Systematic Review and Meta-Analysis

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Minodronate in the treatment of osteoporosis

A systematic review and meta-analysis

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Abstract

Background: The goal of this study was to review relevant randomized controlled trials or case-control studies to determine the clinical efficacy of minodronate in the treatment of osteoporosis.

Method: The relevant studies were identified on PubMed, Cochrane, and Embase databases using appropriate keywords. Pertinent sources in the literature were also reviewed, and all articles published through October 2019 were considered for inclusion. For each study, we assessed odds ratios, mean difference, and 95% confidence interval (95% CI) to evaluate and synthesize outcomes.

Result: Thirteen studies comprising 3740 patients were included in this study. Compared with other drugs, minodronate significantly decreased N-telopeptide of type I collagen/creatinine (weighted mean difference [WMD]: –13.669, 95% confidence interval [CI]: –23.108 to –4.229), bone alkaline phosphatase (BAP) (WMD: –1.26, 95% CI: –2.04 to –0.47) and tartrate-resistant acid phosphatase 5b (WMD: –154.11, 95% CI: –277.85 to –30.37). Minodronate combined with other drugs would significantly decrease BAP (WMD: –3.10, 95% CI: –5.20 to –1.00) than minodronate. Minodronate-naïve would significantly decrease BAP (WMD: –3.00, 95% CI: –5.47 to 0.53) and tartrate-resistant acid phosphatase 5b (WMD: –128.20, 95% CI: –198.11 to –58.29) than minodronate-switch. The incidence of vertebral fracture was significantly decreased in the minodronate group than the other drugs (relative risk: 0.520, 95% CI: 0.363–0.744).

Conclusion: Minodronate has better clinical efficacy in the treatment of osteoporosis than other drugs (alendronate, risedronate, raloxifene, or eldecalcitol).

Abbreviations: 95% CI = 95% confidence interval, AE = adverse event, BAP = bone alkaline phosphatase, BMD = bone mineral density, GIOP = glucocorticoid-induced osteoporosis, NTx/Cre = N-telopeptide of type I collagen/creatinine, OP = osteoporosis, ORs = odds ratios, PICOS = participants, interventions, comparisons, outcomes, and study design, PMO = postmenopausal osteoporosis, PMOP = postmenopausal osteoporosis, PMOP = postmenopausal osteoporosis, TRACP–5b = tartrate-resistant acid phosphatase 5b, WMD = weighted mean difference.

Keywords: meta-analysis, minodronate, osteoporosis

1. Introduction

Osteoporosis (OP) is a systemic skeletal disease characterized by decreased bone mass and destruction of bone microstructure, resulting in increased bone brittleness and risk of fracture[1] OP can be categorized as primary OP which refers to senile and postmenopausal osteoporosis (PMO), and as secondary OP which is associated with a variety of factors, such as endocrine

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disorders, nutritional deficiencies, drug use, liver and kidney disease, alcoholism, and so on.[2] The bone cortex and trabecular structure are destroyed in the condition of osteoporosis, which often results in brittle fractures. People with osteoporosis are more likely to break bones than the general population. At the same time, due to the destruction of bone tissue structure, it becomes difficult to bear bone implants in the human body, leading to the failure rate of fracture fixation up to 10% to 25%.[3,4] With the extension of the human life span and the development of social aging, fractures caused by osteoporosis not only greatly increase the morbidity and mortality of the elderly, but also significantly increase the economic burden of public social health.[5] OP can occur at any age, but it is more common in postmenopausal women and older men. OP is divided into 2 categories: primary and secondary. Primary OP includes postmenopausal OP, senile OP, and idiopathic OP. Postmenopausal OP usually occurs within 5 to 10 years after menopause. Senile OP disease points to the osteoporosis that commonly occurs after 70 years of age. Idiopathic OP mainly occurs in adolescents and the etiology is not yet known. Secondary OP is osteoporosis caused by any disease and/or drug that affects bone metabolism and other known causes.[6]

The goal of OP medication is to reduce the risk of brittle fractures. According to the mechanism of action, OP drugs can be divided into inhibitors of bone absorption, promoters of bone formation and drugs of dual action.[7] The pathophysiological basis of OP is that the balance between bone resorption and bone formation is broken, and bone resorption exceeds bone formation, leading to bone loss. Bone resorption inhibitors reduce bone resorption and bone damage. Bone formation promoters can act on osteoblasts and significantly increase bone formation. Bone resorption inhibitors include bisphosphonates, calcitonin, estrogens, selective estrogen receptor modulators, Denosumab, and cathepsin K inhibitors. The main promoters of bone formation are parathyroid hormone analogs such as Teriparatide and Abaloparatide. Strontium ranelate is a commonly used clinical dual-acting drug.[8] First-line treatment for most PMO patients with a high risk of fracture includes alendronate, risedronate, zoledronic acid, and denosumab. For initial treatment in patients who cannot be treated oral drugs and are at high risk of fracture, tripaceptidine, or zoledronic acid may be considered.[9]

So far, bisphosphonates are the most widely used anti-bone resorption drugs. Minodronic acid (ym–529, ono–5920, yh–529), synthesized by Yarnanouchi, is a third-generation azaryl bisphosphonate derivative.[10,11] Its anti-bone resorption activity is 100 to 1000 times higher than that of palmidronate, and it can also antagonize osteolysis caused by myeloma and tumor.[12,13] This study aimed to perform a meta-analysis of all available literature to obtain updated evidence to advocate the clinical efficacy of minodronate in the treatment of OP and to provide a basis for its selection in the clinical treatment.

2. Methods

2.1. Search strategy

In order to identify studies pertaining to the clinical outcomes of minodronate in the treatment of OP, we reviewed the Cochrane, Pubmed, and Embase databases for relevant articles published through October 2019 following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement. We also reviewed the references of all identified articles to retrieve associated additional studies. Search terms were as follows: minodronic acid, minodronic acid hydrate, minodronate, osteoporosis, GIOP, PMO, OP, Glucocorticoid-Induced Osteoporosis, PMOP, postmenopausal osteoporosis. These terms were used in combination with "AND" or "OR." This literature review was performed independently by 2 investigators, with a third one to resolve any disputes if needed.

