Formosan Journal of Musculoskeletal Disorders 2 (2011) 113–117

Contents lists available at SciVerse ScienceDirect

Formosan Journal of Musculoskeletal Disorders

journal homepage: www.e-fjmd.com

Review Article

Parathyroid hormone for osteoporosis treatment

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ARTICLE INFO

Article history:
Received 1 August 2011
Received in revised form
14 September 2011
Accepted 14 September 2011
Available online 6 November 2011

Keywords:
fracture healing
osteogenesis
osteoporosis
parathyroid hormone

ABSTRACT

Osteoporosis may cause disastrous fractures and is a great threat to old people. Different medicines, including calcitonin, selective estrogen receptor modulators (SERM) and bisphosphonates, have been developed to treat the condition. In contrast to these bone resorption antagonists, parathyroid hormone (teriparatide) which works through the regulation of calcium and phosphate metabolism can increase bone deposition. Patients given teriparatide (20 μg) daily for 2 years experienced a significant increase in hip bone bone mineral density (BMD) of 3.5% and 3.9% after 1 and 2 years, respectively, as well as a significant increase in vertebra BMD of 7.2% and 10.9% after 1 and 2 years, respectively. Teriparatide treatment also reduced the risk of one or more new vertebral fractures in postmenopausal women with osteoporosis by 65% and the risk of multiple new vertebral fractures by 77%. Furthermore, teriparatide resulted in a 53% decrease in the risk for nonvertebral osteoporotic fractures and a 90% decrease in moderate or severe new nonvertebral fractures. Compared to alendronate, 12-month treatment with teriparatide resulted in greater increases in femoral neck and total hip BMD. Also, patients treated with teriparatide tended to be at lower risk of nonvertebral fractures, 4.1% in the teriparatide group versus 13.7% in the alendronate group. If there is a need to switch from bisphosponates to teriparatide, a 6-month interval is recommended to prevent interference with the osteogenic effects of teriparatide. Other effects of teriparatide, including stimulation of bone healing and osteoconduction in porous joint replacement materials that may be extensively applied to orthopedic clinical practice, warrant further studies and confirmation.

1. Introduction

After two centuries of dynamic development in osteoporosis medical treatments, currently a variety of drugs are available to patients. However, all of these agents are antiresorptive drugs, including estrogens, selective estrogen receptor modulators such as raloxifene, and bisphosphonates such as alendronate, risedronate, ibandonate and zoledronate. Although these drugs act on different signal transduction pathways, their ultimate effects are focused on inhibiting osteoclast-mediated bone resorption. Recent studies on osteoporosis treatments have turned to the development of new-generation drugs that promote new bone formation. Such new drugs, called osteogenic stimulators, include the complete human recombinant parathyroid hormone (hrPTH 1-84), and the human recombinant parathyroid hormone peptide 1-34, teriparatide (Lilly, Indianapolis, IN, USA) (Fig. 1). This article presents the results of a thorough literature review on teriparatide, with a focus on its major effects and safety shown by clinical trials.

2. Parathyroid hormone

Parathyroid hormone (PTH) is produced by the parathyroid gland and aids in the regulation of calcium and phosphate metabolism (Fig. 2). Human PTH affects calcium and phosphate metabolism in the bones and kidneys. Upon a decrease in blood calcium, PTH stimulates multiple pathways to raise the calcium level, including stimulating bone resorption (osteoclasis) which releases extra calcium from the bone, reducing renal calcium excretion, increasing renal phosphate excretion, and promoting bioactive vitamin D production by the kidney which enhances calcium and phosphate absorption by the small intestines.[1] The net effect on the bone is to stimulate the bone remodeling cycle of osteogenesis1 and osteoclasis.

