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Review Article

The Role of Recombinant Parathormone derivative in Bone healing. Making the Unfavorable, Favorable - A Systematic Review

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ABSTRACT

Background: Teriparatide is a recombinant parathormone derivative encompassing the first 1-34 amino acids off PTH, which is said to contain potent anabolic capability. It is said to induce osteoblastogenesis thereby placing an essential role in bone healing. The aim of this systematic review is to evaluate the best available evidence from randomized controlled trials analyzing the effectiveness of teriparatide on bone regeneration and healing in osteoporotic patients and patients with fractures. **Aim:** This systematic review aims to assess whether Teriparatide enhances bone regeneration and healing in terms of improving clinical, radiographic, histologic parameters and Biomarkers of Bone formation and resorption. **Materials and Methodology:** A comprehensive search was done in databases such as 'PubMed', 'Google Scholar and 'Cochrane' databases based on pre-determined eligibility criteria. Randomized control trials assessing the effectiveness of Teriparatide in Bone healing in fractures as well as osteoporosis were selected after thorough screening. **Results:** The selected 13 studies compared teriparatide to either placebo or another anti-resorptive drug. Out of the 13, 8 studies were done to evaluate the improvement and healing of bone in Osteoporotic patients whereas 5 studies were done on improvement in fracture healing. The studies evaluated outcome parameters such as Clinical and Radiological improvement, Biomarkers of Bone resorption and formation and Safety.6 studies assessed clinical parameters, 12 studies assessed radiological parameters, 7 studies assessed biomarkers, 11 studies assessed safety parameters by means of occurrence of any adverse effects. All the 8 studies done on osteoporotic patients showed a good improvement. Of the 5 studies on fracture healing, only 2 studies showed beneficial effects while the other 3 did not show any benefits. **Conclusion:** Teriparatide could have beneficial effects in bone healing in osteoporotic patients and is well tolerated. However, the results are inconclusive whether they have beneficial effects in treating fractures. More Homogenous Randomized control trials are required to ascertain whether teriparatide could improve bone healing.

Key words: Teriparatide, Parathormone, Fracture, Bone healing, Recombinant derivative.

INTRODUCTION

Wound Healing is one of the most complex biological processes that occur throughout the life of humans. Immediately after an Injury, there is a coordinated response of various cellular and intracellular pathways to restore homeostasis.[1] Unlike invertebrates like salamanders, which are capable of regenerating their limb or missing appendages,[2] We Humans do not possess any such magical capabilities. Our System needs a programmed and well-orchestrated healing cascade in order to repair itself.

Poor Healing after trauma, surgery or a chronic disease condition affects millions worldwide. When this is the case for Healthy individuals, the prognosis for those who are systemically compromised is even poor. In addition to this, in this fast paced world, fractures have become very common, be it from a fall or an RTA or due to any chronic condition. An impaired fracture healing leads to delayed union, non-union and other defects, which may lead to further complication, thus affecting the quality of life of the patients.[3] Numerous grafting techniques and regenerative materials have been studied and investigated for effective regeneration. But, they take have been at the back seat because of the complexities and complications involved by their usage.

Unraveling the mysteries and key mechanisms involved in wound healing has led the researchers towards a different approach of using recombinant therapies to facilitate an effective healing process. Thus, identifying better and novel strategies to prevent complications as well as accelerate healing have become a necessity. One such approach is the use of Recombinant Parathyroid hormone.

Parathyroid Hormone is an 84 amino acid polypeptide that is responsible for calcium Homeostasis in our body. Studies have suggested that the N-terminal fragment of the PTH molecule encompassing amino acids 1-34 and called PTH (1-34) is the principal constituent responsible for Biological activity.[4,5] The effect of this fragment on bone formation process, initially recognized in 1930s has been brought to the forefront only recently after studies proved that Osteoblasts that are responsible for bone formation express the PTH receptors

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while Osteoclasts do not. Teriparatide is a recombinant form of these 34 amino-terminal residues that is manufactured using a genetically modified strain of Escherichia coli and has a molecular mass of 4117.8 daltons.[6] It is currently used as subcutaneous injection for osteoporotic patients. Apart from this recognized application, there is growing evidence suggesting its potential to accelerate healing of fractures as well. It is said to increase the bone mineral density. Although the exact mechanism remains unknown, it is said to increase osteoblastogenesis, reduced osteoblast apoptosis, activate growth factors such as IGF-1 and TGF-beta in the immediate bone marrow environment.

Andreassen *et al.* in 1999 showed that intermittent administration of PTH (1-34) at 60 and 200 microgram doses produced increases in callus volume of 42% and 72% respectively.[7] In the same year, Holzer *et al.* found similar results of increased callus volume in histological sections after daily PTH (1-34) administration in rats.[8]

Komatsubara *et al.* in 2004 showed that intermittent teriparatide at 30 microgram per kg before and after osteotomy accelerated the fracture healing process in rats up to 12 week osteotomy.[9] In 2010 Mognetti *et al.* noted that 40 microgram per kg per day of teriparatide accelerated callus formation.[10] Alkhiary *et al.* showed that beneficial effects from teriparatide is not just limited to the periods during which treatment is given but also continues after. In his study, he found that there was a sustained anabolic effect throughout the remodeling phase.[11]

Studies have shown that teriparatide proved to be useful in situations where sub-optimal fracture repair mechanisms are expected like smoking, diabetes, patients under corticosteroid treatment, metabolic bone diseases, oestrogen deficiency etc. Nozaka *et al.* in 2008 examined the effects of Teriparatide in ovariectomized rats and found that the drug reduced bone resorption parameters.[12]

The effects of teriparatide on humans have also been reported earlier. Chintamaneni *et al.* in 2010 reported a case of a 67-year-old male who had sustained a fracture of the body of the sternum as a result of a motor vehicle accident, which subsequently failed to heal resulting in a painful atrophic non-union. This patient was then administered 20 microgram teriparatide per day and showed significant healing in a short period of 3 months.[13] There were few other case reports by Rubery and Bukata *et al.* where teriparatide showed benefits in Bone healing in type III odontoid fractures in osteoporotic women.[14]

In animal experiments and case reports they have proved to be beneficial. However, in clinical studies their results are in conflict. Evidence based evaluation of the potential role of teriparatide in bone healing is limited. This provides an impetus for the present systematic review. This systematic review aims to assess the Literature evidence for the role of teriparatide in bone regeneration and healing in terms of clinical, radiographic, histologic parameters and Biochemical markers in patients with fractures and patients with osteoporosis.

MATERIALS AND METHODOLOGY

Structured question

Does teriparatide facilitate Bone healing in osteoporosis and facilitate healing of fractures?

