RESEARCH ARTICLE

Bisphosphonates for Osteoporosis in Nonmetastatic Prostate Cancer Patients Receiving Androgen-deprivation Therapy: A Systematic Review and Meta-analysis

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Abstract

This systematic review was conducted to assess the efficacy and safety of bisphosphonates for prevention and treatment of osteopenia or osteoporosis in men with non-metastatic prostate cancer receiving androgen-deprivation therapy. We searched for randomised controlled trials (RCTs) of bisphosphonates compared with placebo from Pubmed, Embase, the Cochrane Library, and ISI - Science Citation Index. Meta-analyses of pre-specified outcomes (bone mineral density, fractures, and adverse events) were performed using Review Manager. Ten RCTs with a total patient population of 1,017 were identified. There was generally more improvement in bone mineral density of the lumbar spine for patients who received bisphosphonate treatment than placebo or other medical treatment at 12 months (WMD 6.02,95%CI 5.39 to 6.65). Similar effects were also observed for total hip, trochanter or femoral neck bone mineral density. However, there was no significant reduction in fractures. Fever and gastrointestinal symptoms were the most common adverse events (10.4% vs. 1.2%; 0.10% vs. 0.03%). Currently, our meta-analysis suggested that oral and intravenous bisphosphonates caused a rapid increase in spine and hip or femoral BMD in non-metastatic prostate cancer patients receiving androgen-deprivation therapy. Fever and gastrointestinal symptoms were common with the use of bisphosphonates. These short-term trials (maximum of 12 months) did not show fracture reduction. In future, more efficient performance of higher quality, more rigorous, large sample, long-term randomised controlled trials (>12 months) are needed where outcomes are detailed.

Keywords: Bisphosphonates - osteoporosis - prostate cancer - androgen-deprivation therapy - meta-analysis

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Introduction

Prostate cancer (PCa) is the most common cancer in men in many Western countries and is the second leading cause of cancer death in men (Frydenberg et al., 1997). In 2008, prostate cancer accounted for 14% (903,500) of the total new cancer cases and 6% (258,400) of the total cancer deaths in males, respectively (Grivas et al., 2012). In 2009, an estimated 192,280 new cases were diagnosed and prostate cancer accounted for 25% of new cancer cases in men in the United States annually (Jemal et al., 2009). Androgen deprivation therapy (ADT), specifically surgical or medical castration, is the first line of treatment against metastatic prostate cancer (Sharifi et al., 2005). ADT is also frequently used in men with high-risk, localized prostate cancer, or lymph-node positive prostate cancer treated with radical prostatectomy and pelvic lymphadenectomy (Bolla, 1999; Messing et al., 1999; Sharifi et al., 2005; Higano, 2008). However, ADT has some adverse effects, including hot flashes, skeletal complications, sexual dysfunction, metabolic changes, cognitive and mood changes (Sharifi et al., 2005).

ADT increases bone resorption, reduces bone mineral density, and subsequently increases the risk of fracture in nonmetastatic prostate cancer patients (Higano, 2008; Michaud, 2010). Antihormonal therapy used to inhibit the disease progression or prevent its recurrence can lead to changes in bone metabolism, resulting in the loss of bone mineral density (BMD) since this therapy depletes circulating levels of oestrogens and androgens that maintain bone mass through the suppression of bone reabsorption and promotion of bone formation (Brufsky, 2008). Bone loss in nonmetastatic prostate cancer patients receiving ADT mainly results from ADT-induced testosterone and estrogen deficiencies (Higano, 2004). Testosterone directly affects the bone remodeling

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process by stimulating proliferation and inhibiting apoptosis of osteoblasts (bone-formation cells), while simultaneously stimulating apoptosis of osteoclasts (bone-resorption cells). A deficiency of estrogen will increase bone resorption by activating osteoclasts and decreasing osteoclast apoptosis (Manolagas et al., 2002; Riggs et al., 2002; Balasch, 2003).