If the body continues to produce excess PTH, such as in patients with primary hyperparathyroidism, this will result in faster bone resorption than bone formation, leading to deterioration of osteoporosis. However, even in patients with primary hyperparathyroidism,

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2210-7940/$ – see front matter
doi:10.1016/j.fjmd.2011.09.001

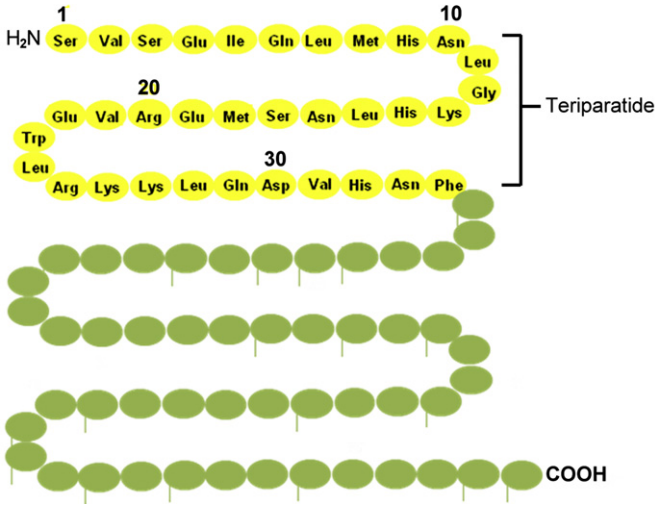

Fig. 1. Human recombinant parathyroid hormone (hrPTH 1-84) and human recombinant parathyroid hormone peptide 1-34 (teriparatide).

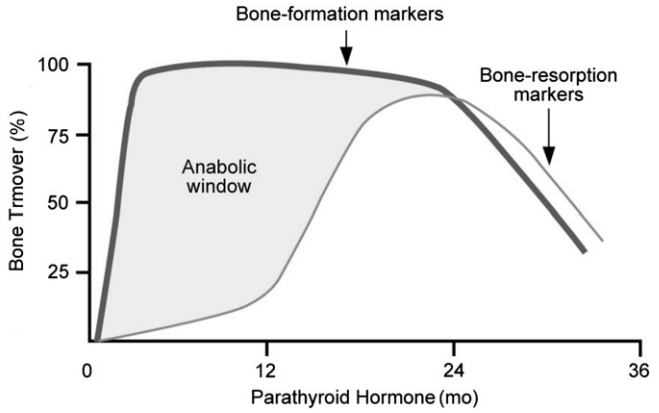

Fig. 3. During parathyroid hormone treatment, bone-formation markers peak first, followed by bone-resorption markers.

some studies have suggested that PTH still provides a degree of protection on the cancellous bone.[2–4] Besides, as a result of some mechanism that is not yet fully understood, intermittent low-dose PTH causes the rate of osteogenesis to surpass osteoclasis, hence strengthening bone mass and microstructure and improving osteoporosis. Biomarker studies have shown that intermittent PTH stimulation results in a rapid rise in bone-formation markers, followed by a rise in bone-resorption markers. The temporal sequence of such increases, called the "anabolic window" (Fig. 3), suggests that the effects of PTH stimulation on the bone remodeling cycle begin with new bone formation, followed by bone resorption. In this window, PTH plays a role in stimulating osteogenesis.[2,3]

Other studies have observed such rapid osteogenesis caused by intermittent PTH.[5,6] In a study that obtained paired bone biopsies from patients, quantitative backscattered electron imaging (qBEI) was adapted to evaluate bone mineralization of the iliac crest before and after PTH treatment. The results revealed little change in calcium concentration after the parathyroid treatment but significant increase in heterogeneity of mineralization, which represented a higher percentage of newly formed bone matrix of lower mineral density stimulated by PTH. Furthermore, an animal study has suggested that PTH stimulated formation of the bone matrix with incomplete mineralization, resulting in a broadened peak of calcium concentration.[7]