Following the PICOS (Participants, Interventions, Comparisons, Outcomes, and Study design) principle, the key search terms included (P) patients with OP; (I) patients treated by minodronate; (C/O) the outcomes including all the related indexes; (S) RTC or case-control study.

2.2. Study selection criteria

The included studies met the following criteria:

(1) randomized controlled trials, or case-control studies;
(2) the research objects were patients with OP, and all the subjects are Japanese;
(3) the treatment with minodronate;
(4) English or Chinese language.

Studies were excluded for meeting the following criteria:

(1) repeated articles or results;
(2) clear data errors;
(3) case reports, theoretical research, conference reports, systematic reviews, meta-analyses, and other forms of research or not designed in a randomized controlled manner;
(4) irrelevant outcomes.

Two investigators independently determined whether studies met with inclusion criteria, with a third resolving any disputes as needed.

2.3. Data extraction and quality assessment

For each included study, 2 categories of information were extracted: basic information and primary study outcomes. Basic information relevant to this meta-analysis included the name of the authors, year of publication, disease, design, interventions, sample size, age, and body mass index. Whereas, the primary clinical outcomes included the bone mineral density (BMD), which was measured by dual-energy X-ray absorptiometry; N-telopeptide of type I collagen/creatinine (NTx/Cre), bone alkaline phosphatase (BAP), tartrate-resistant acid phosphatase 5b (TRACP–5b), vertebral fracture, non-vertebral fracture, drug-related adverse event (AE), drug-related gastrointestinal AE, gastrointestinal disorders, discontinued due to drug-related AE, discontinued due to drug-related gastrointestinal AE. This data extraction was performed independently by 2 investigators, with a third resolving any disputes as needed.

2.4. Statistical analysis

STATA v10.0 (TX) was used for all analyses. The heterogeneity in study results was assessed using chi-square and I^2 tests and appropriate analysis models (fixed-effect or random-effect) were determined. A Chi-squared $P \leq .05$ and an $I^2 > 50\%$ indicated high heterogeneity and a random-effects model was used in this case. A Chi-squared $P > .05$ and an $I^2 \leq 50\%$ indicated acceptable heterogeneity and a fixed-effects model was used instead. Continuous variables are given as mean ± standard

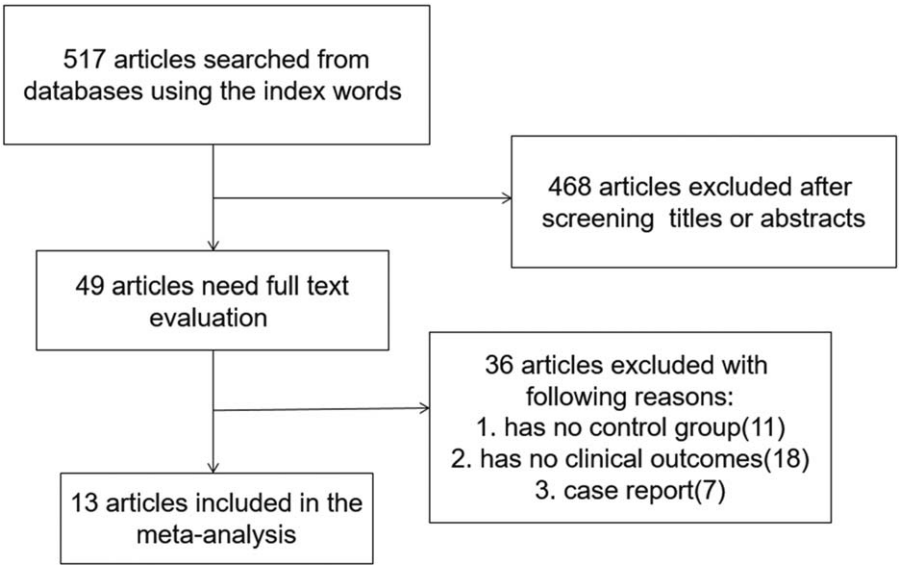

Figure 1. Flow diagram of the literature search and selection strategy.

deviations and were compared on the basis of mean difference, while categorical data are given as percentages and compared based on relative risk (RR)/odds ratios (ORs). BMD, NTx/Cre, BAP, and TRACP–5b were analyzed by mean difference. The other parameters were analyzed by RR.

3. Results

3.1. Overview of included studies

A total of 517 articles were identified by the initial keyword searches, of which 468 were excluded following title/abstract review. The remaining 49 articles were subjected to a complete full-text assessment, leading to 36 articles being excluded for failing to meet the study inclusion criteria. The reasons for the exclusion of these studies were lack of control group (11), lack of clinical outcomes (18), and being a case report (7). We ultimately identified a total of 13 studies[14–26] that met with the inclusion criteria for this meta-analysis, incorporating 3740 patients. Flow diagram of the study selection is outlined in Figure 1.

Table 1 summarizes the basic information for each study, including author names, year of publication, disease, design, interventions, sample, age, and body mass index. By the intervention of the included studies, we divided them into 4 subgroup analyses: minodronate-naïve (minodronate on bisphosphonate-naive patients) versus minodronate-switch (minodronate on patients with previous bisphosphonate use), minodronate versus other drugs, minodronate combined with other drugs versus minodronate, minodronate monthly versus minodronate daily. By the design of the included studies, we divided them into 2 subgroup analyses: randomized control trials (RCTs) and case-control studies.

3.2. BMD

In the all included studies, there was no significant difference in BMD (g/cm^2) in minodronate-naïve versus minodronate-switch (weighted mean difference [WMD]: –0.01, 95% CI: –0.05 to 0.04), minodronate versus other drugs (WMD: –0.00, 95% CI: –0.00 to 0.00), minodronate combined with other drugs versus minodronate (WMD: 0.02, 95% CI: –0.01 to 0.05). There was no significant difference in BMD (YAM, young adult mean) in minodronate-naïve versus minodronate-switch (WMD: –0.460, 95% CI: –4.562 to 3.642), minodronate versus other drugs (WMD: –0.400, 95% CI: –4.697 to 3.897). There was no significant difference in BMD (*T*-score) in minodronate-naïve versus minodronate-switch (WMD: –0.083, 95% CI: –0.421 to 0.254).