At present, there are no established guidelines for bone loss and fracture prevention in men receiving ADT for nonmetastatic prostate cancer. Bisphosphonates, such as pamidronate, alendronate, neridronate, zoledronate, have been shown in some randomized controlled trials(RCTs) to prevent bone loss associated with androgen-deprivation therapy in nonmetastatic prostate cancer patients (Smith et al., 2001; Smith et al., 2003; Morabito et al., 2004; Ryan et al., 2006). However, its efficacy and safety are still uncertain. Therefore, we carried out a systematic reiew and meta-analysis using data from randomised controlled trials to determine the effectiveness and safety of bisphosphonates for osteoporosis in nonmetastatic prostate cancer patients receiving androgen-deprivation therapy.

Materials and Methods

We obtained relevant randomized controlled trials from Pubmed (1966–October 2012), Embase (1974–October 2012), the Cochrane Library (2012 issue 10), ISI-Science Citation Index (1955–October 2012) and Chinese biomedicine literature database (1978–October 2012). We used search engines such as GoogleTM to search related references on the internet, and searched the references of included studies to identify additional potentially relevant studies. Hand searching of the reference lists of included studies and reviews was undertaken and contact was made with experts in the field, unpublished studies were not sought. The search were not restricted by publication year or language.

Briefly, we included studies if they were randomised controlled trials of bisphosphonates compared with placebo. Other inclusion criterias are as follows: no treatment or other therapies to prevent or treat low bone mineral density (osteopenia or osteoporosis) and fractures in patients with nonmetastatic prostate cancer receiving androgen-deprivation therapy, with a treatment period of at least six months; men who have histologically diagnosed, nonmetastatic prostate cancer, have a history of androgen-deprivation therapy, regardless of age and race. Men with bone metastases according to radionuclide bone scans or men with metabolic bone disease, such as Paget's disease, hyperthyroidism or vitamin D deficiency, will be excluded. The search strategy described was used to obtain titles and abstracts of randomized controlled trials that were relevant to this review. The titles and abstracts will be screened independently by two reviewers, who will discard studies that are not applicable, and two reviewers will independently assess retrieved the titles and abstracts of all identified trials to confirm fulfillment of inclusion criteria. Disagreements will be resolved in consultation with the third reviewer. Data extraction will be carried out independently by the same authors using standard data extraction forms. The quality items assessed were randomization, allocation concealment, blinding (participants, investigators, outcome assessors, and data analysis), and completeness of follow-up. For trials with multiple publications we included only the most complete report for each outcome.

The primary outcomes measure were percent changes in the baseline bone mineral density of the lumbar spine and incidence of newly diagnosed or worsening fractures including vertebral and non-vertebral(morphometric or clinical).The second outcomes were percent changes in the baseline bone mineral density of the total hip, femoral neck, trochanter and adverse events.

We analyzed the data using Review Manager (version5.0) and extracted and pooled data for summary estimates. According to Cochrane guideline, for meta-analysis, we combined data on dichotomous outcomes using the Mantel-Haenszel relative risk method; for continuous outcomes we used the inverse variance weighted mean difference (WMD) method and 95% confidence intervals (95%CI). We intended to report results using a fixed effects model throughout, but we had to use a random effects model for percent changes in the baseline bone mineral density of the total hip because of statistical heterogeneity, explored by chi-square test and I2 statistics. Sensitivity analyses were intended to explore important clinical differences among that might be expected to alter the magnitude of treatment effect.

Results

We identified 277 references to potential studies. We included 12 potentially eligible trials and subsequently obtained data for ten of these (Figure 1). Two trials (Magno et al., 2005; Taxel et al., 2010) including a total of 194 patients were not available because the investigators felt unable to provide the data for inclusion in this meta-analysis. Of the 1017 participants, 512 were randomised to receive bisphosphonates and 505 to placebo or other medical treatment. 119 participants withdrew from studies without their treatment allocation being reported.

