REVIEW

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Treatment of bone disorders with parathyroid hormone: success and pitfalls

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Received January 14, 2016, accepted March 31, 2016

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Pharmazie 71: 427–433 (2016) *doi: 10.1691/ph.2016.6008*

Bone diseases such as osteoporosis, osteoarthritis, bone tumours and bone fractures are rather common and not just in the elderly. Parathyroid hormone (PTH) is responsible for maintaining calcium homeostasis, increasing bone mineral density (BMD), increasing cortical and trabecular bone thickness and thus increasing bone strength. Teriparatide (PTH 1-34) has the same effects as endogenous PTH and is pharmacologically used to treat bone diseases such as osteoporosis, osteoarthritis, bone fractures and bone tumours. This review discusses how PTH 1-34 plays a role in managing bone diseases. Clinical studies have shown that short or intermittent dosing of PTH 1-34 has minimal adverse effects, while long-term dosing (over two years) has been linked to *de novo* osteoarthritis and bone deformation. Currently PTH therapy is only approved in the treatment of post-menopausal osteoporosis, however it is also proven to have effects in treating osteoarthritis, bone tumours and bone fractures. If the patient undergoing therapy is closely monitored, the major pitfalls are very unlikely to take place, thus it is highly recommended that patients be closely monitored by a medical practitioner.

1. Introduction

Bone diseases are a major health issue worldwide. There is a variety of notable bone diseases such as multiple myeloma, osteoporosis, osteoarthritis and bone fractures (Bruyère et al. 2014). Endogenous parathyroid hormone (PTH) is responsible for maintaining calcium homeostasis. It also increases BMD, cortical and trabecular thickness, and bone strength (Orth et al. 2014a). Exogenous PTH increases BMD of subchondral bone and subarticular sponginosa, chondrocyte level, cluster formation, thickness of calcified cartilage layer, and enhances articular cartilage repair (Orth et al. 2014a). PTH is shown to be beneficial in the treatment of osteoporosis, osteoarthritis and bone fracture reduction in the elderly. In addition, some trials have shown the shrinkage of bone tumours (Pennisi et al. 2010). Besides teriparatide, a peptide based on the active region of PTH, there are other treatment options for the above bone diseases which include bisphosphonates, calcium supplements, denosumab, selective oestrogen receptor modulators (SERMs) and strontium. These effects are summarised in the Fig.

2. Bone diseases treated with PTH

Osteoporosis is a skeletal disease described as weakened bone which results in increased risk of fractures (Drake et al. 2015). The likelihood of fractures can be correlated to a decrease in bone mineral density (BMD) and an imbalance in bone remodelling in which bone resorption surpasses bone formation. It is most prevalent in people aged 50 years and above, especially in post-menopausal women due to diminishing oestrogen levels. Oestrogen increases viability of osteoblasts. It also usually involves the inhibition of receptor activator of nuclear factor kappa β ligand (RANKL) to prevent osteoclast activity. Hence low oestrogen levels will promote osteoclastogenesis and lead to bone resorption. Osteoarthritis is a disease of the bone that involves the bone plate and subchondral bone (Lajeuness 2004). It is thought to be caused by abnormal cell metabolism which leads to enhanced remodelling of subchondral bone. As a consequence, there is cartilage loss or damage. Damage repair is attempted by the body, but if this repair process fails, osteoarthritis may result. Patients with osteoarthritis are shown to have low PTH stimulation as a result of an abnormality in the PTH receptors within the osteoarthritic cells. This decrease in PTH within the osteoarthritic cells has been shown to cause subchondral bone sclerosis, leading to osteoarthritis. Osteoarthritis is most prevalent in people over 45 years of age; however the younger population can also be affected. Osteoarthritis develops gradually over time. Some risk factors include being overweight, increased age, previous joint injury, joints that have not formed properly, genetic predisposition, and also stress to the joint incurred from occupation or hobbies. When PTH was given to patients at a dose of 10 microgram per kilogram of bodyweight daily for six weeks, a significant increase in bone formation and thickness of hyaline cartilage was observed (Sondergaard et al. 2009).