PICO (Population, Intervention, Comparison, and Outcomes)

- **P** – Patients undergoing treatment for any bone fracture or deformities (regardless of the type or location of fracture or deformity) or for osteoporosis
- **I** – Teriparatide
- **C** - Placebo or other anti-resorptive osteoporotic drugs or no treatment
- **O** – Clinical, Radiographic, Histologic parameter, Biomarkers which reflect bone healing or regeneration

Outcomes of interest

The outcomes of interest in this systematic review are

- Clinical: Time for fracture healing, treatment period, resumption of activities, Reduction in pain by means of VAS (Visual analogue scale), Functional recovery by means of PRWE score (Patient rated wrist evaluation score), improvement in Grip strength, improvement in Gait speed, DASH score (Disability of arms and shoulder), JHRQ (Johanson Hip rating Questionnaire)
- Radiographic: Bone mineral density, radiographic union, callus formation;
- Histological: evidence of new bone formation and characteristics of different tissue compartments.
- Biomarkers: Serum and Bone Alkaline phosphatase(ALP), Serum N-terminal propeptide of type 1 Collagen(P1NP), Serum Osteocalcin(OC), Serum C-telopeptide of type 1 collagen (CTX), Urine N-telopeptide of type 1 collagen (NTX), Serum Osteocalcin and urinary deoxypyridinoline
- Assesment of Safety: By occurrence of Adverse events

Literature search protocol

Publications of interest within the scope of this focused systematic review were searched in

- The electronic database National Library of Medicine (MEDLINE/ PubMed)
- Google scholar
- Cochrane library

The search was limited to human clinical trials. No limitation regarding publication type and publication date was set.

Article eligibility criteria

Inclusion criteria:

- ❖ Articles reporting clinical trials on Teriparatide on Bone regeneration and healing with no restrictions on language, age or gender, ethnicity
- ❖ RCTs on osteoporotic patients under teriparatide drug therapy
- ❖ Studies involving one control group and one Experimental group that involved the administration of teriparatide

Exclusion criteria:

- ❖ Studies on Animals, Case-controlled, cohort studies
- ❖ Studies involving patients with autoimmune disorders such as Rheumatoid Arthritis
- ❖ Studies done using Recombinant PTH fragment (1-84)

Article selection:

Search results

The title and abstract of the entries yielded from the initial electronic database searches were read. After this initial filter, the full-text versions of the studies that could be potentially included in this review were read and a final selection of articles was done after applying the eligibility criteria.

Table 1: Characteristics and Summary of the Included Studies.

S. No	TITLE	Author and year	Study design	Blinding	Randomi-sation	Duration	Patient Consent	Ethical commit-tee approval	Sample size calculation	Nature of sample population	Groups	Sample size	Types of statistical method used	Outcome measures
1	Teriparatide for Acceleration of Fracture Repair in Humans: A Prospective, Randomized, Double-Blind Study of 102 Postmenopausal Women With Distal Radial Fractures	Per Aspenberg *et al*, 2010	A multicentred, prospective, Double-Blinded RCT	Double Blinded	Randomized (Method – Not mentioned)	53 weeks	Obtained	Approved by ethical review Board	Not mentioned	Post menopausal women with Distal Radial Fracture	Group 1-(control group) placebo injections Group 2- teriparatide 20 micro gram injection Group 3- teriparatide 40 micro-gram injections	N = 102 Group 1 = 34 Group 2 = 34 Group 3 = 34	Differences between groups were analysed using the ANOVA and kruskal-Wallis test. Comparison of occurrence of Adverse events were made using Cochran Mantel Haenszel test	Clinical – Assessment of Pain: Reduction in Pain –VAS scores Assessment of Function: Patient Rated Wrist Evaluation Score(PRWE score), Improvement in Grip Strength, Radiological– Analysis of Palmar tilt, Radial Angle and Ulnar variance, Radiographic evidence of cortica bridging Histological – Nil Biomarkers – Nil Safety- by assesing the occurene of adverse events during the course of treatment
2	Does Teriparatide Improve Femoral Neck Fracture Healing: Results From A Randomized Placebo-controlled Trial	Mohit Bhandari *et al*, 2016	A prospective, multicentric,Randomised , double blinded,placebo controlled clinical trial	Double blinded	Randomized (Method – Stratified Randomisation)	12 months	Obtained	Approved by ethical review Board	Not mentioned	Patients with Femoral Neck fracture	Group 1–(control group) placebo injections Group 2 – (Test group) teriparatide 20 micro gram injection	N = 159 Group 1 = 81 Group 2 = 78	Comparisons between treatment groups for secondary end points were made using Fischer's exact test	Clinical – Assessment of Pain: Reduction in Pain –VAS scores, Assessment of Function: improvement in Gait Speed,requirement of revision surgeries Radiological – fracture healing Histological – Nil Biomarkers - Nil Assessment of safety- occurenceof Adverse effects

3	PTH 1-34 (teriparatide) may not improve healing in proximal humerus fractures	Torsten Johansson, 2016	A prospective, Randomized clinical trial	Investigotor was blinded	Randomised (Sealed Envelopes)	4 weeks	Obtained	Approved by ethical review Board	Not mentioned	Patients with Proximal Humeus fractures	Group 1 – (Control group) no therapy Group 2 – (Test group) teriparatide 20 micro gram injection	N= 40 Group 1 = 20 Group 2 = 20	Parametric data assesed using chi-squared test, Non Parametric data assesed using Mann-Whitney U test	Clinical – Assesment of Pain: Reduction in Pain –VAS scores, Assesment of Function: Disability of Arms and Shoulder score(DASH score) Radiological- fracture healing Histological – Nil Biomarkers - Nil Assessment of safety- occurenceof Adverse effects
4	Short-term effects of teriparatide versus placebo on bone biomarkers, structure, and fracture healing in women with lower-extremity stress fractures: A pilot study	Ellen A Almirol *et al*,2016	Randomized ,placebo controlled trial	Double blinded	Randomised (by Block randomization)	8 weeks	Obtained	Approved by ethical review Board.	Not mentioned	Premenopausal women with acute lower extremity stress fractures	Group 1 – (Test Group)- teriparatide 20 micro gram injection per day Group 2 – (Contol Group)- Placebo injection	N=13 Group1 = 6 Group 2 = 7	Comparison between Groups was done using Wilcoxon rank sum test	Clinical – Nil Radiological – Radiographic Fracture healing,changes in Bone structure assesed by Dual energy X-ray absorptiometry(DXA),peripheral quantitative computed tomography(pQCT),MRI Histological – Nil Biomarkers –Serum Alkaline phosphatase(ALP), Serum N-terminal propeptide of type 1 Collagen(P1NP), Serum Osteocalcin(OC), Serum C-telopeptide of type 1 collagen (CTX), Urine N-telopeptide of type 1 collagen (NTX) Assessment of safety- occurenceof Adverse effects
5	Enhancement of hip fracture healing in the elderly: Evidence deriving from a pilot randomized trial	Nikolaos K.Kanakaris *et al*,2015	A prospective, randomised controlled trial	Double blinded	Randomised (Method not mentioned)	4 weeks	Obtained	Approved by ethical review Board	Sample Size calculation done	Elderly with Low energy Hip fractures	Group 1 - control – only vitD and Calcium supplements Group 2-Alendronate(70 mg) injection per day, VitD and Calcium supplements Group 3- Teriparatide(20 microgram)injection per day, Vitamin D and Calcium supplements	N= 30 Group 1 = 10 Group 2 = 11 Group 3= 9	Difference between the groups assessed by means of ANOVA	Clinical – Assessment of Function by Johanson hip rating Questionnaire (JHRQ) , Ambulatory Status Radiological - Nil Histological – Nil Biomarkers - Nil

