sample of 15,608 Israeli women with osteoporosis from an EMR database representing approximately 25 % of the Israeli population. In the NHANES study, women aged ≥50 were classified by both bone mineral density and eGFR, and it was reported that 4.3 % of osteoporotic women had eGFR levels <35 mL/min. This is somewhat higher than the 2.3 % rate reported in the current study, a difference that may be explained by study design differences. Whereas the current study measured age at diagnosis (mean age=66.7 years), the NHANES study reported on women who currently had osteoporosis, who would be expected to have a higher mean age. In fact, the NHANES study included 52 % (363/693) of osteoporotic women who were at least 70 years old, compared with only 32 % (5043/15,608) of these women in the current study. Furthermore, the NHANES study measured bone mineral density as part of the study in order to determine which patients had osteoporosis, and it undoubtedly categorized women as osteoporotic who had been previously undiagnosed. In contrast, the current study included only women who had a record of an osteoporotic fracture or osteoporosis diagnosis during routine medical care, a more stringent requirement for defining osteoporosis. Moreover, the NHANES study used the older MDRD equation to determine eGFR, which modestly overestimates renal impairment compared with the CKD-EPI formula used in the current study. Finally, the current study excluded patients with <1 year of follow-up, which would exclude patients who died less than 1 year after diagnosis or fracture. Regardless of the details, both studies identified a modest percentage of osteoporotic women who are contraindicated for bisphosphonate use due to renal impairment, which translates into millions of women in need of non-bisphosphonate treatment for their osteoporosis.

In a review article examining the relationship between kidney failure and cardiovascular risk, Vanholder and colleagues reported that approximately 335,000 Americans (0.09 % of the total population) have stage 5 renal impairment [22]. This prevalence rate is lower than the 0.3 % stage 5 disease observed in the current study, and it may be a function of population differences, such as the inclusion of both men and women in the American prevalence data and differences in ethnicity and comorbidity.

The current study has a number of limitations, including the fact that contemporaneous creatinine results were not available for 2493 patients who otherwise would have been included in this study. As a retrospective observational analysis, we cannot be sure why some patients did not have creatinine tests performed, although most missing values came from women with fractures, where further inquiry is not obligatory. A total of 5139 patients were excluded because they did not have either sufficient follow-up time and/or a contemporaneous creatinine measurement. These excluded patients tended to be older, have lower BMI, and have a higher rate of prior fractures than patients retained in the study sample. Thus, the patients included in this study may not be fully representative of the overall Maccabi population. The current study also utilized age ≥55 as a cutoff for postmenopausal status; while this is commonly used in osteoporosis studies [23, 24], it is an imperfect surrogate. However, >90 % of women by age 55 are menopausal or postmenopausal, and by age 60, nearly 100 % of women are postmenopausal [25]. Renal function was classified by minimal Scr level over the study period and subsequent conversion to eGFR level, which is simply a surrogate of renal function. However, it is an appropriate measure for this study, since eGFR is used to determine contraindication to bisphosphonates [6]. It is also possible that some patients with vertebral fractures were not included in this study since vertebral fractures are often undiagnosed [26]. While it would have been interesting to assess interactions between age and fractures on renal insufficiency, multivariable analyses were not within the scope of this descriptive study. This study was also not designed to examine osteoporosis as a contributing factor to renal impairment, nor does it account for women with severe renal impairment who may not have been assessed for osteoporosis due to a focus on the clinical management of renal impairment.

Results from this study showed that, among postmenopausal women with osteoporosis, approximately 2.3 % had renal impairment at a level that contraindicated them for bisphosphonate use. This proportion increased for those who were older (age ≥70) and for those who had osteoporosis-related fracture, particularly hip fracture. Thus, renal failure is an important factor in therapeutic choice for these patients. In addition, several risk factors for renal impairment are modifiable, including proteinuria, hypertension, dyslipidemia, and hyperuricemia [27], suggesting that, as a population, the prevalence of renal impairment could be reduced by addressing these risk factors. Beyond that, however, patients with impaired renal function that contraindicates them for bisphosphonates need alternate methods to manage their osteoporosis.

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