Bone fractures occur when trauma occurs at the bone causing it to break. Bone remodelling will naturally begin to repair the bone damage (Pennisi et al. 2010). Bone remodelling functions best in early life and starts to deteriorate upon ageing. In the elderly population, bone resorption occurs at a higher rate as compared to bone formation. This decreases bone strength and leads to bone fractures. PTH 1-34 retards this process and in some cases, eliminates it by increasing serum calcium concentrations and increasing BMD (Orth et al. 2014a). Consequently, the bone thickens and becomes less fragile, decreasing the risk of fractures.

Bone tumours are caused by stimulation of osteolytic bone disease which can result in multiple myeloma (Pennisi et al. 2010). Growth

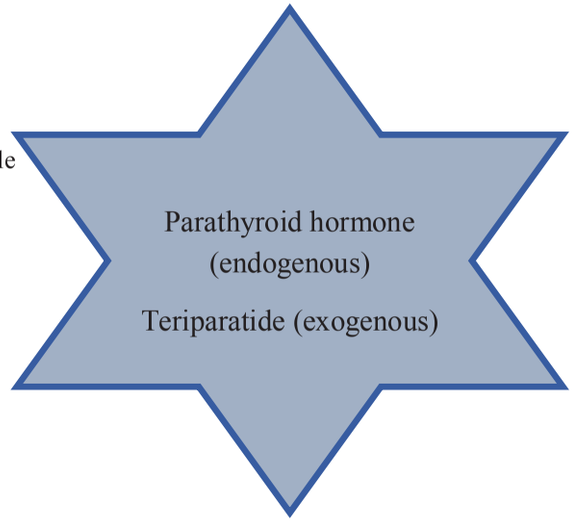
Abbreviations:
ABD, adynamic bone disease, *BMD*, bone mineral density, *BRONJ*, bisphosphonate-related osteonecrosis of the jaw, *CaSR*, calcium-sensing receptors, *CKD*, chronic kidney disease, *ESRD*, end-stage renal disease, *IGF-1*, insulin-like growth factor 1, *P1NP*, amino-terminal propeptide of type 1 procollagen, *PTH*, parathyroid hormone, *PTH 1-34*, Teriparatide, *SERMs*, selective oestrogen receptor modulators, *N-BPs*, nitrogen-containing bisphosphonates, *non-N-BPs*, non-nitrogen-containing bisphosphonates, *RANKL*, receptor activator of nuclear factor kappa β ligand, *ROD*, renal osteodystrophy.

Cost:

- Overall the cost effectiveness of PTH 1-34 treatment shows that for an extra $1226 dollars, 0.046 life-years are gained (Borgstrom et al. 2010)
- It also shows that PTH 1-34 treatment saves money due to decreased need for emergency department visits and other healthcare expenditure (Borgstrom et al. 2010)

Bone tumours:

- Bone tumours are thought to be caused by osteolytic bone disease, this can result in multiple myeloma for example (Pennisi et al. 2010)
- Growth and survival of tumour cells depend on osteoclasts (Pennisi et al. 2010)
- At low Ca^{2+} levels there is a high number of osteoclasts (Lajeuness 2004)
- PTH 1-34 increases serum Ca^{2+} levels and therefore decreases osteoclast level (Orth et al.