In the subgroup analysis of the included case-control studies, there was no significant difference in BMD (g/cm^2) (WMD: –0.007, 95% CI: –0.050 to 0.036), BMD (YAM, %) (WMD: –0.460, 95% CI: –4.563 to 3.642) and BMD (*T*-score) (WMD: –0.083, 95% CI: –0.421 to 0.254) between the minodronate-naïve and minodronate-switch. Besides, there was no significant difference in BMD (g/cm^2) (WMD: 0.023, 95% CI: –0.006 to 0.052) between the minodronate with other drugs and minodronate.

In the subgroup analysis of RCTs, there was no significant difference of BMD (g/cm^2) (WMD: 0.000, 95% CI: –0.004 to 0.003) and BMD (YAM, %) (WMD: –0.400, 95% CI: –4.697 to 3.897) between minodronate and other drugs.

The results are presented in Figure 2 and Tables 2–4.

3.3. Bone turnover markers

In the all included studies, compared with other drugs, minodronate significantly decreased NTX/Cre (WMD: –13.669, 95% CI: –23.108 to –4.229), BAP (WMD: –1.26, 95% CI: –2.04 to –0.47), and TRACP–5b (WMD: –154.11, 95% CI: –277.85 to –30.37). Minodronate combined with other drugs significantly decreased BAP (WMD: –3.10, 95% CI: –5.20 to –1.00) than minodronate. Minodronate-naïve significantly decreased BAP (WMD: –3.00, 95% CI: –5.47 to 0.53) and TRACP–5b (WMD: –128.20, 95% CI: –198.11 to –58.29) than minodronate-switch. There was no significant difference in TRACP–5b in minodronate combined with other drugs versus minodronate (WMD: –97.47, 95% CI: –255.01 to 60.06).

Table 1

The basic characteristics description of included studies.

Study	Design	Intervention		No. of patients		Age		BMI	
		T	C	T	C	T	C	T	C
Shin-ya Tamechika 2018	RCT	Minodronate 50 mg every 4 wk	Weekly alendronate 35 mg or risedronate 17.5 mg	74	71	57.2	54.2	21.6	21.8
Eriko Hasegawa 2018 a	Case-control	Minodronate-naïve	Minodronate-switch	52	68	65.7	62.8	–	–
Eriko Hasegawa 2018 b	Case-control	Minodronate-naïve	Minodronate-switch	52	68	65.7	62.8	–	–
K. Kumagai 2018	RCT	Once-monthly oral minodronate	Once-monthly oral risedronate	42	41	70.8	70.1	22.6	17.9
Shinichi Nakatoh 2018 a	RCT	Minodronate	Raloxifene	41	42	81.6	82.7	21.6	21.7
Shinichi Nakatoh 2018 b	RCT	Minodronate	Eldecalcitol	41	38	81.6	83	21.6	21.4
Shinichi Nakatoh 2018 c	RCT	Minodronate	Raloxifene	41	42	81.6	82.7	21.6	21.7
Shinichi Nakatoh 2018 d	RCT	Minodronate	Eldecalcitol	41	38	81.6	83	21.6	21.4
Mizue Tanaka 2017 a	case-control	Oral mindronate and eldecalcitol	Oral mindronate	50	48	77.2	75	–	–
Mizue Tanaka 2017 b	case-control	Oral mindronate and eldecalcitol	Oral mindronate	50	48	77.2	75	–	–
Shinya Tanaka 2017 a	RCT	Minodronic acid hydrate at a dose of 1 mg daily	Intramuscular injections of elcatonin at a dose of 20 units weekly	17	16	72.6	75.5	21.6	20.9
Shinya Tanaka 2017 b	RCT	Minodronic acid hydrate at a dose of 1 mg daily combined with intramuscular injections of elcatonin at a dose of 20 units weekly	Minodronic acid hydrate at a dose of 1 mg daily	18	17	78.1	72.6	21.1	21.6
Mikio Kamimura 2016	case-control	50 mg/mo of minodronate	75 mg/mo of risedronate	16	14	68.2	68.1	–	–
Michiya Igase 2014	RCT	Monthly 50-mg dose of minodronate	Single weekly 35-mg dose of alendronate	18	19	67.2	67.7	21.6	21.8
Toru Yoshioka 2013	RCT	Minodronate were orally administered for 24 wk at a dose of 1 mg daily	Alendronate were orally administered for 24 wk at a dose of 35 mg weekly	33	26	76.1	77.8	24.4	23.4
Hiroshi Hagino2012	Case-control	Minodronate	Placebo	215	205	71.1	71.1	23.26	23.54
R. Okazaki 2012 a	RCT	Minodronate 50 mg monthly	Mindronate 1 mg daily	229	234	67.3	67.8	22.03	21.88
R. Okazaki 2012 b	RCT	Minodronate 30 mg monthly	Mindronate 1 mg daily	229	234	68.6	67.8	21.87	21.88
Hiroshi Hagino 2009 a	RCT	1 mg minodronate once-daily	5 mg alendronate once-daily	134	135	63.9	65.8	21.6	21.5
Hiroshi Hagino 2009 b	RCT	1 mg minodronate once-daily	5 mg alendronate once-daily	134	135	63.9	65.8	21.6	21.5
T. Matsumoto 2009	RCT	Daily oral 1 mg minodronate	Daily oral placebo	343	331	71.4	71.7	23.4	23.5

BMI = body mass index, RCT = randomized controlled trials.

In the subgroup analysis of included case-control studies, compared with other drugs, minodronate significantly decreased the value of NTX/Cre (WMD: –17.200, 95% CI: –20.595 to –13.805) and BAP (WMD: –1.200, 95% CI: –2.021 to –0.379). Compared with minodronate, minodronate with other drugs significantly decreased BAP (WMD: –3.100, 95% CI: –5.197 to –1.003) and TRACP–5b (WMD: –181.400, 95% CI: –247.189 to –115.611). Compared with minodronate-switch, minodronate-naïve significantly decreased BAP (WMD: –3.000, 95% CI: –5.473 to –0.527) and TRACP–5b (WMD: –128.200, 95% CI: –198.114 to –58.286).

In the subgroup analysis of included RCTs, there was no significant difference of NTX/Cre (WMD: –7.100, 95% CI: –18.475 to 4.275) and BAP (WMD: –1.733, 95% CI: –4.145 to 0.679) between the minodronate and other drugs. The value of TRACP–5b was significantly decreased in minodronate with other drugs versus minodronate (WMD: –20.500, 95% CI: –26.096 to –14.904), minodronate versus other drugs (WMD: –154.112, 95% CI: –277.854 to –30.37).