The characteristics of included studies are shown in Table 1.Ten clinical trials met the inclusion criteria for this review (Smith et al., 2001; Smith et al., 2003; Morabito et al., 2004; Ryan et al., 2006; Greenspan et

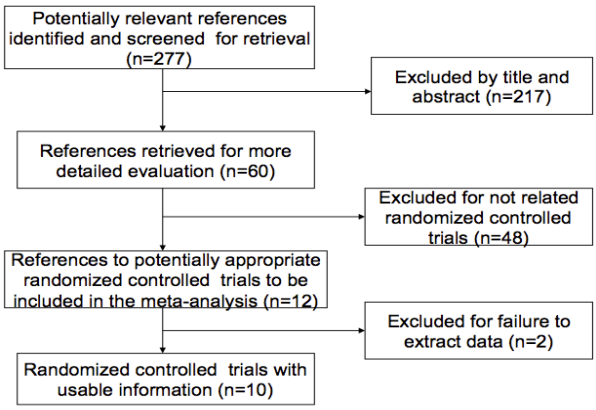

Figure 1. Flow Chart for Selecting Included Studies for Analysis

Table 1. The Characteristics of Included Studies

Study	Intervention/control(I/C)	Participants I/C	Age(years) I/C	Bone mineral density, (g/cm^2) I/C
Smith 2001	Pamidronate, calcium carbonate, vitamin D/ calcium carbonate, vitamin D	21/22	69/65	Lumbar spine 1.111/1.046 Femoral neck 0.822/0.796 Total hip 0.987/0.983 Trochanter 0.776/0.786
Smith 2003	Zoledronic acid, calcium supplement, vitamin D/ calcium supplement, vitamin D	55/51	71.1/70.2	N/A
Morabito 2004	Neridronate, calcium, cholecalciferol supplement/ calcium, cholecalciferol supplement	24/24	74.5/75.2	Lumbar spine 0.730/0.738 Femoral neck 0.679/0.684 Total hip 0.810/0.804
Ryan 2006	Zoledronic Acid, calcium supplement, vitamin D/ calcium supplement, vitamin D	61/59	73/71	Femoral neck 0.819/0.872 Total hip 0.976/1.012 Lumbar spine 1.173/1.181
Michaelson 2007	Zoledronic Acid, calcium carbonate, vitamin D/ calcium carbonate, vitamin D	22/22	66/66	lumbar spine 1.01/1.07 Total hip 0.98/1.01
Greenspan 2007	Alendronate, calcium, vitamin D supplements/ calcium, vitamin D supplements	56/56	70.8/72.2	lumbar spine 1.052/1.079 Total hip 0.925/0.991 Femoral neck 0.725/0.776 Trochanter 0.707/0.775 One-third distal radius 0.724/0.757
Israeli 2007	Zoledronic Acid, calcium Supplement, vitamin D/ calcium Supplement, vitamin D	112/110	N/A	N/A
Ryan 2007	zoledronic acid, placebo	22/20	64.9/65.2	Femoral neck 0.978/0.988 Lumbar spine 1.337/1.424
Bhoopalam 2009a	zoledronic acid, vitamin D, calcium/ vitamin D, calcium	26/24	69.1/68.4	Lumbar spine 1.228/1.290 Lt hip 1.075/ 1.082 Rt hip 1.067/1.085
Bhoopalam 2009b	zoledronic acid, vitamin D, calcium/ vitamin D, calcium	22/21	71.2/73.7	Lumbar spine 1.301/1.300 Lt hip 1.116/ 1.090 Rt hip 1.118/1.101
Casey 2010	zoledronic acid, vitamin D, calcium/ vitamin D, calcium	91/96	74/75	Lumbar spine 1.26/1.27 Lt hip 1.02/ 1.03 Rt hip 0.92/0.91