6	Effect Of Parathyroid Hormone (1-34) On Fractures And Bone Mineral Density In Postmenopausal Women With Osteoporosis	Robert M neer *et al*, 2001	Randomized controlled trial	Not mentioned	Randomised (Method – Not mentioned)	24 months	Obtained	Approved by ethical review Board	Not mentioned	Post menopausal women with Osteoporosis	Group 1 - (Control) Placebo Group 2 - teriparatide 20 micro gram injection per day Group-3- teriparatide 40 micro gram injection per day	N = 1637 Group-1= 544 Group-2= 541 Group-3= 552	Difference between the groups assessed by means of ANOVA	Clinical – Nil Radiological – total body Bone mineral density, Occurrence of Vertebral and Non vertebral fractures Histologic analysis – Nil Biomarkers - Nil Assessment of safety- occurenceof Adverse effects
7	A Randomized Double-Blind Trial to Compare the Efficacy of Teriparatide [Recombinant Human Parathyroid Hormone (1–34)] with Alendronate in Postmenopausal Women with Osteoporosis	Jean-Jacques Body *et al*,2002	Multicentre, Randomized clinical trial	Double Blinded	Randomised (method-not mentioned)	14 months	Obtained	Approved by ethical review Board	Not mentioned	Post menopausal women with Osteoporosis	Group 1 – teriparatide 40 micro gram injection per day Group 2 – 10mg Alendronate Injection per day	N = 146 Group 1 = 73 Group 2 = 73		Clinical - Nil Radiological – Bone Mineral Density , Non vertebral Fractures Histological – Nil Biomarkers – Bone ALP, Bone NTX (N telopeptides corrected for creatinine) Assessment of safety- occurenceof Adverse effects
8	Effects of teriparatide on bone mineral density and bone turnover markers in Japanese subjects with osteoporosis at high risk of fracture in a 24-month clinical study: 12-Month, randomized, placebo-controlled, double-blinded	Akimitsu Miyauchi *et al*, 2010	A randomised prospective ,multicentric,double blind placebo controlled clinical trial	Double Blinded	Randomised (method- block randomization)	12 months	Obtained	Approved by Institutional Review Board	mentioned	Japanese population with osteoporosis at a high risk for fracture	Group 1 - teriparatide 20 micro gram injection per day Group 2 – placebo injection	N = 180 Group 1 = 120 Group 2 = 60	Comparison between the groups was done using two sample t test, Comparison of percent change in bone turnover markers between the groups was done using Wilcoxon rank-sum test	Clinical – Back pain Radiological – Bone mineral density, occurrence of fractures Histological – Nil Biomarkers – markers of Bone turnover- P1NP,Bone ALP, CTX Assessment of safety- occurenceof Adverse effects
9	A randomized, multicenter controlled trial to compare the efficacy of recombinant human parathyroid hormone (1-34) with elcatonin in postmenopausal women with osteoporosis in China.	Zhang Xiu-Zhen *et al*,2009	A randomised prospective ,multicentric, placebo controlled clinical trial	Not mentioned	Randomised (method-not mentioned)	6 months	Obtained	Approved by Institutional Review Board	Not mentioned	Post menopausal women with Osteoporosis	Group 1 – recombinant parathormone derivative 20 microgram injection per day. Group 2 – Elcatonin 20 units injection per week	N = 205 Group 1 = 100 Group 2 = 105	Difference between the Groups was assessed using independent sample t test Adverse reactions were compared using Pearson's X^2 test	Clinical – Nil Radiological – Bone mineral density using DXA Histomorphometric analysis – Nil Biomarkers – Bone specific Alkaline phosphatase, Urinary N-telopeptide/ creatinine Assessment of safety- occurenceof Adverse effects

10	Comparison of parathyroid hormone (1-34) and elcatonin in postmenopausal women with osteoporosis: an 18-month randomized, multicenter controlled trial in China	Li Ying *et al*,2013	A multi-center, randomized, open-label, active-controlled study	Not mentioned	Randomised (method-not mentioned)	18 months	Obtained	Approved by Institutional Review Board	Not mentioned	Post menopausal women with Osteoporosis	Group 1 – recombinant parathormone derivative 20 microgram injection per day. Group 2 – Elcatonin 20 units injection per week	N = 453 Group 1 = 343 Group 2 = 112	To compare the differences between groups on the clinical and radiological assessments – Student's t test	Clinical – Back pain Radiological – Bone mineral density measured using XRD Histological – Nil Biomarkers – Bone specific Alkaline Phosphatase, Urinary C-telopeptide/ creatinine Assessment of safety- occurenceof Adverse effects
11	Efficacy of Teriparatide in Increasing Bone Mineral Density in Postmenopausal Women with Osteoporosis – An Indian Experience	BK Sethi *et al*,2008	A randomised, prospective, multicentre, open-label, controlled study	Open labelled, Not Blinded	Randomised (Method – Block Randomization)	180 days	Obtained	Approved by Institutional Review Board	Sample size calculation done	Postmenopausal Women with Osteoporosis	Group 1 - control – 1000 mg of elemental calcium and 500 IU of vitamin D supplements Group 2 - Test – Teriparatide injection with 1000 mg of elemental calcium and 500 IU of vitamin D	N = 82 Group 1 = 41 Group 2 = 41	Difference between the Groups calculated using Wilcoxon-Mann-Whitney U test Differences in Incidence of Adverse effects between groups was calculated using Z test	Clinical – Nil Radiological – Bone mineral density measured using DXA Histological – Nil Biomarkers – Serum Bone specific Alkaline Phosphatase, Serum Osteocalcin and urinary deoxypyridinoline
12	Comparison between recombinant human parathyroid hormone (1-34) and elcatonin in treatment of primary osteoporosis	Yan Yang *et al*,2015	A prospective, randomised clinical trial	Not mentioned	Randomised (method-not mentioned)	12 months	Obtained	Approved by Institutional Review Board	Not mentioned	Patients with osteoporosis	Group 1 – recombinant parathyroid hormone 20 microgram injection per day Group 2 – Elcatonin 20 Unit injection once a week	N = 60 Group 1 = 45 Group 2 = 15	Difference between the Groups was assessed using Students t test Adverse reactions were compared using Pearson's X^2 test	Clinical - Nil Radiological – Bone mineral density Histological – Nil Biomarkers – Bone specific Alkaline Phosphatase, Urinary c-terminal telopeptides of type 1 collagen/creatinine Assessment of safety- occurenceof Adverse effects
13	The rhPTH (1–34), But not Elcatonin, Increases Bone Anabolic Effi cacy in Postmenopausal Women with Osteoporosis	L.Zhang *et al*,2012	A monocentric, prospective, open labelled, Randomised controlled trial	Open labelled(Not blinded)	Randomised (method-Block randomization)	12 months	obtained	Approved by Institutional Review Board	Not mentioned	Post menopausal women with Osteoporosis	Group 1 – Teriparatide 20 microgram injection per day Group 2 – Elcatonin 200 U injection once a week	N = 124 Group 1 = 89 Group 2 = 35	Parametric data assesed using paired t test, Non Parametric data assesed using Mann-Whitney U test	Clinical – Nil Radiological – Bone mineral Density assessment Histological – Nil Biomakers- Bone specific Alkaline Phosphatase and serum type 1 cross-linked C terminal telopeptide Assessment of safety- occurenceof Adverse effects