Mechanism of action:

- PTH maintains Ca^{2+} homeostasis, increases BMD, increases cortical and trabecular thickness and thus increases bone strength (Sondergaard et al. 2009)
- PTH 1-34 increases serum Ca^{2+} levels, increases BMD, increases chondrocyte level, increase thickness of calcified cartilage layer and increases cartilage repair (Lajeuness 2004)

Bone fractures:

- Occurs when damage is done to bone (Pennisi et al. 2010)
- As we age, bone remodelling deteriorates (Pennisi et al. 2010)
- PTH 1-34 helps prevent bone fractures by increasing serum Ca^{2+} levels and increasing bone thickness (Lajeuness 2004)

Osteoarthritis:

- A bone disease that affects joints via malformation of bone and destruction of cartilage (Sondergaard et al. 2009)
- PTH 1-34 treats osteoarthritis by increasing bone and cartilage thickness, and repairing cartilage damage (Lajeuness 2004)

Osteoporosis:

- A skeletal disease characterised by bone porosity increase (Drake et al. 2015)
- PTH 1-34 treats osteoporosis by increasing BMD and bone thickness to decrease fracture risk and increase bone strength (Lajeuness 2004)

Fig. : Major considerations in the clinical use of parathyroid hormone and teriparatide. The emphasis in this figure is on the positive attributes of use of this therapy for bone ailments.

and survival of cancer cells in the bone depend on the functioning osteoclasts by stimulating growth and protecting the cancer cell from apoptosis process. However, osteoblasts have a role in suppressing the growth of myeloma cell and it retards the stimulatory effects of osteoclasts. There is conflicting evidence on whether PTH treatment has a positive or negative effect on bone tumours. Most trials show that the brown or giant tumour cells get their nutrients from high concentrations of PTH (Cowana et al. 2011). Hence, an anti-PTH medication is administered instead of PTH treatment. This down-regulates the PTH receptors and has been shown to shrink the bone tumours (Mak et al. 2013; Esbirit and Alcaraz 2013).

3. Endogenous PTH

Endogenous PTH is a polypeptide consisting of 84 amino acids. The 1-34 N-terminal fragment is responsible for inducing biological activity (Wang et al. 2012). Teriparatide (PTH 1-34), a polypeptide containing 34 amino acids, was developed using recombinant technology. The parathyroid gland is stimulated to increase production of PTH (Drake et al. 2015). PTH will then stimulate bone resorption mediated by osteoclasts. As a result, serum concentration of calcium is increased (Yang et al. 2015). PTH also increases serum calcium levels by promoting renal calcium reabsorption (Augustine and Horwitz 2013).

4. Benefits of recombinant teriparatide (PTH 1-34) for bone treatment

PTH 1-34 can directly stimulate bone formation to treat osteoporosis (Liu et al. 2014). Anabolic effects on bone are observed when PTH 1-34 is given subcutaneously at intermittent and low daily doses of 20 µg within a period of 18 to 24 months (Miyauchi et al. 2008). This is further illustrated by the significance of the anabolic window. The anabolic window is described as a period in which bone formation exceeds bone resorption (Wang et al. 2012). Bone turnover markers are useful indicators associated with bone remodelling to predict future fracture risks (Farahmand et al. 2013). Examples of bone formation markers include alkaline phosphatase, osteocalcin and amino-terminal propeptide of type 1 procollagen (P1NP). They are predominant during the timeframe of the anabolic window. In comparison, accumulation of bone resorption markers is slower (Pazianas 2015). Thus, the anabolic window supports the rationale of limiting PTH 1-34 treatment to 18 to 24 months as bone turnover markers will deplete overtime, which result in no observable improvements in BMD.

PTH 1-34 enhances osteoblast survival and mediates osteoblast proliferation which is essential to produce insulin-like growth factor 1 (IGF-1) involved in bone development (Yang et al. 2015). Despite only being approved in the treatment of post-menopausal osteoporosis, PTH 1-34 has also been proven to have benefits in the treatment of osteoarthritis (Orth et al. 2013). After 6 weeks of PTH 1-34 treatment with 10 mg per kilogram of body weight daily, patients show an increase in calcium levels and BMD, and significant repair on hyaline cartilage. However, there were no changes in cartilage degeneration, no differences in synovial villi or inflammatory cell infiltrates, and no effect on apoptosis. Findings showed a major improvement in both macroscopic and microscopic cartilage repair.