Both PTH and PTH analogues bind on G-protein-dependent receptors on osteoblasts and renal tubular cells to conduct signal transduction that activates protein kinase C and phospholipase C. These signal transduction pathways increase the number of activated osteoblasts, suppress apoptosis in osteoblasts, attract bone-lining cells, and ultimately increase bone strength, bone mass and bone diameter, as well as stabilize bone structure.[8]

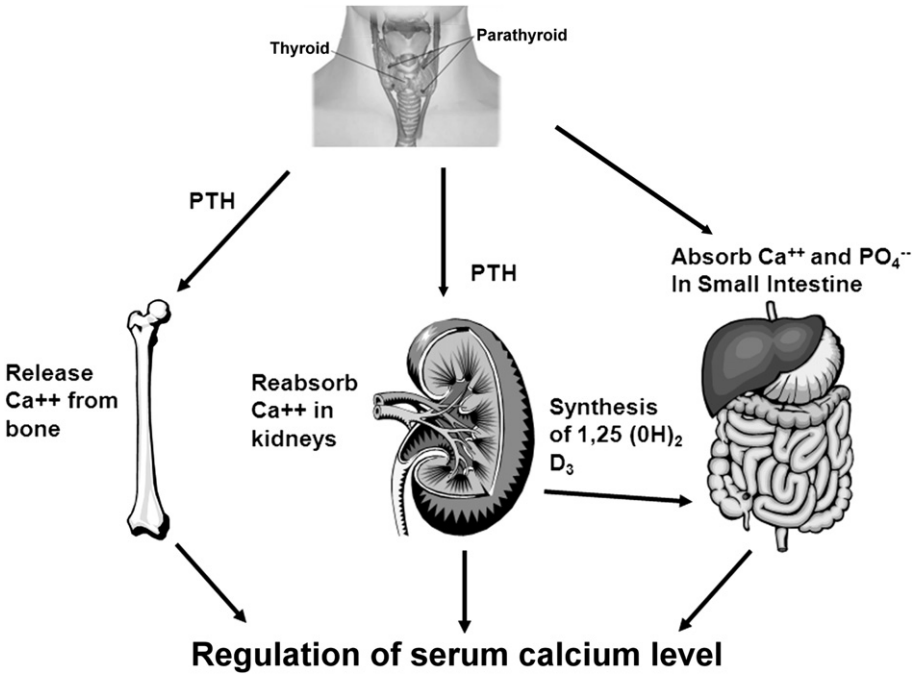

Fig. 2. Role of parathyroid hgormone (PTH) in regulating the balance in calcium and phosphate metabolism.

3. Clinical studies on postmenopausal women with osteoporosis

In a study on 60 patients who had received antiresorptive agents, but experienced fractures as a result of side effects or therapeutic ineffectiveness, subjects were given teriparatide (20 μg) daily for 2 years to evaluate the effect of teriparatide on bone mineral density (BMD).[9] After 1 and 2 years of treatment, there was a significant increase in the patients' hip bone BMD by 3.5% and 3.9%, respectively, as well as a significant increase in vertebra BMD by 7.2% and 10.9%, respectively.

In addition, in the Fracture Prevention Trial study, the effects of different teriparatide doses on the incidence of osteoporosis-induced fractures were compared. This large-scale, prospective, randomized, double-blind, phase III clinical trial was a combined effort of multiple medical centers from several countries, recruiting a total of 1637 postmenopausal women with pre-existing vertebral fracture.[10] The subjects were randomized into three treatment groups, including placebo and teriparatide (20 μg daily and 40 μg daily), for a median study period of 19 months (maximum 24 months). All subjects were supplemented with calcium (1000 mg daily) and vitamin D (400–1,200 mg daily). The primary endpoint was set as the percentage of patients with new vertebral fractures, and secondary endpoints included the percentage of patients with nonvertebral osteoporotic fractures, changes in BMD, and effects on bone turnover markers. The results showed that teriparatide treatment reduced the risk of one or more new vertebral fractures in postmenopausal women with osteoporosis by 65% and the risk of multiple new vertebral fractures by 77%. Furthermore, teriparatide resulted in a 53% decrease in the risk for nonvertebral osteoporotic fractures and a 90% decrease in moderate or severe new non-vertebral fractures. After 12 months of treatment, there was significant improvement in lumbar spine BMD, with 9.7% and 2.8% increases in lumbar spine and femoral neck BMD, respectively.[11]