Table 2: Data Extraction- Studies on Fracture Healing.

S.no	TITLE	Author and year	Outcome parameters										
			Clinical	Mean ± SD (or) Mean difference	P value	Radiographical	Results	P value	Histological	Mean ± SD (or) Mean difference	P value	Biomarker	Mean ± SD (or) Mean difference	P value
1.	Teriparatide for Acceleration of Fracture Repair in Humans: A Prospective, Randomized, Double-Blind Study of 102 Postmenopausal Women With Distal Radial Fractures	Per Aspenberg *et al*, 2010	PRWE score (Patient-Rated Wrist Evaluation) PRWE total score	Placebo- (-63.1±2.8) Teriparatide 20 microgram-(-69.5±2.9) Teriparatide 40 microgram-(-59.8±2.7)	P<0.001	Time to Radiographic Healing (in weeks) Teriparatide 40 microgram Vs Placebo	-1.1 to 0.6 weeks	P=0.523	NIL	-	-	NIL	-	-
			PRWE Pain score	Placebo- (-26.1±1.6) Teriparatide 20 microgram-(-28.4±1.6) Teriparatide 40 microgram-(-24.6±1.5)	P<0.001	Teriparatide 20 microgram Vs Placebo	-2.7 to -0.6 weeks	P=0.006						
			PRWE Function Score	Placebo- (-73.7±2.9) Teriparatide 20 microgram-(-80.7±2.9) Teriparatide 40 microgram-(-69.9±2.8)	P<0.05	Teriparatide 20 microgram Vs Placebo	-2.7 to -0.1 weeks	P=0.053						
			Grip Strength:	Placebo- 17.8 ± 1.9 Teriparatide 20 microgram-17.6±1.9 Teriparatide 40 microgram-17.6±2.0	P<0.05									
2.	Does Teriparatide Improve Femoral Neck Fracture Healing: Results From A Randomized Placebo-controlled Trial	Mohit Bhandari *et al*, 2016	Requirement for Revision Surgery (%) Patients who required Revision Surgery Patients who did not require revision surgery Improvement in Gait Speed ≥ 0.05 m/second and change from baseline ≥0.1 m/second, number (%) <0.05 m/second or change from baseline <0.1 m/second, number (%)	Placebo-14% Teriparatide-17% Placebo-85% Teriparatide-83% Placebo- 47(73) Teriparatide- 51(89) Placebo- 17(27) Teriparatide- 6(11)	P=0.722 P=0.589 P<0.05	Evidence of Healing, number(%) Evidence of No healing, number (%)	Placebo- 61(75) Teriparatide- 57(73) Placebo- 20(25) Teriparatide- 21(27)	P=0.692	NIL	-	-	NIL	-	-

3.	PTH 1-34 (teriparatide) may not improve healing in proximal humerus fractures	Torsten Johansson, 2016	Level of Pain (VAS) Median(range) DASH Score Median(range)	PTH group-Rest-0(0-48) Activity 15 (0-63) Control- Rest- 0(0-20) Activity 15 (0-70) PTH- 11(3-50) Control- 22(0-59)	P= 0.7 . P=0.4	-	-	-	-	-	-	NIL	-	-
4.	Short-term effects of teriparatide versus placebo on bone biomarkers, structure, and fracture healing in women with lower-extremity stress fractures: A pilot study	Ellen A Almirol *et al*,2016	NIL	-	-	Tibial Cortical Area Median(interquartile range)	Teriparatide Group- 269.52 mm^2 (232.6,278.4) Placebo- 256.64 mm^2 (244.3,274.8)	<0.05	NIL	-	-	Serum ALP (IU/L)	Teriparatide-61.5 Placebo- 63.0	0.52
						Cortical Thickness Median(interquartile range)	Teriparatide Group- 5.58mm (4.8,5.9) Placebo- 5.25 mm(5.0,6.0)	<0.05				Serum P1NP (µg/L) Serum OC (ng/ mL) Serum CTX (ng/mL) Urine NTX (nMBCE/ mMCr)	Teriparatide-103.1 Placebo- 47.5 Teriparatide- Teriparatide-16.8 Placebo-9.6 Teriparatide- 0.66 Placebo-0.50 Teriparatide-213.3	<0.05 <0.05 0.28 0.62
5.	Enhancement of hip fracture healing in the elderly: Evidence deriving from a pilot randomized trial	Nikolaos K.Kanakaris *et al*,2015	JHRQ Mean(SD) -Baseline	Group-1-Control- 68(9.0) Group-2- Alendronate -69(8.9) Group-3 test Group- 69(9.2)	-	NIL	-	-	NIL	-	-	NIL	Placebo- 524.4 -	-
			JHRQ Mean(SD) -6 months	Group-1-Control- 64(33.1) Group-2- Alendronate -65(33) Group-3 test Group- 65(31.9)	-									

Table 3: Studies on Osteoporosis.