The results are presented in Figures 3 and 4 and Tables 2–4.

3.4. Fractures

In all included studies, there was no significant difference in the incidence of vertebral fractures in minodronate-naïve versus minodronate-switch (RR: 1.308, 95% CI: 0.084–20.419). There was no significant difference in the incidence of non-vertebral fractures in minodronate-naïve versus minodronate-switch (RR: 0.726, 95% CI: 0.401–1.314). The incidence of vertebral fracture was significantly decreased in the minodronate group than other drugs (RR: 0.520, 95% CI: 0.363–0.744).

In the subgroup analysis of the included case-control studies, there was no significant difference in vertebral fractures (RR: 1.430, 95% CI: 0.410–4.995) and non-vertebral fractures (RR: 0.834, 95% CI: 0.308–2.259) between minodronate and other drugs. There was no significant difference in the vertebral fractures (RR: 1.308, 95% CI: 0.084–20.419) in minodronate-naïve versus minodronate-switch.

In the subgroup analysis of the included RCTs, compared with other drugs, minodronate significantly decreased the incidence of vertebral fractures (RR: 0.469, 95% CI: 0.321–0.685), but had no significant difference in the incidence of non-vertebral fractures (RR: 0.672, 95% CI: 0.320–1.412).

The results are presented in Tables 2–4.

3.5. Adverse event

In all included studies, the incidence of drug-related gastrointestinal AE was significantly higher in the minodronate group than other drugs group (RR: 1.680, 95% CI: 1.037–2.72). There was no significant difference in drug-related AE (RR: 1.039, 95% CI:

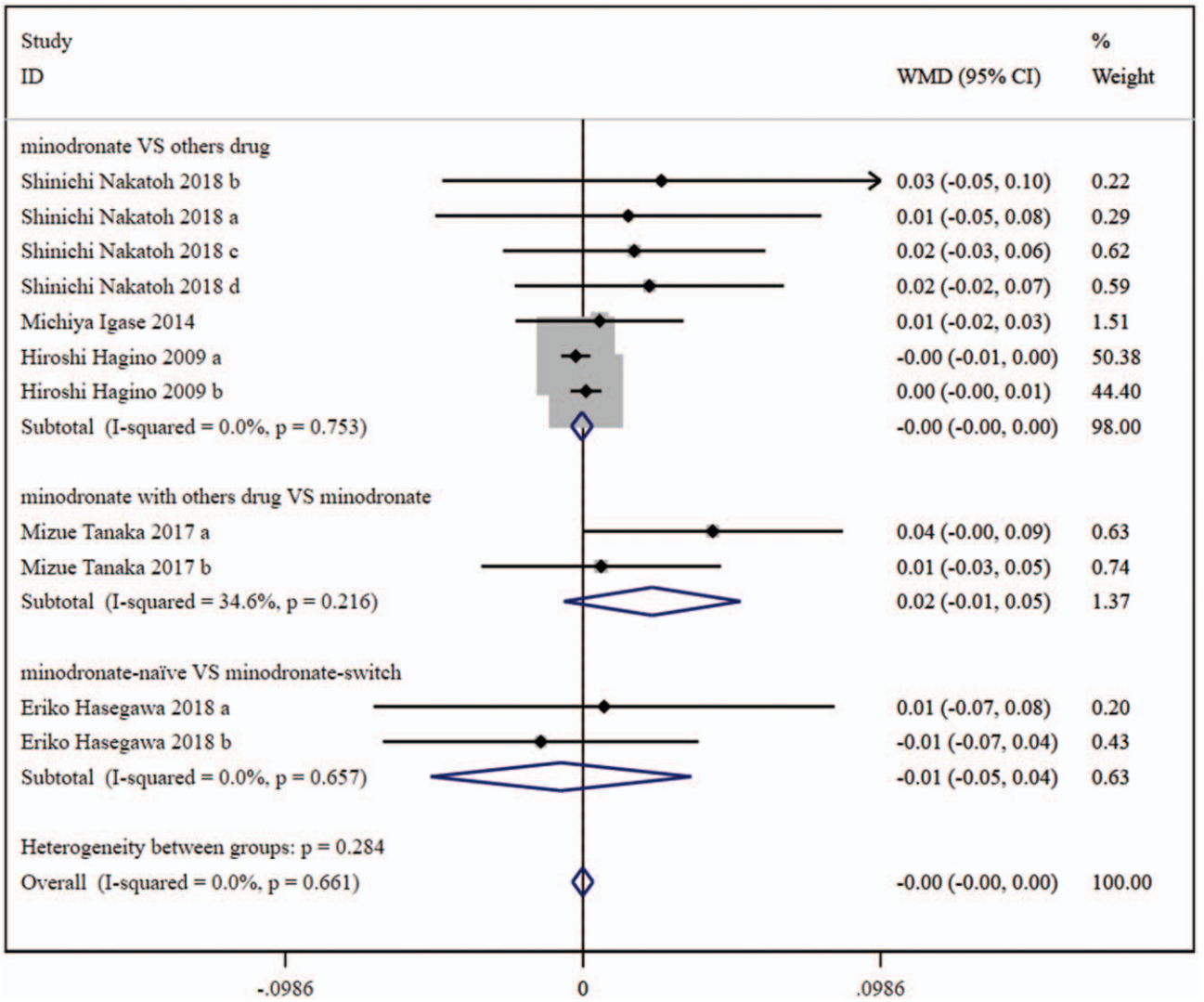

Figure 2. Forest plot for the BMD. BMD = bone mineral density.

0.823–1.310), gastrointestinal disorders (RR: 1.075, 95% CI: 0.936–1.230), discontinued due to drug-related AE (RR: 1.191, 95% CI: 0.647–2.191), discontinued due to drug-related gastrointestinal AE (RR: 1.229, 95% CI: 0.633–2.385) between the minodronate group and other drugs group. There was no significant difference in drug-related AE (RR: 1.056, 95% CI: 0.759–1.470), gastrointestinal disorders (RR: 0.766, 95% CI: 0.497–1.181) between minodronate monthly group and minodronate daily group.