Bhoopalam2009a: ADT<12months; Bhoopalam2009b: ADT>12months. N/A, Not available; Rt, right; Lt, left

Table 2. The Methodological Quality of Included Studies

Entry	Adequate sequence generation?	Allocation concealment	Blinding	Incomplete outcome data	Selective outcome reporting	Other sources of bias	ITT analysis
Smith 2001	Unclear	Unclear	No	Unclear	Yes	Yes	Yes
Smith 2003	Yes	Unclear	Unclear	Yes	Yes	Yes	No
Morabito 2004	Unclear	No	No	Yes	Yes	Yes	Yes
Ryan 2006	Unclear	Unclear	Unclear	Yes	Yes	Yes	Yes
Michaelson 2007	Yes	Yes	Double-blinding	No	Yes	Yes	No
Greenspan 2007	Unclear	Yes	Double-blinding	Yes	Yes	Yes	Yes
Israeli 2007	Unclear	Unclear	Unclear	Unclear	Yes	Yes	No
Ryan 2007	Unclear	Unclear	Unclear	Yes	Yes	Yes	Yes
Bhoopalam 2009	Yes	Unclear	Unclear	Unclear	Yes	Yes	Yes
Casey 2010	Yes	Unclear	No	Yes	Yes	Yes	Unclear

al., 2007; Israeli et al., 2007; Michaelson et al., 2007; Ryan et al., 2007; Bhoopalam et al., 2009; Casey et al., 2010). All trials were published both as abstracts and full review papers. All trials had similar designs, duration of planned intervention(12 months) and outcome measures. None of the studies included children (aged 18 years or less). For the ten available trials, patients ranged from 35 to 222. Seven trials used zoledronic acid to prevent bone loss in men receiving androgen deprivation therapy for nonmetastatic prostate cancer. In these seven trials, the patients of six trials received 4 mg zoledronic acid or placebo every 3 months for one year, the other trial patients received 4 mg zoledronic acid on day 1 only or placebo. The remaining three trials used pamidronate, neridronate or alendronate to prevent bone loss in men receiving androgen deprivation therapy for nonmetastatic prostate cancer, respectively. The duration of ADT was less than one year, but in one trial the duration of ADT was more than one year. Five trials used intention to treat analysis (Smith et al., 2001; Ryan et al., 2006; Greenspan et al., 2007; Ryan et al., 2007; Bhoopalam et al., 2009).

A full description of the methodological quality of included studies is given in Table 2. Overall, we declared the risk of bias as moderate in seven studies(Smith et al., 2003; Ryan et al., 2006; Greenspan et al., 2007; Israeli et al., 2007; Michaelson et al., 2007; Ryan et al., 2007; Bhoopalam et al., 2009) and low in three studies (Smith et al., 2001; Morabito et al., 2004; Casey et al., 2010).

Primary outcome

Percent changes in the baseline BMD of the lumbar spine—Ten studies reported change in the bone mineral

Table 3. Results of Meta-analysis for the Efficacy of Bisphosphonates for Osteoporosis in Nonmetastatic Prostate Cancer Patients Receiving Androgen-deprivation Therapy