S.no	TITLE	Author and year	Outcome parameters											
			Clinical	Mean ± SD (or) Mean difference	P value	Radiographical	Results	P value	Histological	Mean ± SD (or) Mean difference	P value	Biomarker	Results	P value
1.	The rhPTH (1–34), But not Elcatonin, Increases Bone Anabolic Effi cacy in Postmenopausal Women with Osteoporosis	L.Zhang *et al*,2012	NIL	-	-	Bone Mineral Density (% change)	Teriparatide group- 7% Elcatonin group- 2%	P<0.05	NIL	-	-	BSAP- (Reference Range->18.9 U/L) % of subjects within Reference Range	Teriparatide Group- Baseline- 74.5% 12 months- 91.5% Elcatonin Group- Baseline- 61.1% 12 months- 77.8%	P<0.05
												CTX-1 (Reference Range->3.23 U/L) % of subjects within Reference Range	Teriparatide Group- Baseline- 0% 12 months- 4.3% Elcatonin Group- Baseline-0% 12 months- 0 %	
2.	Effect Of Parathyroid Hormone (1-34) On Fractures And Bone Mineral Density In Postmenopausal Women With Osteoporosis	Robert M neer *et al*, 2001	Nil	-	-	Total Body Bone mineral Density	Placebo- -1.3±6.5 PTH 20 microgram – 0.6±5.8 PTH 40 microgram- 1.0 ±6.1	P<0.05	NIL	-	-	NIL	-	-
3.	A Randomized Double-Blind Trial to Compare the Efficacy of Teriparatide [Recombinant Human Parathyroid Hormone (1–34)] with Alendronate in Postmenopausal Women with Osteoporosis	Jean-Jacques Body *et al*,2002	NIL	-	- .	Lumbar Spine BMD Mean(±SE)	Baseline-Alendronate-0 Teriparatide- 0 14 months- Alendronate-5.5 Teriparatide- 14		-	-	-	Bone ALP Median (Interquartile Range) % change	Baseline- Alendronate-0 Teriparatide- 0 12 months- Alendronate-(-50) Teriparatide- (+50)	-
						Femoral neck BMD	Baseline-Alendronate-0 Teriparatide- 0 14 months- Alendronate-2 Teriparatide- 5.5							
						Total Hip BMD	Baseline-Alendronate-0 Teriparatide- 0 14 months- Alendronate-2 Teriparatide- 5.5					NTX Median (Interquartile Range) % change	Baseline- Alendronate-0 Teriparatide- 0 12 months- Alendronate-(-50) Teriparatide- (150)	
						Total Body Bone mineral Density	Baseline-Alendronate-0 Teriparatide- 0 14 months- Alendronate-2 .5 Teriparatide- 4							

4.	Effects of teriparatide on bone mineral density and bone turnover markers in Japanese subjects with osteoporosis at high risk of fracture in a 24-month clinical study: 12-Month, randomized, placebo-controlled, double-blinded	Akimitsu Miyauchi *et al*, 2010	NIL	-	-	Lumbar Spine L2-L4 BMD (% change) Femoral Neck Total Hip Fracture Occurrence Vertebral n(%) Non Vertebral n(%)	Placebo- 0.04± 4.34 Teriparatide-9.82±5.36 Placebo- 0.46± 3.89 Teriparatide-9.82±5.36 Placebo- -0.22± 3.38 Teriparatide-2.66±4.22 Placebo-4(6) Teriparatide-6(4.4) Placebo-4(6) Teriparatide-3(2.2)	P<0.001	NIL	-	-	PINP median(% change) CTX median(% change) Bone ALP	Baseline-Placebo-0 Teriparatide- 0 12 months- Placebo-25 Teriparatide- 75 Baseline- Placebo-0 Teriparatide- 0 12 months- Placebo-10 Teriparatide- 50 Baseline- Placebo-0 Teriparatide- 0 12 months- Placebo-(-30) Teriparatide- (-25)	<0.05 0.05 0.05
5.	A randomized, multicenter controlled trial to compare the efficacy of recombinant human parathyroid hormone (1-34) with elcatonin in postmenopausal women with osteoporosis in China.	Zhang Xiu-Zhen *et al*,2009	NIL	-	-	BMD % Increase L1-L4 Femoral Neck	rhPTH- 5.51% Elcatonin-1.55% rhPTH- 0.65% Elcatonin-0.11%	P<0.05	NIL	-	-	BSAP (mean % Change)- NTX/cr	rhPTH- 90 Elcatonin- 0 rhPTH- 55 Elcatonin- 0	-
6.	Comparison of parathyroid hormone (1-34) and elcatonin in postmenopausal women with osteoporosis: an 18-month randomized, multicenter controlled trial in China	Li Ying *et al*,2013	Pain Relief scores mean±Standard Deviation	Elcatonin group-1.55±0.74 Test group-1.66±0.75	P=0.3									

7.	Efficacy of Teriparatide in Increasing Bone Mineral Density in Postmenopausal Women with Osteoporosis – An Indian Experience	BK Sethi *et al*,2008	NIL	-	-	% Change in DXA Lumbar Spine BMD Femoral Neck BMD	Control- 1.06±4.81 Teriparatide- 6.58±6.50 Control- 2.12±5.92 Teriparatide- 1.97±4.25	P<0.05	Nil	-	-	BSAP Mean % Change Osteocalcin- Urinary DPD	Baseline- Control-0 , Teriparatide-0 6 months-Control-20.4 Teriparatide-108.3 Baseline- Control-0 , Teriparatide-0 6 months-Control-144.9 Teriparatide-280.3 Baseline- Control-0 , Teriparatide-0 6 months-Control-(-29.0) Teriparatide-180.9	P<0.05
8.	Comparison between recombinant human parathyroid hormone (1-34) and elcatonin in treatment of primary osteoporosis	Yan Yang *et al*,2015	Nil	-	-	Bone Mineral Density L2-L4 g/cm^2 Femoral Neck	Control-0 Teriparatide-0.1 Control-0 Teriparatide-0.1	P<0.05	Nil	-	-	BSAP(microgram/Litre) uCTX(microgram?mmol)	Control-0(-25) Teriparatide- 25 Control-50 Teriparatide- 600	P<0.05

Results of literature selection process

The initial search yielded 219 entries in PubMed database, Google scholar and Cochrane library. Excluding all animal studies, case series, case reports, systematic review and duplicate studies, 20 articles were human clinical trials. Out of this, the total of 15 articles were selected after reviewing the titles and abstracts. 2 articles were excluded after full-text review. A final selection of 13 articles, were made (Figure 1).

RESULTS

The selected 13 studies compared teriparatide to either placebo or another anti-resorptive drug. Out of the 13, 8 studies were done to evaluate the improvement and healing of bone in Osteoporotic patients whereas 5 studies were done on improvement in fracture healing (Figures 2 and 3). The studies evaluated outcome parameters such as Clinical and Radiological improvement, Biomarkers of Bone resorption and formation and Safety.6 studies assessed clinical parameters, 12 studies assessed radiological parameters,7 studies assessed biomarkers, 11 studies assessed safety parameters by means of occurrence of any adverse effects (Figure 3). All the 8 studies done on osteoporotic patients showed a good improvement. Of the 5 studies on fracture healing (Figure 4), only 2 studies showed beneficial effects while the other 3 did not show any benefits (Figure 5).