In the subgroup analysis of the included case-control studies, compared with other drugs, minodronate significantly increased the incidence of drug-related gastrointestinal AE (RR: 2.452, 95% CI: 1.046–5.747) but had no significant difference in the incidence of drug-related AE (RR: 0.896, 95% CI: 0.570–1.407).

In the subgroup analysis of included RCTs, there was no significant difference in all AE related indexes in minodronate versus other drugs, minodronate monthly versus minodronate daily.

The results are presented in Tables 2–4.

3.6. Quality and bias assessment

An assessment of study quality and risk of bias was performed using multiple complementary methods including funnel plots, Begg and Mazumdar rank test, and Egger test. There was clear symmetry in the log WMD funnel plot for BMD for these studies, suggesting a low publication bias risk (Fig. 5). The results of Begg and Mazumdar rank test ($Z=0.16$, $P=.876$), and Egger test ($P=.145$) both suggested that there was no significant risk of bias among study results.

4. Discussion

Osteoporosis is a bone disease characterized by low bone mass and structural degeneration of bone tissue. Currently, the drugs used in the clinical treatment of osteoporosis, such as estrogen, selective estrogen regulator, calcitonin, and bisphosphonates, are mainly conducive to reducing bone absorption. Other treatments, such as fluoride and parathyroid hormones, can increase bone formation. Anti-resorption therapy is very effective in treating

Table 2

The meta-analysis of indexes in all included studies.

Index	N (case/control)	Interventions	ES (95% CI)	P^*	I^2	$P^\dagger$	*P*-value Begg	*P*-value Egger
BMD (YAM, young adult mean, %)‡								
	104/136	Minodronate-naïve VS minodronate-switch	−0.460 (−4.562, 3.642)	.723	0.0%	.826	.317	–
	33/26	Minodronate VS others drug	−0.400 (−4.697, 3.897)	–	–	.855	–	–
BMD (*T*-score)‡								
	104/136	Minodronate-naïve VS minodronate-switch	−0.083 (−0.421, 0.254)	.955	0.0%	.682	1.000	–
NTX/Cre (nmol BCE/mmol Cr)‡								
	49/40	Minodronate VS others drug	−13.669 (−23.108, −4.229)	.095	64.1%	.005	1.000	–
Vertebral fractures§								
	52/68	Minodronate-naïve VS minodronate-switch	1.308 (0.084, 20.419)	–	–	.848	–	–
	674/648	Minodronate VS others drug	0.520 (0.363, 0.744)	.186	37.7%	.000	1.000	.134
Non-vertebral fractures§								
	674/648	Minodronate VS others drug	0.726 (0.401, 1.314)	.952	0.0%	.290	.308	.152
Drug-related AE§								
	458/468	Minodronate monthly VS mindronate daily	1.056 (0.759, 1.470)	.848	0.0%	.747	.317	–
	734/712	Minodronate VS others drug	1.039 (0.823, 1.310)	.778	0.0%	.748	1.000	.964
Drug related gastrointestinal AE§								
	391/381	Minodronate VS others drug	1.680 (1.037, 2.72)	.458	0.0%	.035	1.000	0.788
Gastrointestinal disorders§								
	458/468	Minodronate monthly VS mindronate daily	0.766 (0.497, 1.181)	.891	0.0%	.228	.317	–
	477/466	Minodronate VS others drug	1.075 (0.936, 1.230)	.961	0.0%	.308	.317	–
Discontinued due to drug-related AE§								
	477/466	Minodronate VS others drug	1.191 (0.647, 2.191)	.923	0.0%	.574	1.000	–
Discontinued due to drug-related gastrointestinal AE§								
	477/466	Minodronate VS others drug	1.229 (0.633, 2.385)	.831	0.0%	.543	1.000	–

AE = adverse event, BMD = bone mineral density, CI = confidence interval, NTX/Cre = N-telopeptide of type I collagen/creatinine.

* *P* value of heterogeneity Chi-squared.

† *P* value of Pooled statistic.

‡ ES [95% CI]: WMD [95% CI].

§ ES [95% CI]: RR [95% CI].

Table 3

The meta-analysis of indexes in the included case-control studies.

Index	N (case/control)	Interventions	ES (95% CI)	P^*	I^2	$P^\dagger$	*P*-value Begg	*P*-value Egger
BMD (g/cm^2)	104/136	Minodronate-naïve VS minodronate-switch	−0.007 (−0.050, 0.036)§	.657	0.0%	.740	.317	–
	100/96	Minodronate with others drug VS minodronate	0.023 (−0.006, 0.052)§	.216	34.6%	.123	.317	–
BMD (YAM, young adult mean, %)	104/136	Minodronate-naïve VS minodronate-switch	−0.460 (−4.563, 3.642)§	.732	0.0%	.826	1.000	–
BMD (*T*-score)	104/136	Minodronate-naïve VS minodronate-switch	−0.083 (−0.421, 0.254)§	.955	0.0%	.682	1.000	–
NTX/Cre (nmol BCE/mmol Cr)	16/14	Minodronate VS others drug	−17.200 (−20.595, −13.805)§	–	–	.000	–	–
BALP/BAP (U/L)	50/48	Minodronate with others drug VS minodronate	−3.100 (−5.197, −1.003)§	–	–	.017	–	–
	52/68	Minodronate-naïve VS minodronate-switch	−3.000 (−5.473, −0.527)§	–	–	.004	–	–
	16/14	Minodronate VS others drug	−1.200 (−2.021, −0.379)§	–	–	.004	–	–
TRACP-5b (mU/dL)	52/68	Minodronate-naïve VS minodronate-switch	−128.200 (−198.114, −58.286)‡	–	–	.000	–	–
	50/48	Minodronate with others drug VS minodronate	−181.400 (−247.189, −115.611)‡	–	–	.000	–	–
Vertebral fractures	52/68	Minodronate-naïve VS minodronate-switch	1.308 (0.084, 20.419)‡	–	–	.848	–	–
	215/205	Minodronate VS others drug	1.430 (0.410, 4.995)‡	–	–	.575	–	–
Non-vertebral fractures	215/205	Minodronate VS others drug	0.834 (0.308, 2.259)‡	–	–	.722	–	–
Drug-related AE	215/205	Minodronate VS others drug	0.896 (0.570, 1.407)‡	–	–	.632	–	–
Drug related gastrointestinal AE	215/205	Minodronate VS others drug	2.452 (1.046, 5.747)‡	–	–	.039	–	–

AE = adverse event, BMD = bone mineral density, CI = confidence interval, NTX/Cre = N-telopeptide of type I collagen/creatinine, TRACP-5b = tartrate-resistant acid phosphatase 5b.

