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Renal Safety of Bisphosphonates– A Systematic Review

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ABSTRACT

Background: Thoughbisphosphonates are the gold standard for the treatment of different metabolic bone disorders including osteoporosis for more than five decades, its safety and tolerability in patients with compromised kidney function is not well known. With age-related bone disorders and renal insufficiency becoming more prevalent worldwide, it is essential to understand the effect of bisphosphonates on patients with compromised renal function. This review aims to analyze the clinical data available on safety of bisphosphonates on patients with different levels of renal function.
Methodology: A broad search of PubMed and the Cochrane Central Register of Controlled Trials was conducted to select randomized controlled trials and clinical trials that evaluated the safety and tolerability of bisphosphonate in patients with different levels of renal function between 2000 and 2018.
Results: Out of 30388 titles and abstract reviewed, 16 articles were included in the final analysis. Except for risedronate causing a significant increase in eGFR at months 3 and 12 and zoledronic acid increasing serum creatinine by 2.77% from baseline, all bisphosphonates are relatively safe and well tolerated by the kidneys.
Conclusion: The evidence from this review suggests that the bisphosphonates are generally well tolerated with ten trials registering no drug-related withdrawals and other studies showing only very nominal withdrawals due to adverse effects.

1. Introduction

Osteoporosis has become one of the leading global health burdens incurring high costs to the health systems and it is an independent risk factor for fractures in general population with its risk increasing with increasing age. The prevalence of osteoporosis is steeply rising with increasing lifespan [1]. Bisphosphonates (BPs) are bone-seeking anti-resorptive agents, which are commonly used to treat different forms of osteoporosis. There are many studies supporting the efficacy of bisphosphonates in the treatment of different types of osteoporosis [2-7]. Available in both oral and injectable forms, bisphosphonates are considered as a drugof choice for the prevention of fractures. Bisphosphonates reduces the fracture risk effectively and have increased risk-to-benefit ratio in the treatment of osteoporosis [8]. Although bisphosphonates have long been the gold standard treatment for treating numerous metabolic bone disorders including osteoporosis, myeloma, bone metastasis, Legg-Perthes disease, Anti-cancer, malignant hyperparathyroidism, and other conditions involving bone fragility, they are not usually recommended in patients with compromised kidney function largely because of the drug being excreted metabolized through the kidneys, putting more burden on the already failing kidneys [9,10].

Pharmacokinetics of Bisphosphonates

Bisphosphonates are administered either intravenously or orally. Oral bisphosphonates are absorbed into the bloodstream from the gastrointestinal lumen by two routes:

1. Transcellularly, transported through epithelial cells into the blood.
2. Intercellularly, where the bisphosphonates gain access to the circulation via the tight junctions between the epithelial cells. The oral bioavailability of BPs is very low, ranging 1-7%. Moreover, oral absorption is impaired in the presence of food and calcium, magnesium, or aluminum containing drinks [10,11]. When bisphosphonates are absorbed, about 40% gets into the bone and stays there for more than 10 years and are either slowly released back into the systemic circulation or excreted unchanged [12].

Mechanism of Action of Bisphosphonates

The major mechanism by which bisphosphonates act is by “osteoclast inhibition.” During osteoclastic bone resorption, bisphosphonates impairs the cell function of osteoclasts by inhibiting their enzyme activity [13]. This makes them a wonderful choice in all bone disease associated with bone diseases caused by osteoclast activity. Moreover, bisphosphonates can reduce the progression of soft tissue calcification and it also has the potential to reduce the progression of vascular calcification [14-16]. Since bone remodeling and vascular calcification occur in patients with decreased renal function, there has been an increased

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interest in administering bisphosphonates as a treatment option to correct the bone and mineral disorders in patients with compromised renal function.

Bisphosphonates and Renal Function

Since bisphosphonates are eliminated primarily through kidneys unchanged, it is important to understand the impact of long-term use of bisphosphonates on renal function. The safety newsletter of United States Food and Drug Administration (US FDA) reported 24 cases of acute renal failure and renal impairment between April 2007 and February 2009, associated with the use of zoledronic acid in osteoporosis patients [17]. In another report FDA reported 9 cases of renal injury requiring dialysis and 11 cases of fatal acute renal failure between March 2009 and April 2011, associated with the use of zoledronic acid infusion [18].