DISCUSSION

This Systematic review provides a summary of the clinical evidence for the efficacy of teriparatide for treating individuals with Osteoporosis as well as for healing of fractures. The 13 selected trials used teriparatide injections to treat fractures as well as Osteoporosis.

8 trials conducted were on osteoporotic individuals. 5 studies were on healing of fractures. There were different outcome parameters assessed in these studies. 6 studies assessed clinical parameters, 12 studies assessed radiological parameters, and 7 studies assessed Biomarkers. Out of the 13 studies, 11 studies assessed safety parameters by the occurrence of adverse side effects except studies by BK Sethi *et al.* in

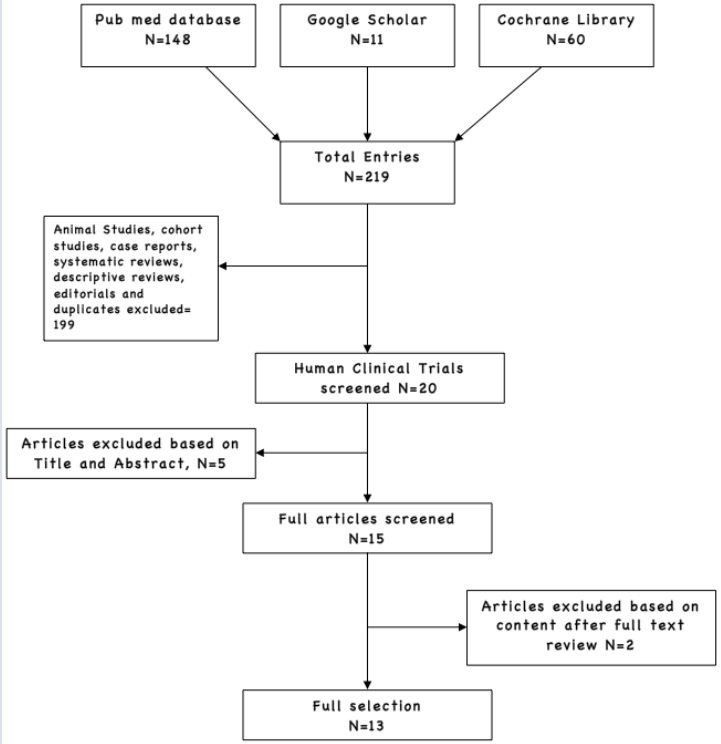

Figure 1: Search flowchart.

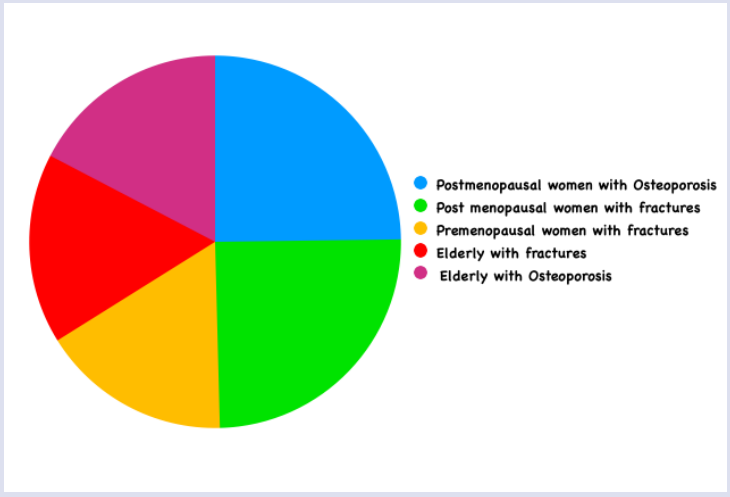

Figure 2: Nature of sample population.

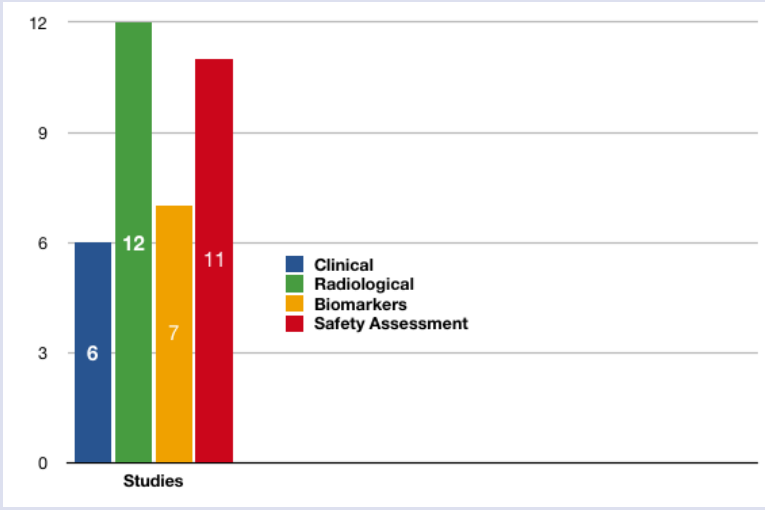

Figure 3: Parameter assessed.

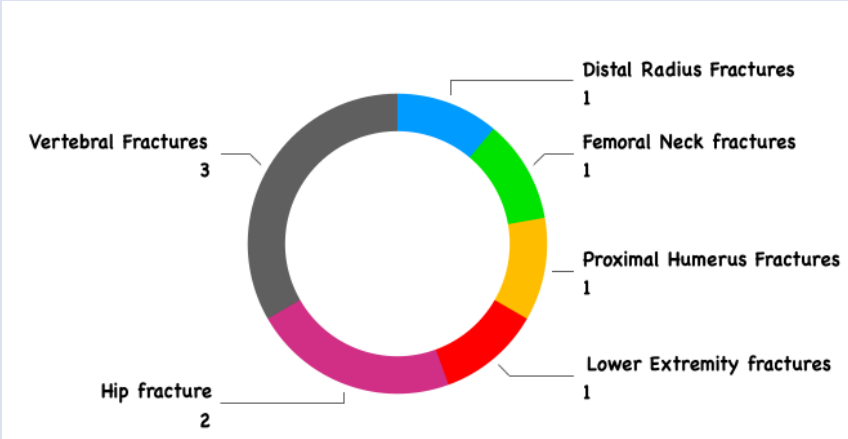

Figure 4: Type of fracture.

