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The efficacy of teriparatide on lumbar spine bone mineral density, vertebral fracture incidence and pain in post-menopausal osteoporotic patients: A systematic review and meta-analysis☆

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ABSTRACT

Objective: Teriparatide has been increasingly utilized in the management of osteoporosis. The efficacy of low and high dose teriparatide on lumbar spine bone mineral density, vertebral fracture incidence and pain is unknown. We sought to determine the efficacy of teriparatide on these patient-important outcomes using a systematic review and meta-analysis.

Methods: A systematic search of electronic databases (MEDLINE, EMBASE, CENTRAL, CINAHL) was performed to identify randomized controlled trials (RCTs) that evaluate teriparatide to any comparator for the treatment of osteoporosis in postmenopausal women. The Grades of Recommendation Assessment, Development and Evaluation (GRADE) criteria were used by two independent reviewers to assess the strength and quality of evidence.

Results: A total of 20 studies (n = 6024) were included in this review, with 2855 patients receiving teriparatide and 3169 patients receiving placebo or control treatment. A teriparatide dose of 20 μg/day increased lumbar spine bone mineral density (BMD) (standardized mean difference (SMD) 0.34 standard deviation (SD) units higher (95% CI 0.19–0.48 SDs higher) in comparison to placebo. Relative to anti-resorptive agents, 20 μg/day of teriparatide had a range from 0.14 SD units to 0.96 SD units higher (95% CI, 0.08 SDs lower to 0.36 SDs higher, CI, 0.33–1.59 SDs higher, respectively). 20 μg/day teriparatide had a significant effect on pain severity to placebo or control (SMD 0.80, 95% CI, 1.16–0.43 SDs lower) and also decreased the incidence of vertebral fractures compared to placebo (relative risk 0.31, 95% CI 0.21 to 0.46). Arthralgia and extremity pain incidence were also calculated; there were 15 and 8 fewer events per 1000 patients with the use of 20 μg/day of teriparatide compared to placebo or control, respectively.

Conclusion: High quality evidence supports the utilization of teriparatide 20 μg/day dose to significantly improve lumbar spine BMD and decrease incidence of vertebral fractures and pain severity relative to all comparators. 40 μg/day dose of teriparatide demonstrated significantly better results with prolonged treatment. This data is valuable for clinicians involved in the care of this growing demographic of patients. Further investigation on the safety and efficacy of teriparatide in higher doses for the long-term treatment of osteoporosis in postmenopausal women should be conducted through high-quality clinical trials.

1. Introduction

Osteoporosis, now the most common metabolic disorder in the world, disproportionately affects females and the elderly increasing their risk of fractures and other complications (Akhter et al., 2018; Lin and Lane, 2004). Diagnosis is commonly made in the latter phase of the

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disease or subsequently from a related complication such as a fracture, given the latent presentation of symptomology (Akhter et al., 2018; Lin and Lane, 2004). The most common form, post-menopausal osteoporosis, results from an estrogen deficiency translating to a heightened bone turnover rate.

Management of osteoporosis is an interdisciplinary process which involves exercise, nutrition, pharmacotherapy, and surgery (Akhter et al., 2018). First line pharmacotherapy includes bisphosphonates, which prevent bone resorption ultimately preventing fractures. A second line treatment that is a recombinant form of parathyroid hormone (PTH), teriparatide, works to prevent new fractures by increasing and subsequently maintaining anabolic equilibrium between bone formation and resorption (Akhter et al., 2018; Marcus, 2011; Ohtori et al., 2012). Teriparatide has been increasingly used in spine surgery to prevent osteoporotic related surgical complications (Akhter et al., 2018; Lin and Lane, 2004; Marcus, 2011; Ohtori et al., 2012; Ohtori et al., 2013; Rizzoli et al., 2011; Parfitt, 1989; Ejersted et al., 1993; Oxlund et al., 1993).

Teriparatide has shown efficacy across multiple studies, notably in postmenopausal women, for faster bone healing, vertebral and non-vertebral fracture prevention and treatment, and fracture associated pain (Akhter et al., 2018; Marcus, 2011; Ohtori et al., 2012; Ohtori et al., 2013; Rizzoli et al., 2011; Eriksen and Robins, 2004; Fukuda et al., 2014; Pietrogrande and Raimondo, 2013; Ebata et al., 2017). It also reduces hardware complications following spinal fusion, as well as improves bone mineral content (BMC), bone mineral density (BMD), fusion duration, and fusion rates (Ohtori et al., 2012; Ohtori et al., 2012; Yagi et al., 2016; Chaudhary and Lee, 2017; Aslan et al., 2011). Current systemic reviews and meta-analyses investigating teriparatide pose methodological concerns, lack of focus on patient-important outcomes, and a low number of events across outcomes resulting in low statistical power. The purpose of this review is to determine the efficacy of teriparatide on lumbar spine bone mineral density, vertebral fracture incidence and pain in postmenopausal osteoporotic women.

2. Methods

The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement was followed (Moher et al., 2007). Outline of the review was consistent with the Cochrane Handbook for Systematic Reviews of Interventions (Higgins and Altman, 2011).

2.1. Identification of studies

We performed a comprehensive literature using the Cochrane Central Register of Controlled Trials (CENTRAL), EMBASE, CINAHL and MEDLINE databases from date of inception to current. Ongoing clinical trials and reference lists of included studies were manually searched to extract relevant articles.

2.2. Assessment of eligibility

Independent screening was performed by two authors using an electronic form. A resolve-by-consensus strategy was utilized for all discrepancies. The following criteria was used for the inclusion of a study:

(i) Postmenopausal women with osteoporosis
(ii) Teriparatide is administered without being combined with any other intervention
(iii) Randomized controlled trials (RCTs) only.

No restrictions were made based on publication date, study design, language, or follow-up. Any comparator at any duration of treatment to teriparatide was considered in this study to maximize potentially eligible data and produce quality evidence backed with larger sample sizes than seen in previous reviews.

2.3. Assessment of risk of bias and data extraction

The Cochrane Collaboration's tool for risk-of-bias assessment was utilized by two independent reviewers (Review Manager, 2014). Study authors were contacted for any uncertainties. A single risk of bias assessment was reported when issues related to the risk of bias were identical across the outcomes used in a study (Higgins and Altman, 2011). A piloted electronic data extraction form was utilized. Study authors were contacted if any uncertainty was present.

2.4. Statistical analyses, evaluation of heterogeneity, and sensitivity analyses

Cohen's kappa coefficient was used to calculate agreement for reviewers' assessment of study eligibility. A kappa value of $\geq$0.65 was considered adequate. All data were pooled using the Mantel-Haenszel method. For a particular dose to be pooled (e.g. 40 μg/day of teriparatide) for any given outcome, there needed to be at least two studies using this particular dose against a comparator agent. We quantified heterogeneity using the X^2 test for heterogeneity and the I^2 statistic, which were interpreted according to the Cochrane Handbook (Higgins and Altman, 2011). We hypothesized a priori that grouping studies by study duration would decrease heterogeneity, and that studies of longer study duration would yield greater pooled effect sizes across all of our studied outcomes. Hence, a subgroup analysis based on treatment duration ($\geq$12 months or <12 months) was conducted for all outcomes of interest. To explore the impact of bias through a lack of blinding and incomplete outcome data, a sensitivity analysis was conducted excluding studies with concerns of high-risk bias (i.e. two or more "high" risk of bias items).

2.5. Quality of evidence assessment

GRADE was used to summarize the quality of evidence for or against the use of teriparatide by each outcome (Higgins and Altman, 2011). Data from RCTs were considered high-quality evidence, but could have been rated down according to risk of bias, imprecision, inconsistency, indirectness, or publication bias (Higgins and Altman, 2011).