As bone and mineral disorders and renal insufficiency are more prevalent with age and bisphosphonates are the first line drug for the treatment of bone related disorders, it is critical to understand the impact of bisphosphonates on patients with impaired renal function [19]. Since both oral and parenteral bisphosphonates carry warnings regarding their use in patients with impaired renal function [20-23], it is important to understand its effects on patients with different levels of renal function. This review aims to examine the clinical data available regarding the renal safety in patients with different levels of renal function treated with bisphosphonates and to discuss the potential use of bisphosphonates in patients with bone and mineral disorders who have compromised kidney function.

2. Materials and Methods

Search Strategy

An extensive search was conducted to select randomized controlled trials and clinical trials that evaluated the safety and tolerability of bisphosphonate in patient with different levels of kidney function. We searched PubMed and the Cochrane Central Register of Controlled Trials between the years 2000 and 2018. Data from randomized controlled trials of approved bisphosphonates were obtained. We included English language, randomized controlled trials. No restrictions were placed on the dose or formulation of the intervention. All trials must have studied the impact of bisphosphonates on renal function. No restrictions were placed on the biomarkers used to assess the renal function.

Recovery of Trials

Our initial search returned 30388 articles, out of which 52 potentially relevant articles were identified. Potentially eligible studies were identified by four authors by screening titles and abstracts by using the search keywords. All trials were then assessed independently by four authors and potentially relevant studies were selected in accordance with the predefined inclusion criteria. Any disagreementwas reviewed and resolved by the fifth independent reviewer. Authors of individual trials were contacted if necessary. After careful review of the abstracts, out of 52 articles, 34 articles did not satisfy the inclusion criteria and were excluded from the analysis. On further scrutiny, out of 28 articles, 12 articles were again excluded because they did not contain enough information. Finally, data from only 16 studies were included in the final review. The flow of article selection process is shown in Figure 1.

Data Abstraction and Study Appraisal

We extracted the following general data from each study: country of origin, year of publication, number of randomized patients per each treatment arm, sex ratio, mean age in years, name of the bisphosphonates used in the trial, dose of each bisphosphonates, duration of follow up, and outcomes of the study. The primary outcome of interest was the impact of bisphosphonates on the renal function. Secondary outcomes were the impact of bisphosphonates on improvement in BMD (Bone Mineral Density).