Despite mostly positive results, it has also been shown that PTH 1-34 can also have negative outcomes (Sondergaard et al. 2009). Some cases have displayed that PTH 1-34 induced early osteoarthritic degeneration by excessively increasing BMD, causing cartilage calcification which resulted in cartilage degeneration (Orth et al. 2014a).

Besides treating osteoporosis and osteoarthritis, PTH 1-34 therapy has also been proven to help in reducing the rate of bone fractures in the elderly (Orth et al. 2013). This is achieved by enhancing BMD, increasing trabecular thickness and increasing serum calcium levels (Miyauchi et al. 2008). This results in stronger bones due to an increased bone mass (Farahmand et al. 2013). However in some cases, the risk of bone fractures can actually increase with excessive administration of PTH therapy, by means of 40 mg per kilogram of their body weight daily or more (Ichchou et al. 2010). This results in bone resorption and faulty remodelling, which in turn can cause fractures (Orth et al. 2013).

PTH has the ability to aid in management of bone cancer as it is shown to increase bone mass, bone formation, and decrease the progression of multiple myeloma (Pennisi et al. 2010). PTH also increases the synthesis of osteoblasts, however the synthesis of osteoclasts remains the same. However, in brown cell tumours and giant cell tumours, this evidence is conflicting as trials show that increased levels of PTH provide nutrients which allows tumour growth (Cowana et al. 2011; Mak et al. 2013; Esbirit and Alcaraz 2013).

5. Clinical trials involving PTH treatment

A randomised, double-blind controlled study was conducted on women aged 50 and above including post-menopausal women (Miyauchi et al. 2008). Results indicated that lumbar spine BMD improved when given PTH 1-34 at daily doses of 10 µg, 20 µg and 40 µg after 24 weeks. In addition, bone formation markers such as P1NP also increased during 4 to 24 weeks' treatment at the 20 µg dose. It has been shown that doses above 40 mg per kilogram of bodyweight daily for more than 20 weeks could cause renal failure (Orth et al. 2013). Another randomised trial involving men who had glucocorticoid-induced osteoporosis showed that P1NP marker increased after treatment with PTH 1-34 at 18 months (Farahmand et al. 2013). A trial conducted on middle-aged women with osteoarthritis showed major benefits with low dose treatment (10-20 mg per kilogram of body weight daily for 6 weeks) (Orth et al. 2013). The test group showed an increase in calcium levels, significant repair of hyaline cartilage, enhanced BMD, increased cluster formation and thickened calcified cartilage layer. Moreover, the chondrocyte numbers were much higher in the test group as compared to the control group (Orth et al. 2013, 2014a). However, there were no changes in collagen I formation, osteocyte levels, type II collagen formation and histological architecture. Overall the trial showed that calcium homeostasis was maintained. BMD, cortical and trabecular thickness had increased, which led to an increase in bone strength and reduced fracture and joint degradation. Another trial which comprised males and females between 50 and 60 years old included higher doses of PTH therapy (more than 40 mg per kilogram of body weight daily for 24 weeks) (Orth et al. 2014b). The trial concluded that this concentration of the medication induced early osteoarthritic degeneration due to the calcification of the joint cartilage and a BMD that stiffened the joint (Orth et al. 2014a).

6. Pitfalls of PTH treatment – adverse effects, contraindications, warnings and drug interactions

Pitfalls of PTH treatment include continuous administration, adverse effects caused by the drug, contraindications of the drug with particular diseases, drug interactions and also warnings with regards to the appropriateness of PTH administration. Continuous dose of PTH 1-34 predominantly leads to bone resorption, associated with increased levels of bone resorption markers (Augustine and Horwitz 2013).