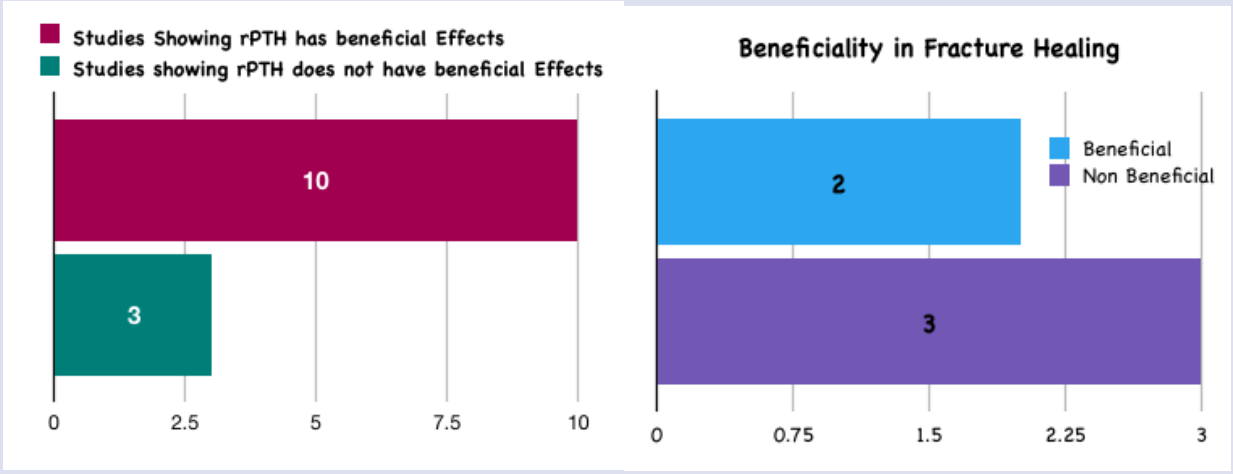

Figure 5: Based on beneficiality.

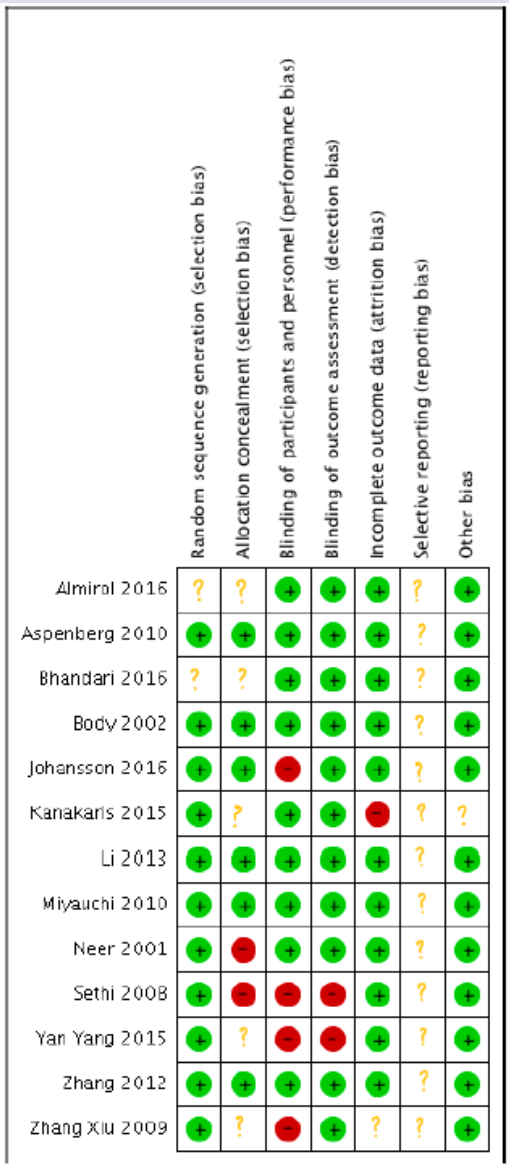

Figure 6: Risk of bias.

osteoporotic patients and Nikolaos K Kanakaris *et al.* in healing of hip fracture in elderly. All the 8 studies done on osteoporotic patients were effective whereas out of 5 studies in healing of fractures, 2 were beneficial whereas 3 were non beneficial. This could mean that Teriparatide may be a potential viable therapy for the treatment of osteoporosis, however, it lacked the effectiveness for healing fractures. None of the studies reported any serious side effects associated with the use of teriparatide. The most common side effects that the patients experienced were nausea, Gastrointestinal disturbances, occasional headaches.

6 of the 8 studies done in Osteoporotic individuals evaluated biomarkers such as ,CTX-1(serum C-telopeptide of type 1 collagen),BSAP(Bone specific Alkaline phosphatase),urine N-telopeptide of type I collagen, bone NTX (N telopeptides corrected for creatinine),P1NP(serum N-terminal propeptide of type 1 collagen),BSAP,osteocalcin and found significant differences. 1 study evaluated only clinical parameter and found significant reduction in pain relief scores whereas 7 of the studies evaluated radiological improvements and observed a significant improvement in Bone mineral Density.

In fracture healing, Bhandari *et al.*[15], Kanakaris *et al.*[16] and Johansson *et al.*[17] did not find any significant improvement with the usage of teriparatide. Mohit Bhandari *et al.* studied whether teriparatide 20 microgram injection could improve femoral neck fracture healing and found that there was no significant difference between the groups in radiographic evidence of healing, further they also found that there were no differences in patients who required revision surgeries to potentiate healing. Thus, Teriparatide did not decrease the risk of revision surgery or improve fracture healing. Similarly, Johansson *et al.* and kanakaris in their study did not observe an improvement in clinical parameters such as Level of Pain or the DASH score in treated patients when compared to the control group.

2 of the authors, Per Aspenberg *et al.* and Almirol *et al.*, in their study found significant improvements in teriparatide treated group in healing of fractures. Per Aspenberg *et al.* in their study assessing efficacy of 20 microgram and 40 microgram teriparatide for treating distal radial fractures observed a significant difference between the placebo group and teriparatide group in clinical parameters –PRWE score as well as improvement in grip strength in patients treated with Teriparatide.[18] The time to radiographic healing was shortened in the teriparatide group when compared to placebo group. However, time to radiographic healing was not statistically significant. Similar results were obtained by Almirol *et al.* who evaluated the effects of teriparatide versus placebo to treat lower extremity stress fractures and observed a significant improvement in Tibial cortical Area and thickness in patients treated with teriparatide. They also assessed biomarkers such as serum ALP, serum P1NP, serum osteocalcin, serum CTX, urine NTX. However, significant differences were observed only in serum P1NP and serum osteocalcin.[19]

In osteoporotic individuals, all studies showed beneficial results. Some had very significant improvements compared to others.Neer *et al.* in his study observed that women with postmenopausal osteoporosis showed reduction in risk of new vertebral(RR 0.35,95% CI 0.22-0.55) and non vertebral fracture (RR 0.47, 95% CI 0.25-0.88) fracture after treatment with teriparatide 20 microgram compared with placebo for a median of 21 months.[20] The Study by Miyauchi *et al.* supported the concept of "Anabolic Window" with teriparatide therapy, which was characterized by a rapid and an early increase in P1NP-markers of Bone formation followed by an associated increase in markers of bone resorption. (serum CTX). Other studies by L. Zhang *et al.*, Body *et al.*, Neer *et al.*, Zhang Xiu-Zhen, Li Ying and Sethi *et al.* assessed Bone mineral density following treatment with Teriparatide in post menopausal women with osteoporosis and found significant improvement in BMD.[21-25]