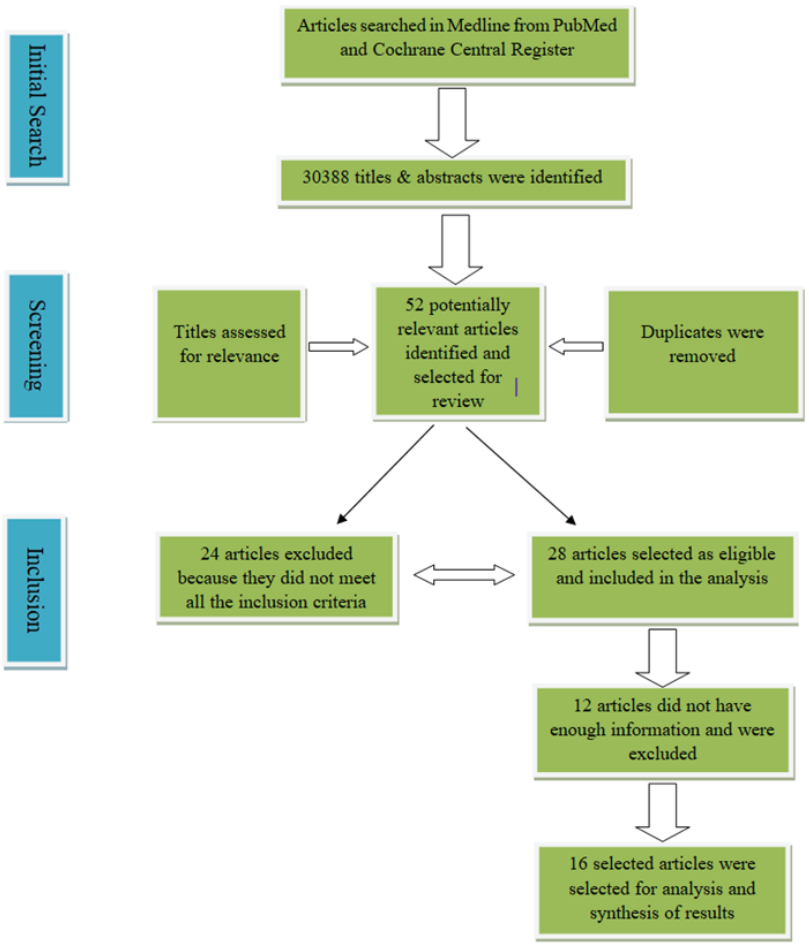

Figure 1: Flow of the Article Selection Process.

Methodological Quality of Included Trials

The methodological quality of the trials was assessed based on methods of randomization, allocation concealment, blinding, sample size calculation and drop-out rate. For methods of randomization, trials were rated as follows: appropriate randomization procedure (A), inappropriate randomization (B), or unclear (C). Allocation of concealment was rated as: concealed appropriately (A), not concealed (B), or unclear (C). Blinding was rated as: double-blind (A), single blind (B), no blinding (C), or unclear (D). Sample size calculation was assessed as: appropriate calculation procedure (A), inappropriate calculation (B), or unclear (C). The drop-out rate (loss to follow-up) was assessed as: ≤5.0% (A), 5.1-10.0% (B), 10.1-15.0% (C), > 15.1% (D), or unclear (E) [24].

3. Results

Table 1 summarizes the 16 trials included for the analysis. The trials were sorted chronologically based on when the trial was conducted, the year of publication, and number of patients per treatment arm, sex ratio, and mean age of the participants.

Primary and secondary Outcomes

Table 2 summarizes the effectiveness and tolerability data of bisphosphonates from all 16 studies. The primary outcomes of renal function, i.e. GFR, serum creatinine (SCr) and creatinine clearance(CrCl) were reported in 15 trials. In the remaining one trial, the reported outcome measures were TnPO4, PTH and excretion of drug.

Methodological Quality of Trials

Table 3 summarizes the methodological quality of 16 studies included for analysis. There was more than 40% loss to follow up in three studies and more than 25% loss to follow up in two studies. It was unclear how randomization was carried out in 11 trials. There were no data available on how allocation concealment was done in any of the studies where blinding was done. 14 trials did not mention how the sample size was arrived at. The methodological quality of trials is shown in Table 3.

Heterogeneity of Trials

All 16 trials that were included in the analysis were heterogenous in that they had various inclusion and exclusion criteria and different treatment protocols, which are shown in Table 1 and Table 2.

4. Discussion

Table 3 shows that all the trials included in this analysis have taken SCr levels as their primary outcome, as creatinine is a direct biomarker of renal function. CrCl levels can be calculated from SCr, which was taken as an outcome measure in 9 trials. One trial showed that risedronate caused a significant decrease in eGFR and a significant increase in SCr at 3 and 12 months [26]. In another trial, Zoledronic acid increased SCr by 2.77 % post-treatment from baseline [40] and 1.34% in another trial [33]. This is shown in Figure 2.

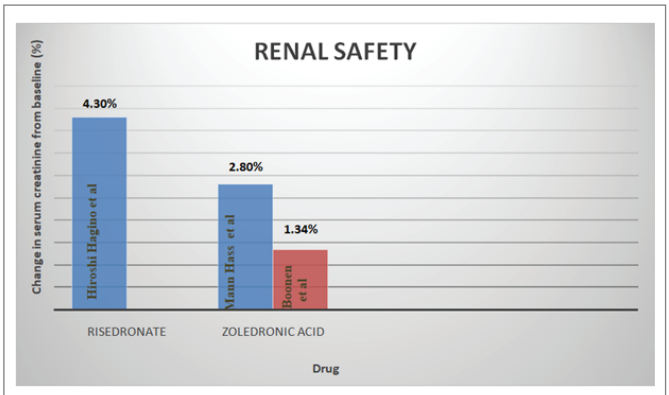

Figure 2: % increase in Serum Creatinine from Baseline

The long-term efficacy of bisphosphonates is rather encouraging. Four trials studied the impact of bisphosphonates on renal function for more than 12 months and these trials reported no detectable change in SCr or only transient changes in renal function [33,35,38,41], which supports the long-term tolerability of bisphosphonates by the kidneys.