Parameters	N*	Sample size (I/C)	Heterogeneity	Pooled MD or OR (95% CI)	Z Test
Primary outcome					
Percent changes in the baseline BMD of the lumbar spine	10	393/412	Chi^2=11.18, *P*=0.26, I^2=20%	6.02 (5.39, 6.65)	Z=18.67, *P*< 0.00001
Incidence of fractures	4	264/259	Chi^2=1.49, *P*=0.69, I^2=0%	1.40 (0.53, 3.67)	Z=0.68, *P*=0.50
Secondary outcome					
Percent changes in the baseline BMD of the total hip	8	333/356	Chi^2=17.00, *P*=0.02, I^2=59%	2.82 (2.05, 3.58)	Z=7.23, *P*<0.00001
Percent changes in the baseline BMD of the femoral neck	7	254/262	Chi^2=3.58, *P*=0.73, I^2=0%	2.91 (2.16, 3.67)	Z=7.60, *P*<0.00001
Percent changes in the baseline BMD of the trochanter	3	73/70	Chi^2=2.49, *P*=0.29, I^2=20%	3.50 (2.38, 4.63)	Z=6.09, *P*<0.00001
Withdrawals due to severe adverse events	6	397/391	Chi^2=2.77, *P*=0.74, I^2=0%	0.88 (0.61, 1.28)	Z=0.65, *P*= 0.52
Withdrawals due to adverse events	5	297/287	Chi^2=1.97, *P*=0.74, I^2=0%	1.06 (0.48, 2.33)	Z=0.14, *P*=0.89
Total withdrawals	6	353/343	Chi^2=6.82, *P*=0.23, I^2=27%	1.46 (0.97, 2.21)	Z=1.81, *P*=0.07
ITT analysis of the lumbar spine	5	172/174	Chi^2=5.47, *P*=0.24, I^2=27%	5.05 (4.05, 6.04)	Z=9.98, *P*<0.00001

*Number of included studies; I, intervention; C, control; MD, mean difference; OR, odds ratio; BMD, bone mineral density; ITT, intention To Treat

density of the lumbar spine from baseline to 12 months, results of meta-analysis were showed in the Table 3. There was generally more improvement after bisphosphonates treatment in bone mineral density for patients who received bisphosphonates treatment than placebo or other medical treatment (WMD=6.02, 95%CI 5.39 to 6.65, *P*<0.00001).

Incidence of fractures—The results from four studies for incidence of fractures at 12 months showed that there were no significant difference between two groups (OR=1.40, 95%CI 0.53 to 3.67, *P*=0.50) (Table 3). In these four trials, only one trial reported radiographically diagnosed new or worsening vertebral fractures in the zoledronic acid group and in the non-zoledronic acid group (*p*=0.29) (Smith et al., 2003).

Secondary outcome

Percent changes in the baseline BMD of the total hip-Eight studies reporting change in the bone mineral density of the total hip from baseline to 12 months, there was significant heterogeneity between studies so we carried out random effect meta-analyses (Table 3). After bisphosphonates treatment, there was generally more improvent in bone mineral density for patients who received bisphosphonates treatment than non-bisphosphonates treatment (WMD=2.82, 95%CI 2.05 to 3.58, *P*<0.00001).

Percent changes in the baseline BMD of the femoral neck—Results from seven studies reporting this outcome from baseline to 12 months were showed in Table 3. There was a statistically significant difference between groups (WMD=2.91, 95%CI 2.16 to 3.67, *P*<0.00001). There was generally more improvent in bone mineral density for patients who received bisphosphonates treatment than non-bisphosphonates treatment.

Percent changes in the baseline BMD of the trochanter—Results from three studies reporting this outcome from baseline to 12 months were showed in Table 3. There was a statistically significant difference between groups (WMD=3.50, 95%CI 2.38 to 4.63, *P*<0.00001). There was generally more improvent in bone mineral density for patients who received bisphosphonates treatment than non-bisphosphonates treatment.

Adverse events-All ten studies reported on adverse events,but the data of one trial (Ryan et al., 2007) could not be obtained because of AEs including nonmetastatic and metastatic prostate cancer. We were able to present combined data in a meta-analysis for fatigue, anaemia, flushing, upper respiratory infection, fever, flu syndrome, arthralgia, constipation, myalgia, limb pain, urinary frequency, hypertension and gastrointestinal symptoms (Table 4). The pooled results showed that the risk of fever and gastrointestinal symptoms were significantly higher after bisphosphonates treatment than placebo (fever:10.4% vs. 1.2%; OR=7.99, 95%CI 2.08 to 30.61, *P*=0.002; gastrointestinal symptoms: 0.10% vs. 0.03%; OR=2.89, 95%CI 1.18 to 7.04, *P*=0.02), while there was no significant difference in other adverse events.