3. Results

3.1. Study characteristics

Of 1202 articles screened, 20 studies were eligible for final inclusion (6024 patients), (Fig. 1, Table 1). Study duration ranged from 6 to 30 months. Publication date of these studies ranged from 2001 to 2018. Majority of the studies declared an open-label teriparatide arm (13/20 or 65%) (Anastasilakis et al., 2008a; Anastasilakis et al., 2008b; Deng et al., 2018; Genant et al., 2017; Gonnelli et al., 2006; Kung et al., 2006; Langdahl et al., 2017; McClung et al., 2014; Neer et al., 2001; Panico et al., 2011; Sethi et al., 2008; Tsai et al., 2013; Yang et al., 2016; Finkelstein et al., 2010), 10 studies (50%) were multi-national (Genant et al., 2017; Kung et al., 2006; Langdahl et al., 2017; McClung et al., 2014; Neer et al., 2001; Arlot et al., 2005; Cosman et al., 2010; Henriksen et al., 2013; Leder et al., 2015; Miller et al., 2016), while the remaining 10 studies (50%) were conducted in a single country (Ohtori et al., 2013; Anastasilakis et al., 2008a; Anastasilakis et al., 2008b; Deng et al., 2018; Gonnelli et al., 2006; Panico et al., 2011; Sethi et al., 2008; Tsai et al., 2013; Yang et al., 2016; Finkelstein et al., 2010; Miyauchi et al., 2008). Across all 20 studies, a total of 2855 patients in the teriparatide arm and 3169 patients in the control arm were included. Mean age (standard deviation [SD]) of the teriparatide and control arms were 67.2 (4.1) years and 66.8 (3.6) years, respectively. There was lost or missing data for 366 patients in the teriparatide arm (12.9%) and 524 patients in the control arm (16.5%). The teriparatide arm comprised of patients subject to 20 μg/day (Anastasilakis et al., 2008a; Anastasilakis

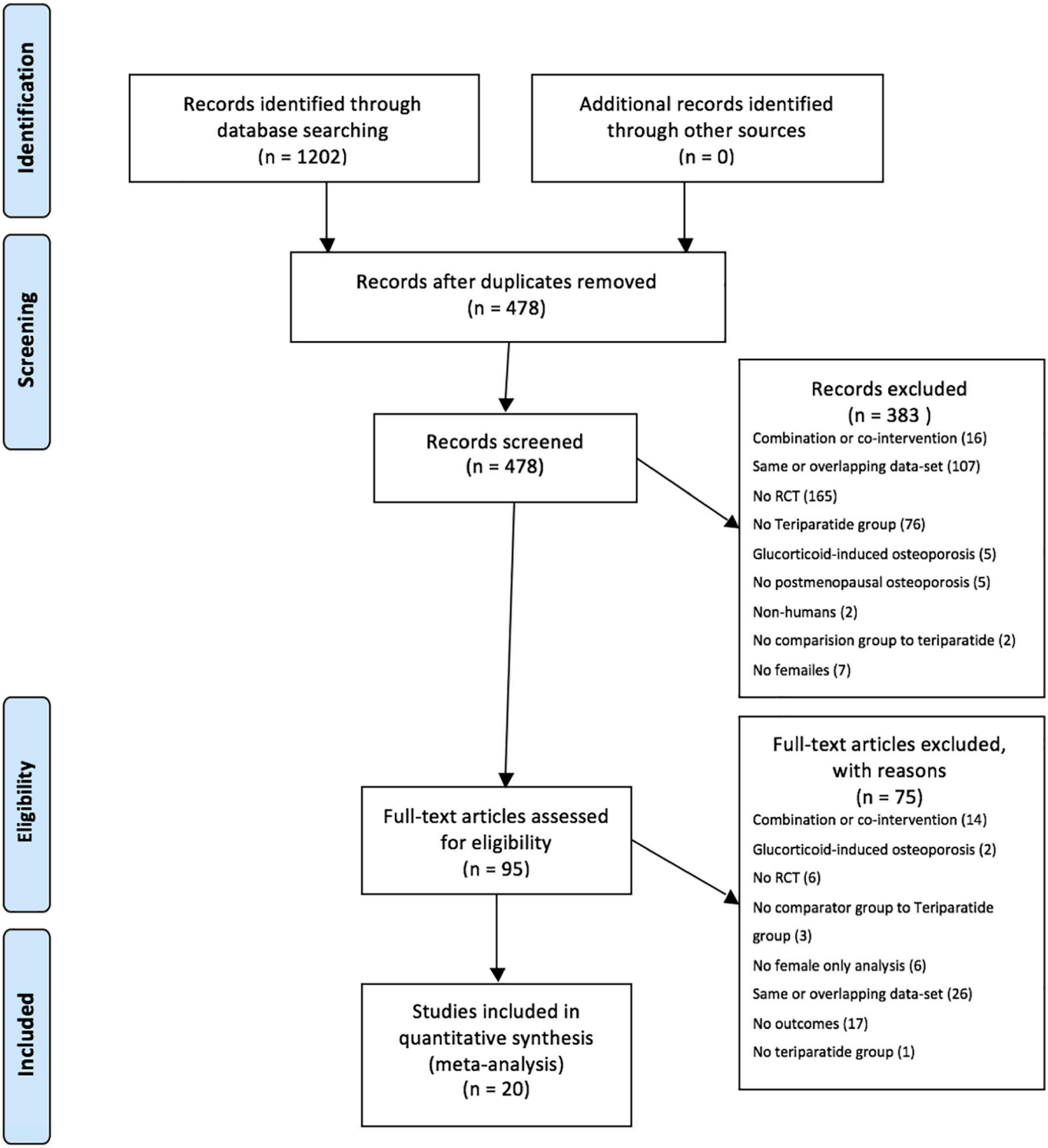

Fig. 1. Flow of trials included in the study.

et al., 2008b; Deng et al., 2018; Genant et al., 2017; Gonnelli et al., 2006; Kung et al., 2006; Langdahl et al., 2017; McClung et al., 2014; Neer et al., 2001; Panico et al., 2011; Sethi et al., 2008; Tsai et al., 2013; Yang et al., 2016; Arlot et al., 2005; Cosman et al., 2010; Henriksen et al., 2013; Leder et al., 2015; Miller et al., 2016; Miyauchi et al., 2008) or 40 μg/day of teriparatide (Neer et al., 2001; Finkelstein et al., 2010; Cosman et al., 2010; Miyauchi et al., 2008) injected subcutaneously (Ohtori et al., 2013; Anastasilakis et al., 2008a; Anastasilakis et al., 2008b; Genant et al., 2017; Gonnelli et al., 2006; Kung et al., 2006; Langdahl et al., 2017; McClung et al., 2014; Neer et al., 2001; Panico et al., 2011; Sethi et al., 2008; Tsai et al., 2013; Yang et al., 2016; Finkelstein et al., 2010; Arlot et al., 2005; Henriksen et al., 2013; Leder et al., 2015; Miller et al., 2016; Miyauchi et al., 2008) or delivered through a transdermal patch (Deng et al., 2018; Cosman et al., 2010). The control arm comprised of patients subject to placebo (Genant et al., 2017; McClung et al., 2014; Neer et al., 2001; Yang et al., 2016; Cosman et al., 2010; Henriksen et al., 2013; Leder et al., 2015; Miller et al., 2016; Miyauchi et al., 2008) as well as the following comparative agents: abaloparatide

Table 1
Study characteristics table.