Table 2 shows that diverse study population with various comorbid conditions were included in the trails, which ensures that the safety data obtained for this review is unbiased to a specific population and Table 3 shows that 11 of 16 trials were conducted for at least one year or more, which again reinforces the long-term safety of bisphosphonates on the renal function.

The data from this review suggests that bisphosphonates are generally well tolerated even in patients with compromised renal function. No drug-related withdrawals were reported in 10 trials whereas in other trials the drug-related withdrawal is either negligible or unclear. Other non-serious adverse events occurring from the bisphosphonates included mild gastrointestinal distress, eczema back pain, upper and lower respiratory tract infections, etc. The extent of its safety and efficacy may be different in patients with varying kidney function and it should also be noted that each bisphosphonate is unique in terms of pharmacokinetics.

Table 1: Details of the Included Trials

Ref	Country	Year	No. of Randomized Patients Per Each Treatment Arm	Sex Ratio (M/F)	Mean Age in Years
[25]	Germany	2015	34 (17 in each arm)	Only women	57.5±11.1
[26]	Japan	2014	852 (2.5 mg OD RIS-429; 75 mg OM-423)	8/421; 5/418	67.7±6.0
[29]	Norway	2012	129 (IBN-66; Placebo-63)	48/18; 51/12	51.4±6.5
[30]	Spain	2011	39 (PAM-24; Placebo-15)	14/6; 12/3	48.2±12.3
[31]	USA	2011	801 patients (IBN Inj-268; IBN Inf-264; ALEN-269)	Only women	65.3±4.8
[32]	Australia	2008	24 (Arm 1 =12; Arm 2 = 12)	07:05; 7:5	59.2±9.2
[33]	Portugal	2008	5035 (ZA – 2521; Placebo – 2514)	Only women	73±5.4
[34]	Spain	2007	84 (Treatment – 39; Control – 45)	20/19; 22/23	56±9.7
[35]	USA	2007	6459 (eGFR <45 ml/min – 581; eGFR ≥45 ml/min – 5877)	Only women	72.6±4.4
[36]	Turkey	2007	127 (ALEN – 47; RIS – 44; RAL – 36)	Only women	62.6±7.7
[37]	Korea	2005	44 (Study-22; Control-22)	11/11; 17/5	8.5±2.39
[38]	Belgium	2005	309 patients (Placebo-152; Study-157)	Only women	55.6±12.7
[39]	Spain	2003	26 (Study – 14; Control – 12)	9/5; 7/5	57.3±5.1
[40]	Germany	2002	20 (Placebo – 10; ZA – 10)	4/6; 4/6	52.5±7.8
[41]	USA	2002	58 (Study-29; Control-29)	19/10; 20/9	47.4±2.0
[42]	USA	2000	21 patients (G 1 - 6; G 2 - 6; G 3 - 6; G 4 – 3)	4/2; 1/5; 6/0; 3/0	59.7±9.2

Ref – Reference; M/F – Male/Female; OD – Once daily; OM – Once monthly; RIS – risedronate; PAM – pamidronate;

IBN – ibandronate; ALEN – alendronate; ZA – Zoledronic acid; RAL – Raloxifene; G - Group

Table 2: Results of Studies Analyzing the Effect of Bisphosphonates on Bone and Renal Function