Six trials reported severe adverse events in study period, the pooled results of this meta-analysis demonstrated that there was no significant difference between the two groups (Table 3: 16.6% vs.18.4%; OR=0.88, 95%CI 0.61 to 1.28, *P*=0.52).

We have presented data for withdrawals due to adverse events and total withdrawals (Table 3). Six studies described withdrawals from the study. Data from these six trials did not show any significant difference between treatment and control groups for withdrawals due to adverse events or in total for any reason during study period.

Sensitivity analysis

Considering the patients with the differences in BMD, fracture, or adverse events between oral and intravenous bisphosphonates, so we performed sensitivity analysis. The percent increase in BMD at the lumbar spine still increased

Table 4. Results of Meta-analysis for Complications Compared Bisphosphonates with Control

Complications	N*	Sample size	Heterogeneity (Bisphosphonates/control)	Pooled OR (95% CI)	Z Test
Fatigue	7	445/436	Chi^2=3.68, *P*=0.72, I^2=0%	1.01 (0.67, 1.52)	Z=0.04, *P*= 0.96
Anaemia	3	130/126	Chi^2=0.65, *P*=0.72, I^2=0%	0.67 (0.20, 2.17)	Z=0.68, *P*= 0.50
Flushing	5	277/270	Chi^2=4.25, *P*=0.37, I^2=6%	1.03 (0.69, 1.54)	Z=0.13, *P*= 0.90
Arthralgia	4	264/259	Chi^2=2.26, *P*=0.52, I^2=0%	1.52 (0.69, 1.54)	Z=1.58, *P*= 0.11
Constipation	4	220/211	Chi^2=3.40, *P*=0.33, I^2=12%	0.57 (0.29, 1.12)	Z=1.64, *P*= 0.10
Musculoskeletal pain	4	220/211	Chi^2=4.67, *P*=0.20, I^2=36%	0.99 (0.56, 1.75)	Z=0.02, *P*= 0.99
Limb pain	2	116/110	Chi^2=0.22, *P*=0.64, I^2=0%	1.45 (0.49, 4.26)	Z=0.68, *P*= 0.50
Hypertension	2	104/101	Chi^2=0.16, *P*=0.69, I^2=0%	0.58 (0.13, 2.49)	Z=0.74, *P*= 0.46
Gastrointestinal symptoms	3	209/208	Chi^2=0.95, *P*=0.62, I^2=0%	2.89 (1.18, 7.04)	Z=2.33, *P*= 0.02
Fever	2	173/169	Chi^2=1.50, *P*=0.22, I^2=33%	7.99 (2.08, 30.61)	Z=3.03, *P*= 0.002
Upper respiratory infection / Flu syndrome	4	277/270	Chi^2=8.03, *P*=0.05, I^2=63%**	2.03 (0.68, 6.06)	Z=1.27, *P*= 0.21
Urinary frequency	2	111/107	Chi^2=2.54, *P*=0.11, I^2=61%**	1.14 (0.29, 4.48)	Z=0.19, *P*= 0.85

*Number of included studies; **Random-effect model; OR, odds ratio

significantly at 12 months when oral bisphosphonates were analysed separately to intravenous bisphosphonates; oral bisphosphonates, BMD for percent change 5.10 (95% CI 3.49 to 6.71), intravenous bisphosphonates, BMD for percent change 6.05 (95%CI 5.37 to 6.72). This was also observed for the effect on the total hip or femoral neck BMD (12 months).

The risk of fracture at 12 months was still no significant difference when oral bisphosphonates were analysed separately to intravenous bisphosphonates; oral bisphosphonates, the risk of fracture 1.00 (95%CI 0.06 to 16.39), intravenous bisphosphonates, the risk of fracture 1.46 (95%CI 0.52 to 4.09, *P*=0.47).