* *P* value of Heterogeneity Chi-squared.

† *P* value of Pooled statistic.

‡ ES (95% CI): WMD (95% CI).

§ ES (95% CI): RR (95% CI).

Table 4

The meta-analysis of indexes in the included RCTs.

Index	N (case/control)	Interventions	ES (95% CI)	P^*	I^2	$P^\dagger$	*P*-value Begg	*P*-value Egger
BMD (g/cm^2)	450/449	Minodronate VS others drug	0.000 (−0.004, 0.003)[§]	.753	0.0%	0.841	.230	.019
BMD (YAM, young adult mean, %)	33/26	Minodronate VS others drug	−0.400 (−4.697, 3.897)[§]	–	–	0.855	–	–
NTX/Cre (nmol BCE/mmol Cr)	49/40	Minodronate VS others drug	−7.100 (−18.475, 4.275)[§]	–	–	0.221	–	–
BALP/BAP (U/L)	115/106	Minodronate VS others drug	−1.733 (−4.145, 0.679)[§]	.221	33.8%	0.159	1.000	.604
TRACP-5b (mU/dL)	18/17	Minodronate with others drug VS minodronate	−20.500 (−26.096, −14.904)[§]	–	–	0.000	–	–
	117/115	Minodronate VS others drug	−154.112 (−277.854,−30.37)[§]	.000	96.4%	0.015	.497	.562
Vertebral fractures	459/443	Minodronate VS others drug	0.469 (0.321, 0.685)[‡]	.370	0.0%	0.000	1.000	.280
Non-vertebral fractures	459/443	Minodronate VS others drug	0.672 (0.320, 1.412)[‡]	.890	0.0%	0.294	.296	.226
Drug-related AE	519/507	Minodronate VS others drug	1.097 (0.836, 1.439)[‡]	.770	0.0%	0.503	.602	.934
	458/468	Minodronate monthly VS mindronate daily	1.056 (0.759, 1.470)[‡]	.848	0.0%	0.747	.317	–
Drug related gastrointestinal AE	176/176	Minodronate VS others drug	1.354 (0.750, 2.445)[‡]	.585	0.0%	0.314	1.000	–
Gastrointestinal disorders	458/468	Minodronate monthly VS mindronate daily	0.766 (0.497, 1.181)[‡]	.891	0.0%	0.228	.317	–
	477/466	Minodronate VS others drug	1.075 (0.936, 1.235)[‡]	.961	0.0%	0.308	.317	–
Discontinued due to drug-related AE	477/466	Minodronate VS others drug	1.191 (0.647, 2.191)[‡]	.923	0.0%	0.574	1.000	–
Discontinued due to drug-related gastrointestinal AE	477/466	Minodronate VS others drug	1.229 (0.633, 2.385)[‡]	.831	0.0%	0.543	1.000	–

AE = adverse event, BMD = bone mineral density, CI = confidence interval, NTX/Cre = N-telopeptide of type I collagen/creatinine, TRACP-5b = tartrate-resistant acid phosphatase 5b.

[*] *P* value of heterogeneity Chi-squared.

[†] *P* value of pooled statistic.

[‡] ES (95% CI): WMD (95% CI).

[§] ES (95% CI): RR (95% CI).