Ref	Drug	Inclusion Criteria	Study Duration	Dose	Effect on Renal Function	Effect on BMD and Other Related Diseases	Withdrawals due to AEs (%)
[25]	ZA + IBN	1. Patients 18 years or more with healthy kidneys 2. Breast cancer with bone metastasis and not previously treated with bisphosphonates.	6 months	4 mg ZA vs 4 mg ibandronate (both for 15 mins over 28 days)	All patients, both ZA and Ibandronate treated, experienced only temporary renal dysfunction without any evidence of irreversible damage in terms of acute nephrotoxicity. So, both are well tolerated and safe with regard to renal toxicity	NA	Nil
[26]	RIS	Male and female aged ≥50 years. Diagnosed with osteoporosis based on the criteria for primary osteoporosis of the Japanese Society for Bone and Mineral Research [27,28]	12 months	75mg Once Monthly and 2.5mgOnce Daily	% changes in each group are similar despite of CKD stages	Lumbar spine improved/ BTM improved	8.5
[29]	IBN	1. Patients over 18 years receiving a single live or deceased renal transplant. 2. Not previously treated with bisphosphonates during the last year and not undergone parathyroidectomy.	12 months	3mg every 3 months	There were no more transplant rejections nor were there more kidney function related adverse events in ibandronate group. Serious adverse effects were 15% less.	Effective against bone loss in total femur and ultra distal radius, and the reduction in bone biomarkers was more pronounced in the ibandronate group/	Nil
[30]	PAM	1. Adults kidney graft recipients 2. BMD T score of -1 at lumbar spine	12 months	30mg of pamidronate sodium	There is no ADR in the study population, rejection -18%; both groups have C-Terminal telopeptide reductions from baseline	Osteopenia; vertebral pain(5%) was observed in study group; Peripheral fracture(9%) for pamidronate group	7.7
[31]	IBN + ALEN	1. Women aged 60 years and older 2. At least 5 years post-menopause(GFR <60 ml/min) 3. History of one or more osteoporotic fracture/ BMD < -2.0 at the LS/TH	1 year	Ibandronate 3mg every 3 months IV injection, Ibandronate 3mg IV infusion, Alendronate 70 mg weekly	Ibandronate shown to have a low incidence of renal adverse effects (2.5%-5.6%) at doses 0.5to 3mg with no cases of ARF	NA	2.1
[32]	ZA+ thalidomide/ prednisolone	1. Multiple myeloma 2. Received 6-7 weeks of high dose therapy 3. Autologous stem cell transplants(ASCT)	16 months	Arm 1(ZA 4 mg IV q 4 weeks; Thalidomide 100 mg at bedtime for 14 days, then 200mg at bedtime till end of study if tolerated; and Prednisolone50 mg PO on alternate days) Arm 2 (ZA and Prednisolone)	There is no detectable increase in SCr in patients receiving combination therapy, conferring that there is no renal safety risks	Unclear	Unclear
[33]	ZA	1. Postmenopausal women with osteopenia 2. Femoral neck BMD T-score ≤ 2.5 w/wo vertebral fracture 3. T-score ≤ -1.5 with at least 2 mild / moderate vertebral fracture	3 years	Once yearly 5mg given over at least 5 mins, 3 annual treatments	No differences in mean changes in SCr, CrCL or adverse renal events were found, transient changes in renal function can occur but in long run. Renal function was not different from control patients.	NA	0.13
[34]	ALEN + VitD+ Calcium	1. Patients between ages 12 and 24 months after renal transplantation 2. Serum creatinine of <2 mg/dl	1 year	10mg/day	Alendronate is effective for the treatment of renal transplant patients with established osteoporosis. It does not produce negative effects on renal function	Improvements in BMD of the lumbar spine (LS) and of the femoral neck (FN) were statistically significant after1 year of treatment	Nil
[35]	ALEN	1. Women with Vertebral and Arm Fracture 2. Serum creatinine <1.27mg/dl	4 year	Unclear	Among osteoporotic women with normal serum creatinine, but reduced eGFR, alendronate is safe and effective	Women with a reduced eGFR had a 5.6%increase in total hip BMD compared with4.8%	Nil
[36]	ALEN + RIS + RAL	1. Women with femoral neck fracture 2. Serum creatinine <2mg/dl	12 months	Alendronate dose- 70mg once weekly. Risedroante-35mg. Raloxifene- 60mg (calcium 1200 mg/d for all patients)	No significant difference between basal and final renal function	Femoral and lumbar spine	Nil
[37]	PAM	1. Children receiving steroids 2. School screening urinalysis and showed microscopic hematuria and persistent or intermittent proteinuria over 1 year	3 months	Control- calcium 50mg/day Study -pamidronate- 125mg+calcium for 3 months	No statistical differences between groups. Pamidronate is effective in preventing Steroid Induced Osteoporosis in children	BMD is decreased in control group	Nil
[38]	IBN	1. Women of or more than 18 years old with breast cancer and bone metastases demonstrated by X-ray or CT scan 2. Organization performance status ≤ 2	2 years	6mg	2 years of Ibandronate Tx have no effect on time to deterioration in renal function in patients with metastatic bone disease, supporting the low incidence of renal adverse events in this clinical trial.	NA	Unclear
[39]	RIS +VitD + Calcium	1. 12 to 24 months after renal transplant 2. 18 to 70 years old 3. Serum creatinine of <2 mg/dL, iPTH of <240 pg/mL, and BMD with a t score of <-2.5.	6 months	35mg/week	There is no negative effect on renal function	Effective in intervention group than control group	Nil
[40]	ZA	1. Adult hemodialysis patients, who received their first or second cadaveric renal allograft 2. Serum creatinine < 2mg/dl within 2 weeks after transplantation	6 months	4 mg ZA or placebo in 25 ml NS over 15 mins	Renal function did not change after ZA infusion. Scr baseline values and values after 6 months were similar within the groups as well as btw the groups (ZA vs placebo)	Mineral content of lumbar spine and Z score improved significantly in patients receiving ZA but decreased in placebo, Femoral Neck remained same but decreased in ZA and placebo group respectively	Nil
[41]	ALEN	1. Patients who are more than 1 year post-renal transplantation 2. Preserved renal function (Serum creatinine ≤2.5mg/dl)	2 years	10mg/day	Alendronate therapy did not adversely affect renal function	BMD increased at lumbar spine and hip, no significant change in BMD at the wrist	Nil
[42]	RIS	1. Surgically sterile men/women 2. At least 18 years of age 3. Creatinine Clearance levels more than 80 ml/min to less than 30 ml/min 4. Post-menopausal women	6 weeks	30mg	There is a decrease in Risedronate clearance which is related to decrease in renal function (82%) & 69% decrease in Vd but no evidence of drug related laboratory changes	NA	Nil