In the study of oral bisphosphonates, none of the participants in either the intervention or the control group experienced fever, anaemia, flushing, limb pain. The symptom of fatigue was no significant difference when oral bisphosphonates were analyzed separately to intravenous bisphosphonates (oral bisphosphonates, OR=0.74,95%CI 0.16 to 3.45; intravenous bisphosphonates, OR=1.24, 95%CI 0.77 to 1.99). The symptoms of upper respiratory infection/flu syndrome were no significant difference between oral and intravenous bisphosphonates (oral bisphosphonates, OR=1.95, 95%CI 0.61 to 6.25; intravenous bisphosphonates, OR=2.14, 95%CI 0.41 to 11.30). The symptom of arthralgia was no significant difference between oral and intravenous bisphosphonates (oral bisphosphonates, OR=2.10,95%CI 0.89 to 4.97; intravenous bisphosphonates, OR=1.55, 95%CI 0.73 to 3.30). The symptom of musculoskeletal pain was also no significant difference between oral and intravenous bisphosphonates (oral bisphosphonates, OR=0.22, 95%CI 0.04 to 1.10; intravenous bisphosphonates, OR=1.36, 95%CI 0.72 to 2.57). The symptom of constipation was also no significant difference between oral and intravenous bisphosphonates (oral bisphosphonates, OR= 0.59, 95%CI 0.18 to 1.92; intravenous bisphosphonates, OR=0.56, 95%CI 0.24 to 1.27). Other adverse events also showed no significant difference between oral and intravenous bisphosphonates treatment.

Five trials performed ITT analysis, so we carried out meta-analysis by ITT. The percent increase in BMD at the lumbar spine still increased significantly at 12 months (WMD=5.05, 95%CI 4.05 to 6.04, *P*<0.00001) (Table 3). This was also observed for the effect on the total hip, femoral neck or trochanter BMD (12 months).

Discussion

Osteoporosis is a common consequence of ADT for prostate cancer. Up to 20% of men on ADT for localized prostate cancer will fracture within 5 years (Adler, 2011). Currently, a systematic review and meta-analysis has confirmed that the use of androgen deprivation therapy in patients with PCa reduces bone mineral density, increasing the risk of fractures (Serpa et al., 2010). Maillefert et al demonstrated that there was a 4.6% decrease in BMD at the lumbar spine and a 3.9% decrease at the femoral neck after 1 year of ADT (Maillefert et al., 1999). Eriksson et al reported that orchiectomy also resulted in substantial changes, with a 15% decrease in trochanter BMD after 1 year (Eriksson et al., 1995). And recent years, a large number of patients with nonmetastatic prostate cancer receiving androgen-deprivation therapy used bisphosphonates for preventing osteoporosis, but the effectiveness and safety of bisphosphonates are still unclear.

In this systematic review we considered data from 1017 participants across ten randomised controlled trials of moderate to poor quality. Based on data from a single trial, the oral alendronate was associated with decreased BMD at the lumbar spine, total hip and femoral neck regions in patients with nonmetastatic prostate cancer receiving androgen-deprivation therapy (Greenspan et al., 2007). Nine other trials assessing different bisphosphonate regimens (agent and frequency) in this population group also showed improved lumbar spine BMD. The trials with hip, femur or trochanter BMD as a measure showed positive effects on this outcome. Although the inclusion criteria, duration of follow up and the magnitude of effect were different for the trials, similar trends for BMD effect were seen, suggesting that the beneficial effects of bisphosphonates might be generalisable to a fairly broad population of people with nonmetastatic prostate cancer receiving androgen-deprivation therapy. Bone mineral density is only an intermediate outcome, however, the more clinically important endpoint is the occurrence of new fractures. Our pooled results showed that there was no

significant effect of treatment on fractures for participants in one year.