The exact cellular mechanisms that is responsible for the anabolic impact of teriparatide on bone is not fully known. Dobnig and Turner stated that intermittently administered parathormone enhances bone formation by possibly increasing the number of osteoblasts and their activity. In their study they found that after infusion of thymidine to label all cells progressing through mitosis during treatment, it was found that almost all osteoblasts induced by parathormone were unlabeled in 16 month old rats.[5] Based on this, they postulated that the increased number of osteoblasts seen is due to the activation of resting bone lining cells to become mature osteoblasts. Similar results were obtained by other researchers like Li *et al.*, Watson *et al.*.[26,27] This view was further supported by Leaffer *et al.* who found ultra structural evidence consistent with thee previous studies.[28]

Jilka *et al.* stated that intermittent parathormone could also postpone osteoblast apoptosis. The mitogenic effect may be mediated by induction of potent mitogens for osteoprogenitor cells such as Transforming growth factor β (TGF β) and Insulin like growth factor-1 (IGF-1).[29] This hypothesis was further substantiated by experiments by Watson *et al.* Okazaki *et al.* postulated that teriparatide acted in an autocrine and paracrine fashion and thereby improved callus formation and played a huge role in regulating chrondrocyte differentiation.[30] In addition, Nakazawa *et al.* in their study showed that PTH had an additional effect on mesenchymal (chondroprogenitor) cells by stimulating their proliferation and increasing their recruitment into the chondrocyte lineage. As a result, a higher proportion of progenitor cells achieved full osteoblast differentiation.[31]

Thus, the present review was undertaken to evaluate the efficacy of teriparatide in bone healing. Our aim was to search for the best possible evidence available with respect to teriparatide in bone regeneration and healing in different clinical scenarios and compile them together in a systematic manner to provide more clarity regarding the usage of teriparatide. Invitro studies are also being done at present for bone regeneration in rabbit and rats for their potential use in periodontal and other dentoalveolar conditions. Quality assessment of the 13 selected randomized control trials were carried out. Criteria like Selection bias, Performance bias, detection bias, attrition bias, reporting bias was taken into consideration. Out of the 5 studies done in healing of fractures, 2 studies showed high risk of bias, 2 studies showed moderate risk of bias and 1 study showed low risk of bias. Out of the 8 studies on osteoporosis, 4 studies showed low risk of bias, 2 studies showed moderate risk of bias and 2 studies showed a high risk of bias (Figure 6).

Based on this systematic review, Teriparatide seemed to be beneficial to treat osteoporosis. However, human trials in fractures have yielded conflicting results. The main limitation of this systematic review is that the unpublished data were not included. There is wide heterogeneity with respect to the study population and therefore the possibility of a meta analysis is ruled out. Some studies have favored the use of teriparatide while others have not found any benefits. More high quality clinical trials following similar comparison protocol is essential in order to analyze the efficiency by means of a meta analysis.

CONCLUSION

Teriparatide could have beneficial effects in bone healing in osteoporotic patients. However, the results are inconclusive whether they have beneficial effects in treating fractures. More Homogenous Randomized control trials are required to ascertain whether teriparatide could improve bone healing.

CONFLICTS OF INTEREST

None.

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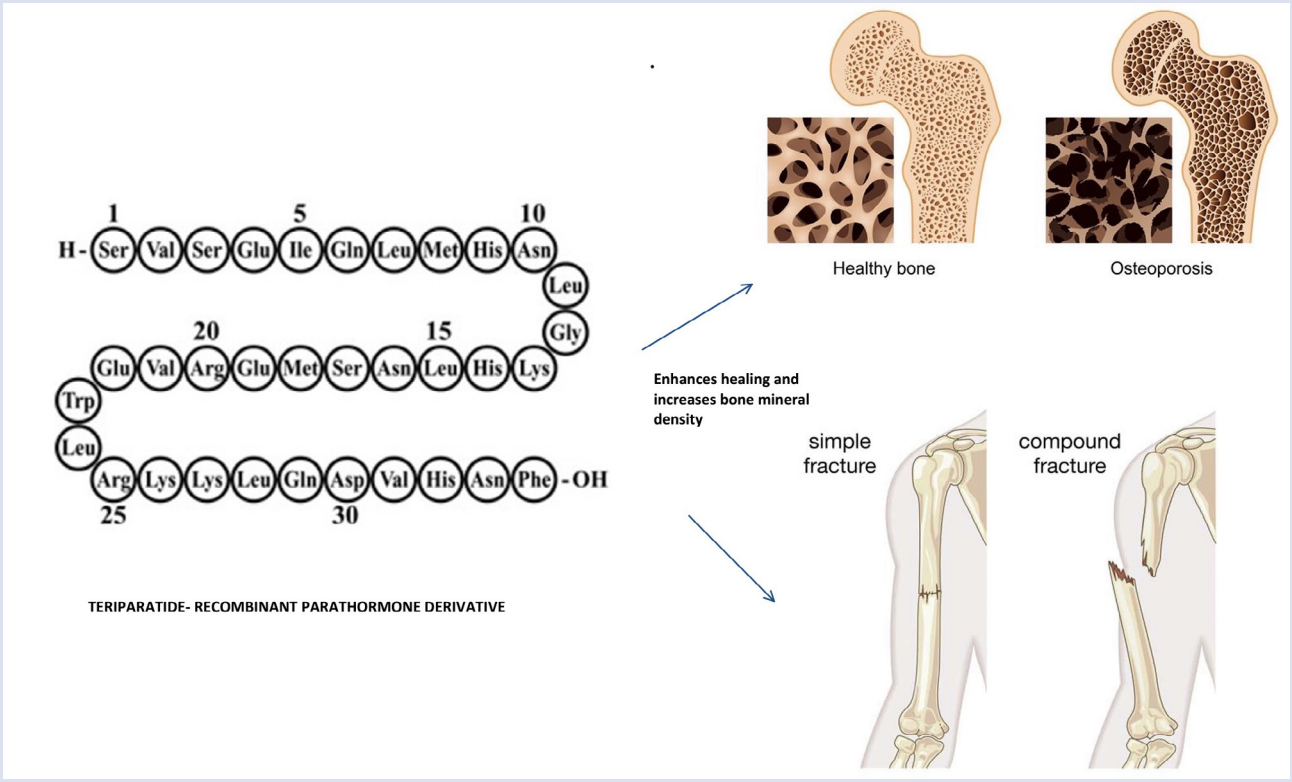
GRAPHICAL ABSTRACT



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