A few studies (Lasco et al. 2011; Lindsay et al. 2009; Bashutski et al. 2010) have concluded that teriparatide treatment was well-tolerated by test subjects as evidenced by the high compliance rate towards treatment regime and low drop-out rates. Liver, renal function and full blood profile tests were conducted before and during treatment. The results showed that there were no observable changes in those areas. There was also absence of new fractures or adverse reactions after the treatment regime had initated. These indicated that PTH 1-34 was well tolerated. However, patients still experienced some minor adverse reactions which depended on concentration administered and duration of treatment. These effects included gastrointestinal, headache, dizziness, rash, palpitations, hypercalcaemia, hyperuricemia, leg cramps, rhinitis, tooth problems (at higher doses), infections, dyspnoea, vertigo and syncope (Linday et al. 2009; Bashutski et al. 2010; Yamamoto et al. 2014). Due to relatively high incidences of syncope after PTH

Table 1: Comparison of drugs used to treat bone diseases

Drug	Indication(s)	Successes	Pitfalls

Bisphosphonates (Ziebart et al. 2011; Monkonnen et al. 2006; Abrahamsen et al. 2010; Osborne et al. 2010; Meunier et al. 2009)
• Nitrogen-containing bisphosphonates
  • Zolendronate
  • Pamidronate
  • Risedronate
  • Ibandronate
• Non-nitrogen-containing bisphosphonate
  • Clodronate
	• Malignant bone tumour
	• Osteoporosis
	• Paget's disease
		• MOA :
		  • accumulating in the osteoclast cytoplasm and causes cell death. This leads to disturbed remodelling of the bone.
		  • prevents angiogenesis
		  • inhibits cells proliferation
		• N-BPs are more potent than non-N-BPs
		• Significantly reduces pain, hypercalcaemia events, fractures risk
		• Improves quality of life
			• High incidence of developing BRONJ in patients treated with bisphosphonates
			• Common side-effects with bisphosphonates: diarrhoea, esophagitis, oesophageal erosion
			• Rare side-effects: Steven Johnson syndrome, toxic epidermal necrolysis
			• Increases risk of developing venous thromboembolism (VTE)
			• Long-term treatment with bisphosphonates causes inhibition of both bone resorption and bone formation markers

Calcium (Heaney et al. 2010; Thomas et al. 2008; Bolland et al. 2014; Kuehn 2013) • Examples • calcium citrate • calcium carbonate	• Postmenopausal osteoporosis • Fracture prevention	• Increases BMD • Decreases serum PTH • Decreases bone resorption • Decreases fractures	• Gastrointestinal effects such as abdominal bloating, constipation • Hypercalcaemia • Cardiovascular events
Denosumab (Goessl et al. 2012; Ford et al. 2013; Scott 2014; Peddi et al. 2013)	• Bone fractures • Bone tumours • Postmenopausal osteoporosis	• Blocks RANK ligand • Stimulates osteoclast differentiation and function, promotes osteoclast survival • Decreases bone resorption • Increase BMD and bone mineral content • Increases bone mass and strength	• Hypocalcemia • Nephrotoxicity • Osteonecrosis of the jaw • Seizures • Atypical femoral fractures • Delayed healing of bone fractures • Anaphylaxis
Raloxifene (SERM) (Wooltorton 2006; Bjarnason et al. 2001; Meunier et al. 1999; Poiana et al. 2006)	• Bone fracture • Osteoporosis	• Selective oestrogen receptor modulator with oestrogenergic agonistic effects on bone and lipid metabolism and antagonistic effects on the breasts and uterus • Increases BMD • Decreases bone resorption • Increases bone formation	• Stroke • Hot flushes • Venous thromboembolism • Cardiovascular events
Strontium (Osborne et al. 2010; Meunier et al. 2009; Quesada-Gomez et al. 2011; Rizzoli et al. 2012; Li et al. 2007)	• Postmenopausal osteoporosis • Painful bone metastases	• Inhibits breakdown of bone and promotes bone development • Reduces risk of vertebral and non-vertebral fracture • Increases bone mineral density within 3 months of treatment and which continues up to 2 years • Long term treatment with strontium has been shown to increase bone formation markers and decreases bone resorption markers • Reduces the pain score and reduces the number of bone metastases • Maximal benefits of treatment can be seen after 4 months of treatment	• Not as effective as PTH therapy as evidenced by bone formation markers • Bone formation effects of strontium is slower than PTH • Concentration of bone formation marker is lower compared to PTH • Common side-effects: • Nausea, headache, increases serum calcium level, pruritic rash • Incidence of developing VTE within 1 year of treatment is higher than placebo • A significant decrease in bone formation markers were observed within 3 months of treatment cessation. This indicates that effects of strontium are reversible