Overall incidence rates for adverse events with bisphosphonates did not differ from placebo regardless of dose, agent or administration route. And there was no significant difference in the number of withdrawals due to side effects, total adverse events, regardless of the dose, agent or administration route analyzed. Although, fever and gastrointestinal symptoms were more common after bisphosphonates treatment (10.4% vs. 1.2%; P=0.002; 0.10% vs. 0.03%; P=0.02).

According to these studies, we found that men initiating ADT should have an assessment of risk factors, including calcium and vitamin D intake levels, lifestyle modification counseling, baseline and follow-up BMD assessments; Based on the above risk factors, men with established osteoporosis should be as candidates for treatment with bisphosphonates. However, we first provide real information about the efficacy of bisphosphonates in nonmetastatic prostate cancer patients under ADT with osteoporosis, and we show that bisphosphonate therapy should also be considered as preventing bone loss in patients under ADT and without osteoporosis. Among these bisphosphonates, zoledronic acid was the best method in our study for all outcomes analyzed.

For the past few years, two new drugs denosumab (Smith et al., 2009) and toremifene (Smith et al., 2010) have been used for reducing fracture risk in men receiving androgen deprivation therapy for prostate cancer. Denosumab is a fully human monoclonal antibody against RANKL, a key mediator of osteoclast formation, function and survival. The study demonstrated that a total of 1,468 subjects were randomized 1:1 to receive 60 mg subcutaneous denosumab every 6 months or placebo for 36 months, denosumab significantly increased bone mineral density of the lumbar spine, total hip and distal 1/3 radius by 7.9%, 5.7% and 6.9%, respectively, compared with placebo ($p < 0.0001$ for each comparison). Toremifene is a second-generation selective estrogen receptor modulators, and in a arge randomized placebo controlled trial, compared with placebo BMD increased significantly at the lumbar spine (2.3%), total hip (1.9%) and femoral neck (1.9%) in the toremifene group ($p <0.0001$ for each comparison) after 24 months. However, our meta-analysis results demonstrated that bisphosphonates significantly increased bone mineral density of the lumbar spine, total hip and femoral neck by 6.02%, 2.82% and 2.91%, respectively, compared with placebo ($p < 0.0001$ for each comparison) after 12 months. Moreover, these two drugs therapies are still in their early clinical trials and have no their effectiveness compared with bisphosphonates.

Our systematic review has also several limitations. Firstly, the moderate to poor methodological quality of the included studies, together with the high number of comparisons, diluted the opportunities for meta-analysis. Only four studies measured fractures as an outcome and the exact reasons of fracture were unclear, adding to the difficulty of interpreting the overall significance of the results. Seven of the ten studies had losses to follow up, one study had no allocation concealment, three studies did not perform blinding and seven studies had unclear descriptions of allocation concealment. Losses to follow-up can threaten the validity of the trial since the event rate may be very different in those lost to follow-up versus those who completed the trial; failure to conceal the participants'treatment allocation could also bias the treatment effect in either direction. Secondly, we only included the data of published studies and unpublished reports tend to show more negative results, so the exclusion of these abstracts might have introduced bias in favor of the interventions. Seven studies reported the effect of zoledronic acid for osteoporosis in nonmetastatic prostate cancer patients receiving androgen-deprivation therapy, while only one study reported the effect of pamidronate, neridronate or alendronate for osteoporosis in nonmetastatic prostate cancer patients receiving androgen-deprivation therapy, respectively. It suggested that we should interpret the effect of pamidronate, neridronate or alendronate with caution.

In conclusion, based on ten RCT trials, oral and intravenous bisphosphonates caused a rapid increase in spine and hip or femoral BMD in nonmetastatic prostate cancer patients receiving androgen-deprivation therapy. Fever and gastrointestinal symptoms were common with the use of bisphosphonates. These short-term trials (maximum of 12 months) did not show fracture reduction or survival benefit. In future, more higher quality and long-term randomised controlled trials (>12 months) where outcomes are detailed description are needed.

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