Lead author	Year	RCT type^	Country	Funding	Teriparatide intervention(s)	Control intervention(s)	Study duration	BMD smeasurement format	Treatment			Control(s)		
									n	LMD, n	Age[#]	n	LMD (n)	Age
Anastasilakis	2008	Open-label parallel-group	Greece	NR	TPTD-I 20 μg/day	– RIS 35 mg/weekly	12 months	g/cm^2	22	0	65.4 ± 1.6	22	0	64.7 ± 1.5
Arlot	2005	Double-blind parallel-group	France, Mexico & U.S.	Eli Lilly and Co.	TPTD-I 20 μg/day	– ALN 10 mg/day	18 months	g/cm^2	21	0	60.9 ± 6.7	21	0	65.5 ± 8.6
Cosman	2010	Double-blind placebo-controlled	U.S., Argentina & Mexico	Zosano Pharma Inc.	TPTD-P 20 μg/day TPTD-P 40 μg/day	– Placebo patch	6 months	g/cm^2	34 33	21	64.1 ± 7.5 64.6 ± 9.9	33	2	64.8 ± 7.1
Deng	2018	Open-label parallel-group	China	Governmental sources	TPTD-P 20 μg/day	– ALN 70 mg/weekly	48 weeks	g/cm^2	43	8	62.9 ± 5.80	22	0	62.8 ± 6.42
Finkelstein	2010	Open-label parallel-group placebo-controlled	U.S.	NIH grants	TPTD-I 40 μg/day	– ALN 10 mg/day	30 months[$]	g/cm^2	31	14	65.0 ± 7.0	31	7	64.0 ± 6.0
Genant	2017	Open-label Parallel-group placebo-controlled	Argentina, Austria, Belgium, Canada & Denmark, Spain & U.S.	Amgen Inc. & UCB Pharma	TPTD-I 20 μg/day	– Placebo injection – ROMO 210 mg/month	12 months	T-score	31	1	65.8 ± 5.7	27 24	0 0	66.1 ± 5.8 64.3 ± 4.7
Gonnelli	2006	Open-label Parallel-group	Italy	NR	TPTD-I 20 μg/day	– Antiresorptive treatment	12 months	g/cm^2	30	3	71.3 ± 7.0	30	2	71.0 ± 6.8
Henriksen	2013	Double-blind Parallel-group Placebo-controlled	Denmark & Estonia	Unigene Laboratories Inc.	TPTD-I 20 μg/day	– Placebo pill	24 weeks	g/cm^2	32	5	66.4 ± 7.1	32	4	65.8 ± 6.2
Kung	2006	Open-label Parallel-group	Hong Kong, Malaysia, Philippines, Singapore & Thailand	Eli Lilly and Co.	TPTD-I 20 μg/day	– Calcitonin 100 IU/day	6 months	g/cm^2	47	11	70.6 ± 7.1	57	19	70.6 ± 6.6
Langdahl	2017	Open-label Parallel-group	Argentina, Belgium, Canada, Colombia, Czech Republic, Denmark, Germany, Spain & U.S.	Amgen Inc., Astellas & UCB Pharma	TPTD-I 20 μg/day	– ROMO 210 mg/month	12 months	T-score	218	18	71.2 ± 7.7	218	20	71.8 ± 7.4
Leder	2015	Double-blind Parallel-group Placebo-controlled	Argentina, India, U.K. & U.S.	Radius Health Inc.	TPTD-I 20 μg/day	– Placebo injection – ABL 80 mg/day	24 weeks	g/cm^2	45	6	64.5 ± 7.5	45 45	3 11	65.0 ± 7.1 64.8 ± 7.2
McClung	2014	Open-label Parallel-group Placebo-controlled	Argentina, Austria, Belgium, Canada, Denmark, Spain & U.S.	Amgen Inc. & UCB Pharma	TPTD-I 20 μg/day	– Placebo injection/monthly or/3 months[$$] – ROMO 210 mg/month – ALN 70 mg/week	12 months	T-score	55	9	66.8 ± 5.7	52 52 51	5 2 0	67.8 ± 6.8 66.3 ± 6.5 67.1 ± 5.8
Miller	2016	Double-blind Parallel-group Placebo-controlled	Argentina, Brazil, China, Czech Republic, Denmark, Estonia, Lithuania, Poland, Romania & U.S.	Radius Health Inc.	TPTD-I 20 μg/day	– Placebo injection – ABL 80 mg/day	18 months	g/cm^2	818	160	68.8 ± 6.6	821 824	184 218	68.7 ± 6.5 68.9 ± 6.5
Miyauchi	2008	Partial double-blind Placebo-controlled	Japan	Eli Lilly and Co.	TPTD-I 20 μg/day TPTD-I 40 μg/day	– Placebo injection	24 weeks	g/cm^2	39 39	2 14	71.5 ± 5.1 72.5 ± 6.1	38	5	69.9 ± 3.6
Neer	2001	Open-label Placebo-controlled	Argentina, Australia, Austria, Belgium, Canada, Czech Republic, Denmark, Finland, Hungary, Israel,	Eli Lilly and Co.	TPTD-I 20 μg/day TPTD-I 40 μg/day	– Placebo injection	24 months	g/cm^2	541 552	35 59	69.3 ± 7.5 70.2 ± 7.0	544	32	69.0 ± 7.5

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Table 1 (*continued*)

Lead author	Year	RCT type^	Country	Funding	Teriparatide intervention(s)	Control intervention(s)	Study duration	BMD smeasurement format	Treatment			Control(s)		
									n	LMD, n	Age[#]	n	LMD (n)	Age
			Italy, New Zealand, Norway, Netherlands, Poland, Sweden & U.S.											
Ohtori	2013	Single-blind Parallel-group	Japan	None	TPTD-I 20 μg/day	– Control without medication	12 months	NR	20	0	78 ± 6.0	22	0	77.0 ± 5.8
Panico	2011	Open-label Parallel-group	Italy	Departmental sources	TPTD-I 20 μg/day	– ALN 70 mg/week	18 months	T-score	42	2	65.0 ± 9.0	39	0	60.0 ± 14
Sethi	2008	Open-label Parallel-group	India	Virchow Group	TPTD-I 20 μg/day	– Suppl. only	6 months	g/cm^2	41	3	61.0 ± 6.3	41	6	63.0 ± 6.3
Tsai	2013	Open-label Parallel-group	U.S.	Massachusetts General Hospital & Amgen Inc.	TPTD-I 20 μg/day	– DENO 60 mg/6 months	12 months	g/cm^2	31	1	65.5 ± 7.9	33	0	66.3 ± 8.3
Yang	2016	Open-label Placebo-controlled	China	None	TPTD-I 20 μg/day	– Placebo pill	12 months	g/cm^2	90	13	64.3 ± 8.5	45	4	63.9 ± 8.2

BMD = bone mineral density; TPTD-I = teriparatide injection (subcutaneous); TPTD-P = teriparatide transdermal patch; RIS = risedronate; ALN = alendronate; ROMO = romosozumab; RCT = randomized controlled trial; Suppl. = 1000 mg of elemental calcium and 500 IU of vitamin D; NIH = National Institute of Health.

[#] Data for Gender and Age is listed for groups that were utilized in the meta-analysis.

[$] Teriparatide intervention began at the 6-month mark.

[$$] Data is reported for pooled placebo which combines patients receiving placebo every month with patients receiving placebo every 3 months.

^ All studies were open-label for teriparatide but varied in blinding regarding the other treatments; the presence of blinding for the latter is used for classifying the RCT.