Drug	Indication(s)	Successes	Pitfalls
Teriparatide (Pennisi et al. 2010; Lejeuness 2004; Orth et al. 2013; Yang et al. 2015; Miyauchi et al. 2008; Lindsay et al. 2009; Bashutski et al. 2010; Yamamoto et al. 2014)	• Postmenopausal osteoporosis • Osteoarthritis • Bone fractures • Bone tumours	• Anabolic effects on bone at low, intermittent dose (20µg) within 18-24months of treatment • Increases BMD • Increases osteoblast survival and proliferation • Repairs hyaline cartilage • Increases trabecular thickness and bone mass • Decreases multiple myeloma progression	• Continuous dose leads to catabolic effects on bone • Gastrointestinal effects, headache, dizziness, rash • Hypercalcaemia, hyperuricaemia • Contraindicated with concurrent medical conditions such as cardiovascular, renal, hyperparathyroidism, hyperuricaemia, and Paget's disease • Drug interactions with digoxin, bisphosphonates and calcium

administration, it was recommended that patients be seated when undergoing the injection (Yamamoto et al. 2014).

Trials have concluded that PTH 1-34 treatment for over two years results in a build-up of antibodies against teriparatide, which diminishes subsequent efficacy (Yamamoto et al. 2014). More dangerous adverse effects are associated with high dose PTH therapy, most notably the growth of brown cell and giant cell tumours, as well as early induced osteoarthritic degeneration (Orth et al. 2014a). There is a variety of contraindications of PTH therapy (Esbitir and Alcaraz 2013). For example, hypercalcaemic patients have an increased risk of bone resorption. Children and adolescents are not recommended to undergo PTH therapy. Although there are low incidences of problems in some patients, trials have shown that pregnant and lactating women are generally fine to take PTH. It is not recommended to go through PTH treatment for people who have previously undergone radiation therapy, specifically if this treatment took place for a long period of time and has been shown to have an effect on the person's bone structure or formation. People with hyperparathyroidism should avoid PTH treatment due to an increased risk of fracture and faulty bone formation from high serum levels of PTH. Patients with Paget's disease of the bone, gout or high serum uric acid concentration should not be treated with PTH either.

Drug interactions with PTH therapy include digoxin, bisphosphonates and calcium supplements (Bruyère et al. 2014). Calcium supplements may be potentially concerning as high serum concentrations of calcium can result in bone resorption, which in turn, result in the faulty formation of bones causing intense pain and loss of quality of life of the patient. Chronic kidney disease (CKD) patients are likely to develop renal osteodystrophy (ROD) with prolonged usage (Cejka et al. 2010; Miller et al. 2007). Teriparatide has been used to counteract the effect of PTH deficiency in ABD patients to improve their BMD (Cejka et al. 2010). According to their result, treatment with teriparatide effective in increasing BMD in the lumbar spine and femoral neck in CKD patient with serum PTH level below normal range. However, this study demonstrated that the increase in BMD may not be significant in CKD patients receiving higher doses of PTH.