Ref – Reference; ZA - Zoledronic acid; IBN – Ibandronate; RIS – Risedronate; PAM – Pamidronate; ALEN – Alendronate; RAL – raloxifene; BTM – Bone Turnover Markers; LS – Lumbar Spine; TH – Total Hip; BMD – Bone Mineral Density; iPTH – Intact Parathyroid Hormone; SCr – Serum Creatinine; CrCL – Creatine Clearance; ARF – acute renal failure; GFR – glomerular filtration rate; NA – Not applicable; AEs – Adverse Events

Table 3: The Methodological Quality of Selected Trials

Ref	Year	Randomization	Allocation Concealment	Sample Size Calculation	Blinding	Lost to Follow
[25]	2015	C	C	C	D	D
[26]	2014	A	C	A	A	D
[29]	2012	A	C	A	A	A
[30]	2011	A	C	C	A	D
[31]	2011	C	B	C	D	B
[32]	2008	C	C	C	D	E
[33]	2008	C	C	C	A	E
[34]	2007	C	C	C	D	A
[35]	2007	C	C	C	D	A
[36]	2007	C	C	C	D	A
[37]	2005	C	C	C	C	A
[38]	2005	C	C	C	A	D
[39]	2003	C	C	C	D	E
[40]	2002	A	C	C	C	D
[41]	2002	A	C	C	C	B
[42]	2000	C	C	C	C	A

5. Conclusion

Disturbances in serum creatinine and other parameters are hallmark of kidney diseases. Based on the data presented here, bisphosphonates maintain normal kidney function in patients with previous history of kidney disease and other comorbid conditions. The evidence presented in this study shows that all bisphosphonate except zoledronic acid and risedronate are safe to be used in patients with compromised renal function. Since the deterioration caused by zoledronic acid and risedronate are only minimal and are reversible, further studies are warranted in cohorts to further discern its tolerability.

6. Declarations

Funding

Not applicable

Conflict of Interests

No potential conflict of interest relevant to this article was reported.

Ethics approval

Not Applicable

Consent to Participate

Not Applicable

Consent for Publication

The authors do not have any conflict of interest in publishing this article.

Availability of Data and Materials

The datasets analyzed during the current study will be available from the corresponding author on reasonable request.

Code Availability

Not Applicable

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