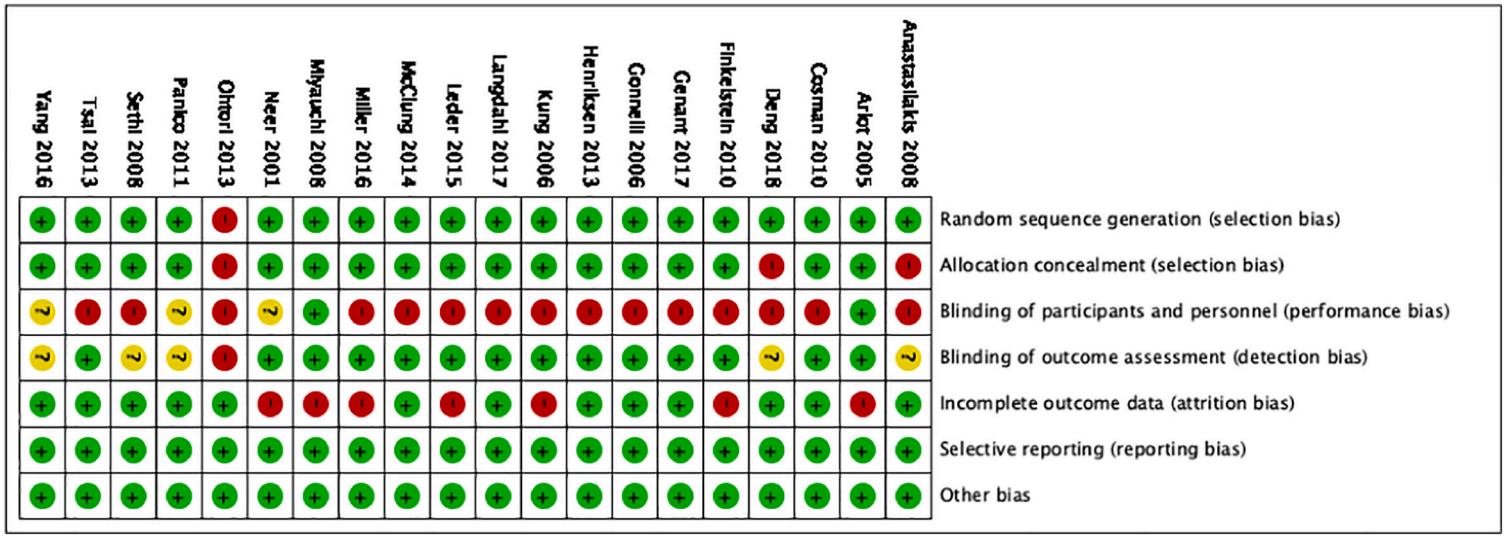

Fig. 2. Risk of bias (ROB) summary; judgment of review authors for each ROB item for included trials. Green circles indicate low risk of bias, yellow circles indicate unclear risk, and red circles indicate high risk of bias. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

Table 2
Cumulative summary of GRADE and findings table. MD – mean difference, SMD – standard mean difference, RR – relative risk ratio, BMD – bone mineral density.

Quality assessment								Number of patients		Subgroup Analysis	Effect	Effect	Quality
# of trials	Outcome	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Publication bias	Teriparatide	Control		Relative (95% CI)	Absolute (95% CI)	
19 (Arlot et al. 2005; Anastasilakis et al., 2008a; Anastasilakis et al., 2008b; Cosman et al. 2010; Deng et al. 2018; Finkelstein et al. 2010; Genant et al. 2017; Gonnelli et al. 2006; Henriksen et al. 2013; Kung et al. 2006; Langdahl et al. 2017; Leder et al. 2015; McClung et al. 2014; Miller et al. 2016; Miyauchi et al. 2008; Neer et al. 2001; Panico et al. 2011; Sethi et al. 2008; Tsai et al. 2013; Yang et al. 2016)	Lumbar spine BMD	Serious [0]	Not serious	Not serious	Not serious	+1 dose response (20 vs 40 μg/day)	Not serious	2735	2086	N/A	–	SMD 0.34 SD higher (0.19 higher to 0.48 higher)[1]	⊕⊕⊕⊕ High
										Age	–	SMD 0.35 SD higher (0.19 higher to 0.48 higher)▲	
												SMD 0.32 SD higher (0.11 higher to 0.53 higher)▽	
										N/A	–	MD 0.08 g/cm^2 higher (0.07 higher to 0.09 higher)[2]	
										Age	–	MD 0.09 g/cm^2 higher (0.05 higher to 0.12 higher)▲	
												MD 0.06 g/cm^2 higher (0.01 higher to 0.11 higher)▽	
										Study duration	–	MD 0.06 g/cm^2 higher (0.03 higher to 0.09 higher)[3]	
												MD 0.10 g/cm^2 higher (0.08 higher to 0.12 higher)[4]	
										Study duration	–	SMD 0.08 SD lower (0.16 lower to 0.00 higher)[5]	
										Age	–	SMD 0.08 SD lower (0.16 lower to 0.00 higher)▲	
												SMD 0.07 SD lower (0.48 lower to 0.34 higher)▽	
											–		

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Table 2 (*continued*)

Quality assessment								Number of patients		Subgroup Analysis	Effect	Effect	Quality
# of trials	Outcome	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Publication bias	Teriparatide	Control		Relative (95% CI)	Absolute (95% CI)	
										Study duration		SMD 0.96 SD higher (0.33 higher to 1.59 higher)[6]	
												SMD 0.14 SD higher (0.08 lower to 0.36 higher)[7]	
										Age	–	SMD 0.32 SD higher (0.04 lower to 0.68 higher)▲	
												SMD 0.11 SD higher (0.29 lower to 0.51 higher)○	
										N/A	–	SMD 0.48 SD higher (0.12 higher to 0.84 higher)[8]	
16 (Cosman et al. 2010; Deng et al. 2018; Finkelstein et al. 2010; Genant et al. 2017; Gonnelli et al. 2006; Henriksen et al. 2013; Kung et al. 2006; Langdahl et al. 2017; Leder et al. 2015; McClung et al. 2014; Miller et al. 2016; Miyauchi et al. 2008; Neer et al. 2001; Sethi et al. 2008; Tsai et al. 2013; Yang et al. 2016)	Total hip BMD	Serious[I]	Not serious	Not serious	Not serious	+1 dose response (20 vs 40 μg/day)	Serious[IX]	2692	2043	N/A	–	SMD 0.21 SD higher (0.15 higher to 0.28 higher)[1],[2]	⊕⊕⊕⊖ Moderate
										Age	–	SMD 0.23 SD higher (0.16 higher to 0.30 higher)▲	
												SMD 0.09 SD higher (0.11 lower to 0.30 higher)○	
										N/A	–	MD 0.03 g/cm^2 higher (0.02 higher to 0.04 higher)[3],[4]	
										Age	–	MD 0.03 g/cm^2 higher (0.02 higher to 0.04 higher)▲	
												MD 0.02 g/cm^2 higher (0.02 lower to 0.06 higher)○	
										N/A	–		

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Table 2 (*continued*)

Quality assessment								Number of patients		Subgroup Analysis	Effect	Effect	Quality
# of trials	Outcome	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Publication bias	Teriparatide	Control		Relative (95% CI)	Absolute (95% CI)	
												MD 0.02 g/cm^2 lower (0.06 lower to 0.02 higher)[5]	
										Age	–	MD 0.05 g/cm^2 lower (0.17 lower to 0.07 higher)▲ MD 0.02 g/cm^2 lower (0.05 lower to 0.02 higher)☼	
										N/A	–	SMD 0.09 SD lower (0.35 lower to 0.17 higher)[9]	
										Age	–	SMD 0.09 SD lower (0.35 lower to 0.17 higher)▲	
												SMD 0.17 SD higher (0.36 lower to 0.71 higher)☼	
2 (Ohtori et al. 2013; Panico et al. 2011)	Pain severity	Serious[II]	Not serious	Not serious	Serious[III]	None	Not serious	62	61	N/A	–	SMD 0.73 SD lower (1.10 lower to 0.37 lower)	⊕⊕⊖⊖ Low
5 (Deng et al. 2018; Langdahl et al. 2017; Leder et al. 2015; McClung et al. 2014; Miller et al. 2016)	Arthralgia	Serious[IV]	Not serious	Not serious	Not serious	+1: large effect size	Not serious	1175	1158	N/A	RR 0.84 (0.65, 1.10)	15 fewer per 1000 (33 fewer to 10 more)	⊕⊕⊕⊕ High
										Age	RR 0.83 (0.64, 1.09)	17 fewer per 1000 (35 fewer to 9 higher)▲	
											RR 1.33 (0.22, 8.00)	20 higher per 1000 (47 fewer to 418 higher)☼	
5 (Leder et al. 2015; McClung et al. 2014; Miller et al. 2016; Miyauchi et al. 2008; Neer et al. 2001)	Back pain	Serious[V]	Not serious	Not serious	Not serious	None	Not serious	1498	1500	N/A	RR 0.72 (0.59, 0.87)	41 fewer per 1000 (60 fewer to 19 fewer)	⊕⊕⊕⊖ Moderate
										Age	RR 0.73 (0.60, 0.88)	40 fewer per 1000 (59 fewer to 18	

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Table 2 (*continued*)