7. Comparison of available drug treatments for bone disease – bisphosphonates versus PTH therapy

Drug treatments for bone disease include bisphosphonates, calcium supplements, denosumab, selective oestrogen receptor modulators (SERMs) and strontium. PTH therapy takes place as a second-line treatment for those who do not respond to other treatments (Reginster et al. 2014). PTH is approved for treatment of post-menopausal osteoporosis, and is being tested for treatment of other bone diseases like osteoarthritis, bone fractures and multiple myeloma (Orth et al. 2014a; Pennisi et al. 2015; Augustine and Horwitz 2013). Raloxifene is a SERM used in post-menopausal women to prevent post-menopausal osteoporosis (Esbirit and Alcaraz 2013).

Bisphosphonates are a class of drug that is used to treat bone disease such as Paget's disease, bone tumours and postmenopausal osteoporosis (Mönkönnen et al. 2006). As listed in the **Table**, bisphosphonates can be further divided into two subclasses according to their mechanism of action which includes nitrogen-containing (N-BPs) and non-nitrogen-containing bisphosphonates (non-N-BPs) (Reginster et al. 2014). Non-N-BPs are less potent than N-BPs because they do not contain nitrogen atoms in their structures (Mönkönnen et al. 2006). BPs are metabolised to cytotoxic analogues of ATP. These metabolites can cause cell death by accumulating in the cytoplasm. An example of non-N-BPs is clodronate. Non-N-BPs do not inhibit farnesyl pyrophosphate synthase (FPP synthase). N-BPs inhibit FPP synthase. Inhibition of these enzymes leads to osteoclasts that are unable to perform their normal functions and eventually lead to the death of the osteoclasts. Examples of N-BPs are zoledronic acid and risedronate. However, the use of bisphosphonates have been shown to cause bisphosphonate-related osteonecrosis of the jaw (BRONJ) (Kakehashi et al. 2015). This severe side-effect is not a rare event. In this study, more than 50% of the test subjects developed BRONJ. The trigger of BRONJ is tooth extraction. Patients that developed

BRONJ and received teriparatide showed an improvement in complications, with complete cure in BRONJ symptoms within 12 months. Teriparatide works by promoting osteoblast synthesis, decreasing osteoblast cell death, and thus promoting bone formation. The improvement in BRONJ depended on which bisphosphonate the test group was taking. Test subjects that took risedronate or minodronate had a slower improvement than test subjects that were taking alendronate. This was because the percentage of nitrogen in risedronate and minodronate was higher compared to alendronate. Therefore, they exhibit stronger inhibition activity on osteoblasts which results in a longer recovery period.

8. Conclusion

In conclusion, PTH treatment and recombinant teriparatide treatment are beneficial in the management and prevention of osteoarthritis, osteoporosis and bone fracturing. There is little evidence to indicate whether bone tumour treatment with PTH therapy is efficacious. Despite evidence of both positive and negative effects of PTH treatment, it is fair to acknowledge that the benefits outweigh the risks (Soriano et al. 2014; Appelman-Dijkstra and Papapoulos 2014). It is important to recognise that some patients on medications or have existing health conditions will react differently to PTH therapy. The major pitfalls are shown in patients who already have other conditions such as cardiovascular or renal complications, and bone disorders such as Paget's disease of the bone that are contraindicated with PTH administration (Tezval et al. 2010; Cejka et al. 2010; Miller et al. 2007; Moe et al. 2006). Minor complications like worsening of osteoarthritis or induced osteoarthritis are not common at low doses but occur at higher doses instead (more than 40 mg per kilogram of body weight daily over 20 weeks) (Orth et al. 2013; Tezval et al. 2013). If the patient undergoing therapy is closely monitored, the major pitfalls are very unlikely to take place, thus it is highly recommended that patients undergoing either PTH or recombinant teriparatide treatment be closely monitored by a medical practitioner.

Acknowledgement: CRD is supported by an institutional Academic50 grant.
Conflict of interest: The authors have none to declare.

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