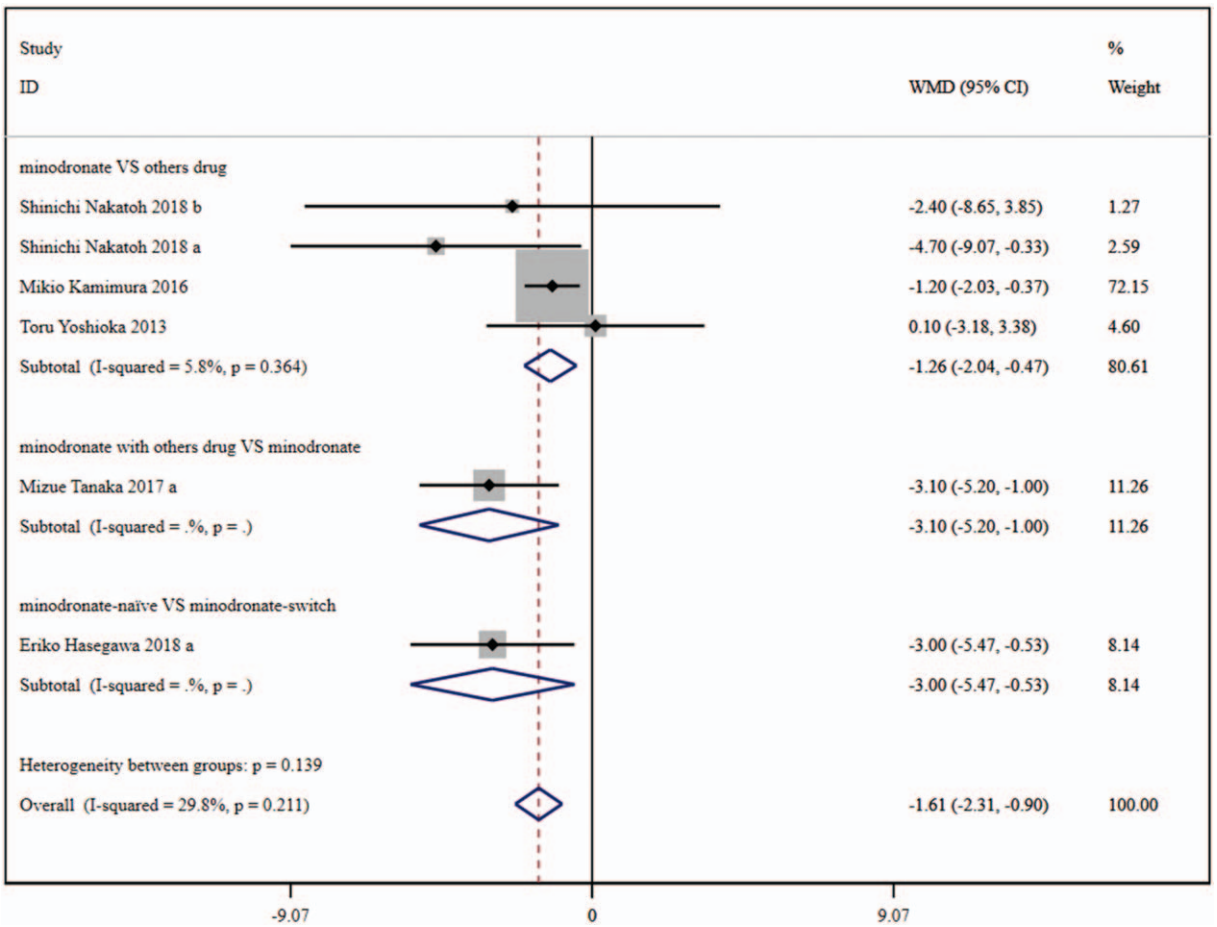

Figure 3. Forest plot for the BAP. BAP = bone alkaline phosphatase.

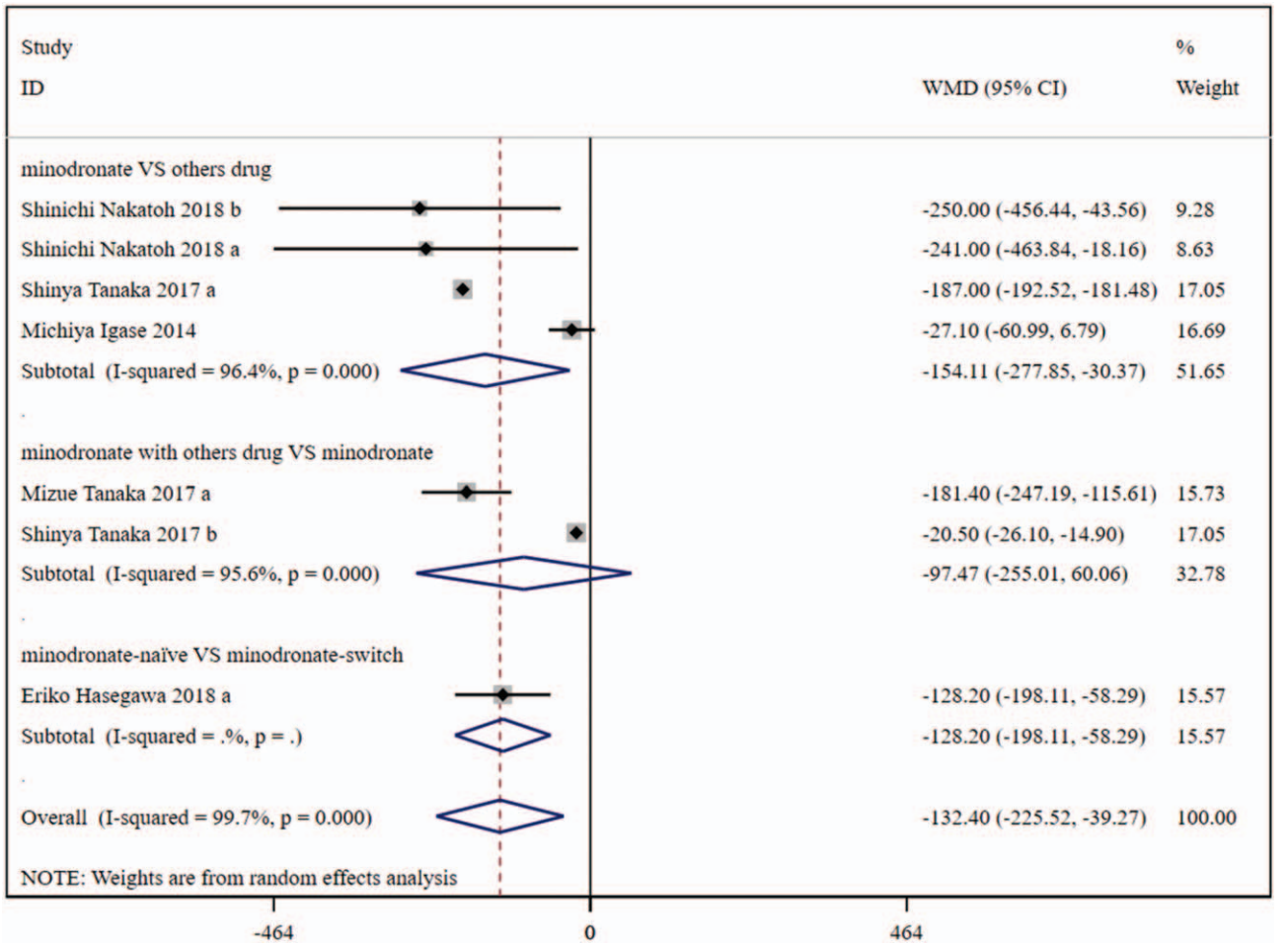

Figure 4. Forest plot for the TRACP–5b. TRACP–5b = tartrate-resistant acid phosphatase 5b.

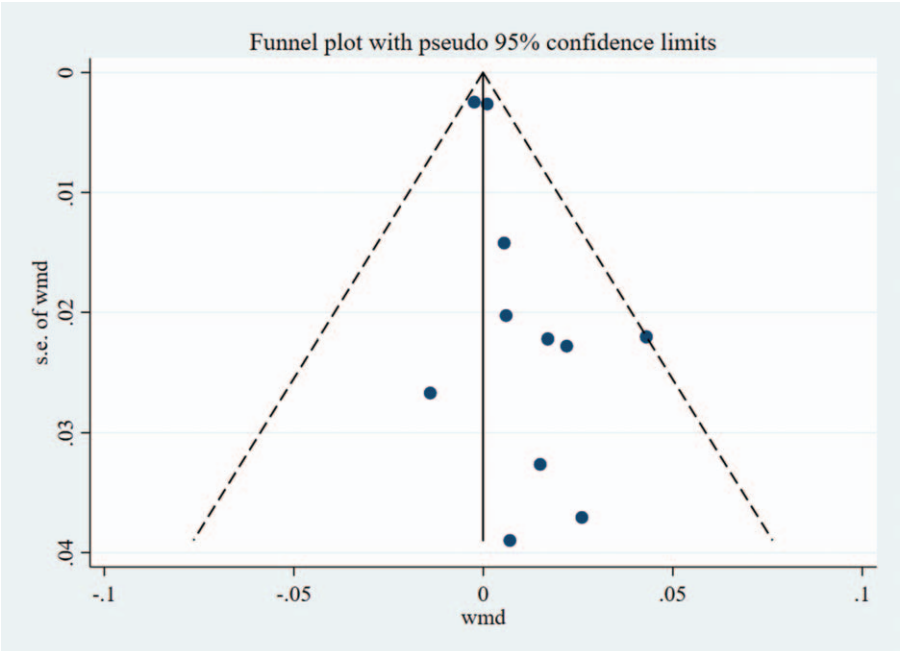

Figure 5. Funnel plot analysis of included studies.