Quality assessment								Number of patients		Subgroup Analysis	Effect	Effect	Quality
# of trials	Outcome	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Publication bias	Teriparatide	Control		Relative (95% CI)	Absolute (95% CI)	
												fewer)▲	
											RR 0.20 (0.02, 1.64)	89 fewer per 1000 (109 fewer to 71 higher)☼	
4 (Kung et al. 2006; McClung et al. 2014; Miller et al. 2016; Miyauchi et al. 2008)	Pain in extremity	Serious[VI]	Not serious	Not serious	Not serious	+1: large effect size	Not serious	958	966	N/A	RR 0.85 (0.57, 1.29)	8 fewer per 1000 (21 fewer to 14 more)	⊕⊕⊕⊕ High
3 (Miller et al. 2016; Neer et al. 2001; Panico et al. 2011)	New vertebral fractures	Serious[VII]	Not serious	Not serious	Not serious	None	Not serious	1401	1404	N/A	RR 0.31 (0.21, 0.46)	54 fewer per 1000 (61 fewer to 42 fewer)	⊕⊕⊕⊖ Moderate
										Age	RR 0.30 (0.18, 0.51)	53 fewer per 1000 (62 fewer to 37 fewer)▲	
											RR 0.15 (0.02, 1.23)	66 fewer per 1000 (76 fewer to 18 higher)☼	

Rated primarily down due to insufficient blinding of participants and personnel, and attrition bias – [0, I, V, VI, VIII]; 1 study with lesser weight on the overall effect size has 4 biases – [II]; and small sample size – [III]; funnel plot showing a publication bias, with more studies with positive findings (favouring teriparatide) than negative findings – [IX].

[1] 20 μg/day of teriparatide vs. placebo or control, for a study duration of less than or equal to 12 months.
[2] 20 μg/day of teriparatide vs. placebo, for a study duration of more than 12 months.
[3] 40 μg/day of teriparatide vs. placebo, for a study duration of less than or equal to 12 months.
[4] 40 μg/day of teriparatide vs. placebo, for a study duration of more than 12 months.
[5] 20 μg/day of teriparatide vs. romosozumab at 210 mg/day or abaloparatide at 80 mg/day, for any given study duration.
[6] 20 μg/day of teriparatide vs. risedronate at 35 mg/week, for a study duration of less than or equal to 12 months.
[7] 20 μg/day of teriparatide vs. alendronate at 10 mg/day (or 70 mg/week) or romosozumab at 210 mg/month or denosumab at 60 mg/6 months, for a study duration of less than or equal to 12 months.
[8] 20 μg/day of teriparatide vs. alendronate at 10 mg/day (or 70 mg/week), for a study duration of more than 12 months.
[9] 20 μg/day of teriparatide vs. alendronate at 70 mg/week or romosozumab at 210 mg/month or denosumab at 60 mg/6 months, for any given study duration.
▲ Pooled mean age of participants in the studies is greater greater than 65.0 years.
☼ Pooled mean age of participants in the studies is less than 65.0 years.

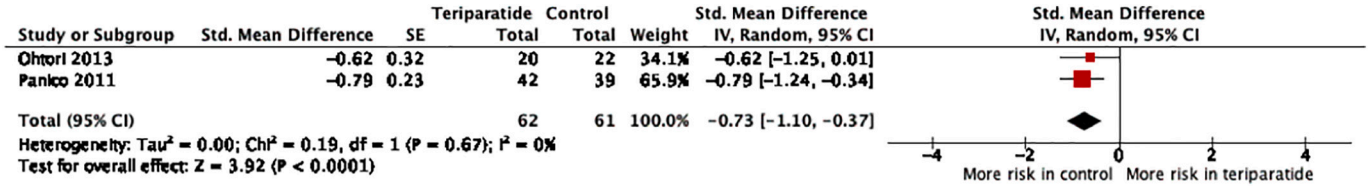

Fig. 3. Forest plot of comparison: pain severity, outcome: 3.1 20 μg/day of Teriparatide vs. Placebo or control, all study durations.

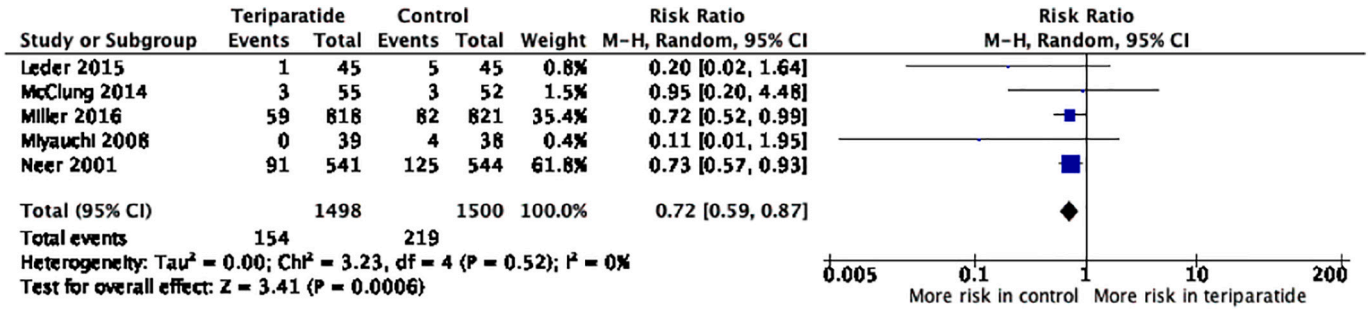

Fig. 4. Forest plot of comparison: back pain, outcome: 5.1 20 μg/day of Teriparatide vs. Placebo or control, all study durations.

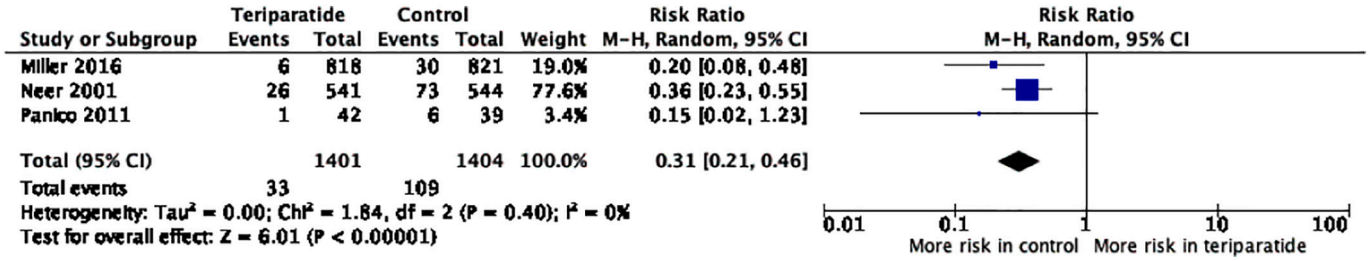

Fig. 5. Forest plot of comparison: new vertebral fractures, outcome: 7.1 20 μg/day of Teriparatide vs. Placebo or control, all study durations.

(Leder et al., 2015; Miller et al., 2016), risedronate (Anastasilakis et al., 2008a; Anastasilakis et al., 2008b), alendronate (Deng et al., 2018; McClung et al., 2014; Panico et al., 2011; Finkelstein et al., 2010; Arlot et al., 2005), romosozumab (Genant et al., 2017; Langdahl et al., 2017; McClung et al., 2014), denosumab (Tsai et al., 2013), supplementation only (Sethi et al., 2008), no medications (Ohtori et al., 2013), a combination of antiresorptive agents (Gonnelli et al., 2006) or calcitonin (Kung et al., 2006).

Agreement between the reviewers for eligibility based on title and abstract screening was very high (kappa = 0.823, 95% CI 0.941 to 0.705). The risk of bias assessment (presented in Fig. 2) showed that 15 studies (75%) had high ROB concern for the blinding participants and research personnel.

3.2. Lumbar Spine BMD

The overall certainty of evidence for lumbar spine BMD (LS BMD) was rated as high-quality (Table 2).

3.2.1. 20 μg/day of teriparatide versus Placebo (1.1 & 1.2)

For LS BMD measurements comparing 20 μg/day of teriparatide to placebo at a study duration of less than or equal to 12 months ($t \leq 12$ months), 9 studies (783 patients in total) reported results that were pooled (Genant et al., 2017; Kung et al., 2006; McClung et al., 2014; Sethi et al., 2008; Yang et al., 2016; Cosman et al., 2010; Henriksen et al., 2013; Leder et al., 2015; Miller et al., 2016; Miyauchi et al., 2008) (Supplementary Fig. 1). The standardized mean difference (SMD) in LS BMD measurement was 0.34 SD units higher with 20 μg/day of teriparatide (95% CI 0.19–0.48 SDs higher) compared to placebo. Heterogeneity in the studies was negligible ($I^2 = 0\%$). A total of 2 studies (2724 patients) were pooled for results on LS BMD measurements comparing 20 μg/day of teriparatide to placebo for $t > 12$ months (Neer et al., 2001; Miller et al., 2016) (Supplementary Fig. 2). The mean difference (MD) in LS BMD was 0.08 g/cm^2 higher with 20 μg/day of teriparatide (95% CI, 0.07 g/cm^2 higher to 0.09 g/cm^2 higher) compared to placebo. The weighted mean LS BMD in the placebo group is 0.0051 g/cm^2. Heterogeneity in the studies was considerably low ($I^2 = 7\%$).

3.2.2. 40 μg/day of teriparatide versus Placebo or Control (1.3)

For LS BMD measurements comparing 40 μg/day of teriparatide versus placebo or a comparator drug (control) at $t \leq 12$ months or $t > 12$ months, reported results of 4 studies (1288 patients) were pooled (Neer et al., 2001; Finkelstein et al., 2010; Cosman et al., 2010; Miyauchi et al., 2008). For the subgroup analysis at $t \geq 12$ months, the MD in LS BMD was 0.06 g/cm^2 higher with 40 μg/day of teriparatide (95% CI, 0.03 g/cm^2 higher to 0.09 g/cm^2 higher) compared to placebo or control (Supplementary Fig. 3). The weighted mean LS BMD in the placebo or control group for the aforementioned subgroup analysis was 0.0011389 g/cm^2. Heterogeneity in the studies for the subgroup analysis of $t \geq 12$ months was negligible ($I^2 = 0\%$). For the subgroup analysis at $t < 12$ months (Cosman et al., 2010; Miyauchi et al., 2008), the MD in LS BMD was 0.10 g/cm^2 higher with 40 μg/day of teriparatide (95% CI, 0.08 g/cm^2 higher to 0.12 g/cm^2 higher) compared to placebo or control (Supplementary Fig. 3). The weighted mean LS BMD in the placebo or control group for said subgroup analysis was 0.0113 g/cm^2. Heterogeneity for the subgroup analysis at $t < 12$ months was negligible ($I^2 = 0\%$). The heterogeneity of subgroup differences was considerably high ($I^2 = 84.4\%$), suggesting an interaction effect of study duration and

Table 3
Sensitivity analysis.*

Sensitivity analysis type	Pooled results	Sensitivity analysis effect		Regular analysis effect	
		Relative (95% CI)	Absolute (95% CI)	Relative (95% CI)	Absolute (95% CI)
Type I – Remove studies with >2 high ROB. (n =)	1.1	–	SMD 0.35 SD higher (0.19 higher to 0.52 higher)	–	SMD 0.34 SD higher (0.19 higher to 0.48 higher)
	1.2	–	MD 0.07 g/cm^2 higher (0.05 higher to 0.09 higher)	–	MD 0.08 g/cm^2 higher (0.07 higher to 0.09 higher)
	1.3.1	–	(No change)	–	MD 0.06 g/cm^2 higher (0.03 higher to 0.09 higher)
	1.3.2	–	(No change)	–	MD 0.10 g/cm^2 higher (0.08 higher to 0.12 higher)
	1.4	–	SMD 0.14 SD lower (0.30 lower to 0.02 higher)	–	SMD 0.13 SD lower (0.28 lower to 0.02 higher)
	1.5.1	–	(NDR)	–	SMD 0.96 SD higher (0.33 higher to 1.59 higher)
	1.5.2	–	SMD 0.16 SD higher (0.08 lower to 0.40 higher)	–	SMD 0.14 SD higher (0.08 lower to 0.36 higher)
	1.6	–	(No change)	–	SMD 0.48 SD higher (0.12 higher to 0.84 higher)
	2.1	–	SMD 0.17 SD higher (0.07 higher to, 0.27 higher)	–	SMD 0.21 SD higher (0.15 higher to 0.28 higher)
	2.2	–	(No change)	–	MD 0.03 g/cm^2 higher (0.02 higher to 0.04 higher)
	2.3	–	MD 0.05 g/cm^2 lower (0.17 lower to 0.07 higher)	–	MD 0.02 g/cm^2 lower (0.06 lower to 0.02 higher
	2.4	–	(No change)	–	SMD 0.09 SD lower (0.35 lower to 0.17 higher)
	3.1	–	SMD 0.79 SD lower (1.24 lower to 0.34 lower)	–	SMD 0.73 SD lower (1.10 lower to 0.37 lower
	4.1	RR 0.69 (0.38, 1.23)	30 fewer per 1000 (60 fewer to 22 more)	RR 0.84 (0.65, 1.10)	15 fewer per 1000 (33 fewer to 10 more)
	5.1	RR 0.73 (0.57, 0.92)	56 fewer per 1000 (90 fewer to 17 more)	RR 0.72 (0.59, 0.87)	41 fewer per 1000 (60 fewer to 1349 fewer)
	6.1	RR 1.72 (0.27, 11.06)	25 more per 1000 (25 fewer to 343 more)	RR 0.85 (0.57, 1.29)	8 fewer per 1000 (21 fewer to 14 more)
	7.1	RR 0.35 (0.23, 0.53)	88 fewer per 1000 (104 fewer to 64 fewer)	RR 0.31 (0.21, 0.46)	54 fewer per 1000 (61 fewer to 42 fewer)

* NDR = no data remaining (as a result of removing applicable studies for the sensitivity analysis); no change = no change in the effect size and 95% confidence interval compared to the regular analysis.

teriparatide on LS BMD.

3.2.3. 20 μg/day of teriparatide versus Romosozumab or Abaloparatide (1.4)

A total of 5 studies (2330 patients) reported results that were pooled to compare LS BMD measurements of 20 μg/day of teriparatide relative to 210 mg per month of romosozumab or 80 mg/day of abaloparatide across any *t* (Genant et al., 2017; Langdahl et al., 2017; McClung et al., 2014; Leder et al., 2015; Miller et al., 2016) (Supplementary Fig. 4). The standardized mean difference (SMD) in LS BMD measurement was 0.08 SD units lower with 20 μg/day of teriparatide (95% CI 0.16 SDs lower to 0.00 SDs higher) compared to 210 mg/month of romosozumab or 80 mg/day of abaloparatide. Heterogeneity in the studies was negligible (I^2 = 0%).

3.2.4. 20 μg/day of teriparatide versus Alendronate or Risedronate or other antiresorptives (1.5 & 1.6)

Results from 1 study (44 patients) were used to compare LS BMD measurements of 20 μg/day of teriparatide to 35 mg/week of risedronate for $t \leq 12$ months (Anastasilakis et al., 2008a; Anastasilakis et al., 2008b) (Supplementary Fig. 5). SMD in LS BMD measurement was 0.96 SD units higher with 20 μg/day of teriparatide (95% CI 0.33–1.59 SDs higher) compared to 35 mg/week of risedronate. As there was only one study in this subgroup, heterogeneity was not assessed. Results pooled from a total of 5 studies (324 patients) were used to compare LS BMD measurements of 20 μg/day of teriparatide to alendronate at various doses or other antiresorptive agents for $t \leq 12$ months (Deng et al., 2018; Gonnelli et al., 2006; McClung et al., 2014; Tsai et al., 2013; Arlot et al., 2005) (Supplementary Fig. 5). SMD in LS BMD measurement was 0.14 SD units higher with 20 μg/day of teriparatide (95% CI, 0.08 SDs lower to 0.36 SDs higher) compared to alendronate or other antiresorptive agents. Heterogeneity for this subgroup was negligible (I^2 = 0%). The heterogeneity of subgroup differences was considerably high (I^2 = 82.8%), suggesting an interaction effect of drug comparator and teriparatide on LS BMD. For $t > 12$ months, a separate analysis pooling 2 studies (123 patients) was used to compare LS BMD measurements of 20 μg/day of teriparatide to alendronate (Panico et al., 2011; Arlot et al., 2005) (Supplementary Fig. 6). SMD in LS BMD measurement was 0.48 SD units higher with 20 μg/day of teriparatide (95% CI, 0.12–0.84 SDs higher) compared to alendronate at various doses. Heterogeneity in the studies was negligible (I^2 = 0%).