osteoporosis, even though it does not usually induce the formation of new bone. So far, the double phosphonic acid salt is still the most widely used drug for bone absorption. The minerals are synthetic analogs of endogenous pyrophosphate deposition inhibitors that inhibit bone resorption and increase BMD. They can be effective in the treatment of osteoporosis, Paget disease, and tumor bone disease but their mechanism is unclear.

Minodronic acid, a new heterocyclic compound, and Bonoteo, a double phosphonic acid compound, belong to the third generation of double phosphonic acid salts that can effectively reduce bone absorption by inhibiting ester synthetase and bone resorption function by inhibiting osteoclast.

Minodronic acid was first approved for sale in Japan in 2009 as a treatment for osteoporosis, in which the drug worked by affecting the transformation of cancellous bone into the cortical bone, and bone quality. It had a great inhibitory effect on bone resorption function of osteoclasts and further reduced bone metabolism and circulation, thereby showing a therapeutic effect on osteoporosis. Compared with other bisphosphonates, minodronic acid significantly improved bone loss in postmenopausal women and age-related osteoporosis. Moreover, in this case, the dosage was significantly reduced (minodronic acid was 1 mg/d, alendronic sodium was 10 mg/d), which improved patient compliance and reduced common gastrointestinal adverse reactions of bisphosphonates.

The anti-resorption effect of minodronic acid is achieved by its inhibitory effect on osteoclasts. The inhibition of the important signal transduction pathways at the molecular level will significantly inhibit the effect of osteoclasts at the cellular level. It will eventually lead to changes in bone morphology and a decrease in bone conversion rate. Bone biopsy after minodronic acid treatment showed that the bone mineralization was normal (there was no significant change in osteoid thickness and mineral salt accumulation rate), while the bone metabolic rate was decreased. The increase in bone density after the treatment is caused by the decrease in bone reconstruction and the positive balance of bone mass.

In a recent clinical review on minodronate, Saeko Fujiwara et al[27] made a retrospective chart review. The most common OP medications prescribed initially were minodronic acid (20.1%), alendronate (19.9%), raloxifene (14.1%), weekly teriparatide acetate (12.4%), and eldecalcitol (11.4%). Majority of patients (62.1%) were still taking their initial medication at the end of the 18 to 24 month follow-up. A high percentage of patients (87.9%) in Japan received OP medications soon after their high-risk diagnosis, with bisphosphonates, selective estrogen receptor modulators, and teriparatide being the predominant treatment options. Tsuyoshi Ohishi et al[28] wrote a review on minodronate, which is a third-generation bisphosphonate that was developed and approved in Japan. High-quality RCTs have revealed an increase in BMD of both the lumbar spine and femoral neck over 3 years of daily minodronate therapy and risk reduction in vertebral fractures over 2 years of therapy (similar to those with alendronate or risedronate). The incidence of adverse events is the same as or less than that with weekly or daily alendronate or risedronate. Minodronate can reduce low back pain in OP patients. However, more clinical studies on minodronate in OP should be conducted to verify hip fracture risk reduction and long-term results.

In our study, we found that compared with other drugs, minodronate significantly decreased NTX/Cre (WMD: –13.669, 95% CI: –23.108 to –4.229), BAP (WMD: –1.26, 95% CI: –2.04 to –0.47), and TRACP–5b (WMD: –154.11, 95% CI: –277.85 to –30.37). Minodronate combined with other drugs significantly decreased BAP (WMD: –3.10, 95% CI: –5.20 to –1.00) than minodronate. Minodronate-naïve significantly decreased BAP (WMD: –3.00, 95% CI: –5.47 to 0.53) and TRACP–5b (WMD: –128.20, 95% CI: –198.11 to –58.29) than minodronate-switch. The incidence of vertebral fractures was significantly decreased in the minodronate group than other drugs (RR: 0.520, 95% CI: 0.363–0.744). However, there was no significant difference in BMD, BMD (YAM), and BMD (*T*-score) in all subgroup analyses. Besides, the incidence of drug-related gastrointestinal AE was significantly higher in the minodronate group than other drugs group (RR: 1.680, 95% CI: 1.037–2.72).

In the subgroup analysis of included RCTs, the value of TRACP–5b was significantly decreased in minodronate with other drugs versus minodronate and minodronate versus other drugs. Compared with other drugs, minodronate significantly decreased the incidence of vertebral fractures.

In the subgroup analysis of included case-control studies, compared with other drugs, minodronate significantly decreased the value of NTX/Cre and BAP. Compared with minodronate, minodronate with other drugs significantly decreased BAP and TRACP–5b. Compared with minodronate-switch, minodronate-naïve significantly decreased BAP and TRACP–5b. Compared with other drugs, minodronate significantly increased the incidence of drug-related gastrointestinal AE.

However, there are certain limitations to the present analysis, which are as follows:

(1) the limited number of included studies;
(2) individual studies had variations in exclusion/inclusion criteria;
(3) the dose of minodronate varied between the studies;
(4) the disease of included patients varied between the studies;
(5) pooled data were analyzed, as individual patient data were not available, precluding more in-depth analyses.

5. Conclusion

In patients with OP, minodronate has significantly efficacy in decreased NTX/Cre, BAP, and TRACP–5b than others drug. The minodronate combination has better efficacy than monotherapy. Minodronate-naïve has better efficacy than minodronate-switch. The incidence of vertebral fracture was significantly decreased in the minodronate group than the other drugs. However, minodronate would increased the incidence of drug-related gastrointestinal AE than others drug.

Author contributions

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