All 4 subgroup analyses based on mean pooled age (MPA) showed negligible heterogeneity for subgroup differences, comparing LS BMD of studies with MPA less than 65.0 years to studies with MPA greater than 65.0 years (I^2 = 0%), (Supplementary Figs. 7–10).

3.3. Total Hip BMD

The overall certainty of evidence for total hip BMD (TH BMD) was rated as moderate due to ROB concerns resulting from insufficient blinding of patients and research personnel, as well as attrition bias (Table 2). The funnel plot for TH BMD was almost symmetric, with some indication of publication bias of studies for positive findings in favor of teriparatide (i.e. Below 1.00 SD units (Supplementary Fig. 11)).

3.3.1. 20 μg/day of teriparatide versus Placebo or Control (2.1)

For TH BMD measurements comparing 20 μg/day of teriparatide to placebo or a comparator drug (control) for any *t*, 11 studies (3507

patients) reported results that were pooled (Genant et al., 2017; Kung et al., 2006; McClung et al., 2014; Neer et al., 2001; Sethi et al., 2008; Yang et al., 2016; Cosman et al., 2010; Henriksen et al., 2013; Leder et al., 2015; Miller et al., 2016; Miyauchi et al., 2008) (Supplementary Fig. 12). The SMD in TH BMD measurement was 0.21 SD units higher with 20 μg/day of teriparatide (95% CI, 0.15–0.28 SDs higher) compared to placebo or control. Heterogeneity in the studies was negligible ($I^2 = 0\%$).

3.3.2. 40 μg/day of teriparatide versus Placebo or Control (2.2)

The results of 4 studies (1288 patients) were pooled to compare TH BMD measurements of 40 μg/day of teriparatide to placebo or control for any *t* (Neer et al., 2001; Finkelstein et al., 2010; Cosman et al., 2010; Miyauchi et al., 2008) (Supplementary Fig. 13). MD in TH BMD was 0.03 g/cm^2 higher with 40 μg/day of teriparatide (95% CI, 0.02 g/cm^2 to 0.04 g/cm^2 higher) compared to placebo or control. The weighted mean TH BMD in the placebo or control group was −0.00507 g/cm^2. Heterogeneity across all studies was negligible ($I^2 = 0\%$).

3.3.3. 20 μg/day of teriparatide versus Romosozumab or Abaloparatide (2.3)

A total of 4 studies (688 patients) reported results that were pooled to compare TH BMD measurement of 20 μg/day of teriparatide relative to 210 mg per month of romosozumab or 80 mg/day of abaloparatide for any *t* (Genant et al., 2017; Langdahl et al., 2017; McClung et al., 2014; Leder et al., 2015) (Supplementary Fig. 14). MD in TH BMD was 0.02 g/cm^2 lower with 20 μg/day of teriparatide (95% CI, 0.06 g/cm^2 lower to 0.02 g/cm^2 higher) compared to romosozumab or abaloparatide. The weighted mean TH BMD in the romosozumab or abaloparatide group was 0.0577 g/cm^2. Heterogeneity in the studies was negligible ($I^2 = 0\%$).

3.3.4. 20 μg/day of teriparatide versus Alendronate or Denosumab or other antiresorptives (2.4)

TH BMD measurements of 20 μg/day of teriparatide to alendronate, Denosumab or other antiresorptives at various doses were compared based on the pooled results of 4 studies (282 patients) (Deng et al., 2018; Gonnelli et al., 2006; McClung et al., 2014; Tsai et al., 2013) (Supplementary Fig. 15). The SMD in TH BMD measurement was 0.04 SD units lower with 20 μg/day of teriparatide (95% CI, 0.27 SDs lower to 0.20 SDs higher) compared to alendronate, Denosumab or other antiresorptive agents. Heterogeneity in the studies was negligible ($I^2 = 0\%$).

All 4 subgroup analyses based on MPA showed negligible heterogeneity for subgroup differences, comparing TH BMD of studies with MPA less than 65.0 years to studies with MPA greater than 65.0 years ($I^2 = 0\%$), (Supplementary Figs. 16–19).

3.4. Pain severity (3.1)

The results of 2 studies (123 patients) were pooled to compare pain severity with the use of 20 μg/day of teriparatide compared to placebo or a control treatment (Ohtori et al., 2013; Panico et al., 2011) (Fig. 3). A large effect was found for pain severity; the SMD was 0.80 SD units lower with 20 μg/day of teriparatide (95% CI, 1.16–0.43 SDs lower) compared to placebo or control treatment. Heterogeneity across the included studies is negligible ($I^2 = 0\%$). The overall certainty of evidence was low, mainly due to ROB concerns and high imprecision (Table 2).

3.5. Back pain (5.1)

Pooling of data from 5 studies (2998 participants) shows a small reduction in the adverse event of back pain with the use of 20 μg/day of teriparatide compared to placebo or control treatment (RR 0.72, 95% CI 0.59 to 0.87) (McClung et al., 2014; Neer et al., 2001; Leder et al., 2015; Miller et al., 2016; Miyauchi et al., 2008) (Fig. 4). We calculated an absolute risk decrease in the 20 μg/day of teriparatide treatment of 41 fewer events of back pain per 1000 patients relative to placebo or control treatment (95% CI, 60 fewer to 19 fewer). Heterogeneity across all included studies is negligible ($I^2 = 0\%$). The overall certainty of evidence was rated down to moderate, primarily as a result of ROB concerns (Table 2).

3.6. New vertebral fractures (7.1)

Pooling of data from 3 studies (2805 participants) (see Table 2 for summary data from studies) shows a large reduction in the incidence of new vertebral fractures with the use of 20 μg/day of teriparatide compared to placebo or control treatment (RR 0.31, 95% CI 0.21 to 0.46) (McClung et al., 2014; Panico et al., 2011; Miller et al., 2016) (Fig. 5). We calculated an absolute risk decrease in the teriparatide arm of 54 fewer events of new vertebral fractures per 1000 patients (95% CI, 61 fewer to 42 fewer) compared to the placebo or control arm. Heterogeneity across all included studies is negligible ($I^2 = 0\%$). The overall rating of certainty was moderate, mainly due to ROB concerns (Table 2).

A subgroup analysis of age on the pooled analysis of new vertebral fractures showed negligible heterogeneity of subgroup differences ($I^2 = 0\%$), (Supplementary Fig. 20).

3.7. Arthralgia and pain in extremity (6.1)

We also investigated arthralgia and extremity pain as adverse events. Arthralgia was assessed by pooling the results of 5 studies that had a total 2333 patients (Deng et al., 2018; Langdahl et al., 2017; McClung et al., 2014; Leder et al., 2015; Miller et al., 2016) (Supplementary Fig. 21). We calculated 15 fewer events of arthralgia per 1000 patients with the use of 20 μg/day of teriparatide compared to placebo or control treatment. Additionally, pain in extremity as an adverse event was assessed by pooling the results of 4 studies that had a total of 1924 patients (Kung et al., 2006; McClung et al., 2014; Miller et al., 2016; Miyauchi et al., 2008) (Supplementary Fig. 22). We calculated 8 fewer events of pain in extremity with 20 μg/day of teriparatide compared to placebo or control.

3.8. Sensitivity analysis

Excluding data from 7 trials (Ohtori et al., 2013; Anastasilakis et al., 2008a; Anastasilakis et al., 2008b; Deng et al., 2018; Kung et al., 2006; Finkelstein et al., 2010; Miller et al., 2016) that had ≥2 high ROB items had a small impact on the results of LS BMD and TH BMD, while a more appreciable impact on the results for the outcomes of adverse events and new vertebral fractures (Table 3).

The amount of absolute change (*sensitivity analysis* minus *original analysis*) in LS BMD measurements was from no change at all to 0.02 SD units higher with respect to SMD, and from 0.01 g/cm^2 lower to no change at all with respect to MD. The amount of absolute change for TH BMD measurements was from 0.04 SD units lower to no change at all with respect to SMD, and from no change at all to 0.03 g/cm^2 lower with respect to MD (Table 3).

After removing 3 studies (Deng et al., 2018; Leder et al., 2015; Miller et al., 2016), there was double the number of fewer events of arthralgia compared to the original analysis (30 fewer versus 15 fewer); the CI however, still includes both no effect and appreciable from the daily 20 μg teriparatide regimen (95% CI, 60 fewer to 20 more) (Table 3).

Removing 2 studies (Kung et al., 2006; Miller et al., 2016) with high ROB for the analysis on the adverse event of pain in extremity altered the direction of risk (RR 1.72, 95% CI 0.27 to 11.06). We calculated 25 *more* events of pain in extremity with 20 μg/day of teriparatide compared to placebo or control; the CI however, includes both no effect and appreciable benefit from the daily 20 μg teriparatide regimen (95% CI, 25 fewer to 343 more) (Table 3).

Removing the lone study (Miller et al., 2016) with high ROB for the

analysis on new vertebral fractures resulted in an absolute change by 34 fewer events of new vertebral fractures (88 fewer per 1000; 95% CI, 104 fewer to 64 fewer) compared to the original analysis (54 fewer per 1000; 95% CI 61 fewer to 42 fewer), (Table 3).

3.9. GRADE

Outcomes were rated as low or moderate on the risk of bias scale predominantly due to the open-label administration of teriparatide posing problems with blinding as well as attrition concerns. Lumbar spine and total hip BMD however had no concerns with the bias domains and had dose response assessments from the 20 μg/day and 40 μg/day teriparatide comparisons, and therefore were of high-quality. An analogous finding was seen with arthralgia and pain in extremity. Evidence for pain severity was of low quality. Blinding and attrition concerns resulted in moderate quality evidence for the outcomes of back pain and new vertebral fractures. Overall, the collective evidence of all outcomes was of high-quality.

4. Discussion

Vertebral compression fractures are common and place a significant burden on patients, caregivers, and the healthcare system. Our meta-analysis of 6024 patients across 20 randomized trials found high-quality evidence supporting the use of 20 and 40 μg/day of teriparatide in increasing lumbar spine and total hip BMD as well as reducing pain severity, number of back pain events, and incidence of vertebral fractures relative to placebo and control treatments. With prolonged treatment ($t \geq 12$ months), a higher 40 μg/day dose of teriparatide demonstrated significantly better results in improving lumbar spine and total hip BMD, but had negligible difference in anti-fracture efficacy. Although the increased dosing regimen may seem promising for select patients, more research is needed to elucidate its long term efficacy and potential adverse effects. Teriparatide had statistically significant efficacy in increasing lumbar spine BMD over alendronate, risedronate, denosumab or other anti-resorptives drugs, and a comparable effect relative to other anabolic agents (romosozumab and abaloparatide). There was also a notable reduction in the incidence of new vertebral fractures with the use of 20 μg/day of teriparatide compared to placebo or control treatment, as we calculated an absolute risk decrease of 54 fewer events per 1000 patients (95% CI, 61 fewer to 42 fewer). Our results further cement the findings of a previous meta-analysis wherein statistically significant dose-dependent increases in hip BMD are observed, particularly in post-menopausal osteoporosis (Shen et al., 2018).

We explored primary outcomes of significant importance to patients, as well as considered adverse events important to patients and clinicians. An increasing number of studies evaluate different forms and dosing of teriparatide on fracture prevention and incidence, BMD, pain, screw loosening, hardware complications, bone fusion and nonunion rates. However, considering the observed dose-dependent effect of teriparatide, no study including ours has aimed at directly evaluating the appropriate dosage and administration interval for achieving optimal patient-important outcomes, indicating potential direction of future research. Despite the manufacturer, *Eli Lilly and Company* (Indiana, United States), guidelines recommending a 20 μg subcutaneous injection daily, numerous investigators have employed teriparatide in randomized trials and other weaker methodological designs in varying frequencies and doses (Neer et al., 2001; Finkelstein et al., 2010; Cosman et al., 2010; Miller et al., 2016; Miyauchi et al., 2008). This suggests a strong interest exists in this community to further explore such variations in dosage and treatment pattern that are not officially prescribed and considered off-label.

Moderate quality evidence suggests that teriparatide at 20 μg/day or 40 μg/day results in higher increases in total hip BMD levels when compared to placebo. Interestingly, we also found that 20 μg/day of teriparatide had smaller increases in total hip BMD levels compared to romosozumab, or abaloparatide, as well as compared to alendronate, denosumab or other antiresorptives. These results should be considered with caution, considering the confidence interval for the effect sizes (Sections 3.2.3 and 3.2.4) contained both no appreciable difference and a greater increase in total hip BMD in teriparatide relative to anti-resorptives. This is consistent with the mixed nature of our findings for the effect of teriparatide on total hip BMD levels; while most studies reported an improvement in total hip BMD levels with 20 μg/day of teriparatide, there were at least 4 studies where total hip BMD actually decreased after treatment with 20 μg/day of teriparatide (Deng et al., 2018; Gonnelli et al., 2006; Kung et al., 2006; Sethi et al., 2008). Clinically, however, use of teriparatide has not been correlated with increased hip fracture risk in patients with osteoporosis (Díez-Pérez et al., 2019).

Other limitations include the paucity of evidence for some outcomes and the exclusion of combination therapy trials. Our investigation of 20 μg/day dose of teriparatide vs risedronate for the outcome of lumbar spine BMD included only one study (n = 44). Additionally, although our statistically significant results are in favor of teriparatide reducing pain severity it is important to note the results are from 2/20 (10%) studies. This highlights a critical need for patient-important outcomes such as pain severity to be included in future trials. To minimize potential impact of co-intervention bias, we included trials in which teriparatide is administered without being combined with any other intervention at any point of the study duration. This had a cost, in which we were unable to determine teriparatide's efficacy as a combination therapy coupled with other anti-resorptive or anabolic agents. A variety of evidence demonstrates teriparatide combined with other therapeutic agents increases total hip and lumbar spine BMD more than either agent alone, or other forms of combination therapy (Tsai et al., 2019; Tsubouchi et al., 2019; Lou et al., 2018; Lou et al., 2017). Based on variable existing evidence coupled with our results (Lou et al., 2017), we observe a variable dose-dependent effect relationship yet questions of optimal evidence-based interval and dosing remain unanswered. High-quality methodologically sound randomized trials evaluating the interval and dosing relationship as well as efficacy relative to other anabolic agents would help delineate teriparatides usage guidelines and facilitate the management of postmenopausal osteoporosis.

5. Conclusion

High-quality evidence supports the utilization of a 20 μg/day dose of teriparatide to significantly improve lumbar spine BMD and decrease incidence of vertebral fractures and pain severity relative to all comparators. An increased 40 μg/day dose of teriparatide demonstrated statistically significantly better results with prolonged treatment. This data is valuable for clinicians involved in the care of this growing demographic of patients.

CRediT authorship contribution statement

Shakib Akhter: Methodology, Software, Writing - original draft. **Abdul Rehman Qureshi:** Methodology, Writing - original draft. **Hussein Ali El-Khechen:** Visualization, Software, Writing - original draft. **Anthony Bozzo:** Methodology, Writing - original draft. **Moin Khan:** Supervision, Writing - review & editing. **Rakesh Patel:** Supervision, Writing - review & editing. **Mohit Bhandari:** Supervision, Writing - review & editing. **Ilyas Aleem:** Conceptualization, Supervision, Writing - review & editing.

Declaration of competing interest

None.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.bonr.2020.100728.

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