Changes in bone turnover markers revealed that in the first month of teriparatide treatment, there was a significant and steady increase in serum bone-specific alkaline phosphatase (BSAP) and procollagen type I C-terminal peptide (PICP), which are biomarkers related to osteoblast activity and bone formation. On the other hand, a significant rise in bone-resorption markers occurred after, rather than before, the rise in bone-formation markers. The markers fell to baseline after discontinuation of teriparatide.

Another study that stemmed from subgroups of the Fracture Prevention Trial further explored the relationship between the increase in BMD and the strengthening of cortical bone and trabecular bone microstructures. Although participants in the treatment saw their BMD gradually drop, the amount in the lumbar vertebra and the entire hipbone 30 months after the treatment was still higher than before treatment ($p \leq 0.001$).[12] Analyses on 2D bone volume, 2D mean wall thickness, 3D trabecular separation, 3D structural model index and 3D connectivity density showed that teriparatide was able to boost lumbar spine BMD through enhancement of all trabecular bone structures. In other words, teriparatide not only increases bone mass, but it also improves bone quality.

In 2003, Jiang et al conducted a study on 51 postmenopausal women who were treated with teriparatide (20 μg) daily for 19 months. 2D histomorphometry and 3D X-ray microtomography were used to compare bone microstructure in paired iliac crest biopsies before and after treatment. They found that teriparatide significantly increased cancellous bone volume, cancellous bone connectivity density, cancellous bone plate-like structure, and cortical thickness, while it decreased marrow star volume. The remarkable enhancement of bone microstructures further lowered the incidence of vertebral and nonvertebral fractures in the subjects.[13]

Body et al[14] have made a preliminary comparison of the effects of teriparatide and alendronate, a typical antiresorptive agent. In their study, 146 postmenopausal women were recruited to elucidate the effects of teriparatide and alendronate on BMD, non-vertebral fracture incidence and bone turnover. According to their results, lumbar spine BMD in teriparatide-treated patients was higher than that of alendronate-treated patients by 2.7% and 5.4% at 3-month and 6-month follow-ups, respectively. The between-group difference increased to 8.3% at the 12-month follow-up ($p < 0.0001$). There was a 5.2% increase in lumbar spine BMD after 3 months of teriparatide treatment, compared to a mere 5.9% increase in lumbar spine BMD after 12 months of alendronate treatment. Compared to alendronate, the 12-month treatment with teriparatide resulted in a much higher increase in femoral neck and total hip BMD. Compared with alendronate, teriparatide showed a tendency of lower risk for nonvertebral fracture, with a 4.1% incidence of nonvertebral fracture in the teriparatide group versus a 13.7% rate in the alendronate group ($p < 0.05$). In another comprehensive study comparing teriparatide and alendronate conducted by McClung et al in 2005, teriparatide had a significantly stronger effectiveness on lowering the risks of fractures than alendronate[15]

3.1. Combination or sequential therapy

There have been several studies on combination or sequential therapies of teriparatide and other osteoporosis drugs. In 1997, Lindsay et al conducted an open, randomized clinical study to elucidate the effectiveness of the combination therapy of teriparatide and hormone replacement therapy.[16] Patients who had received hormone therapy for at least 1 year with stable BMD control were randomized into two groups; the experimental group received teriparatide and hormone replacement therapy, and the control group received single hormone therapy. The intervention period was 3 years. Their results showed that the combination therapy increased lumbar spine BMD by 13%, whereas there was no change in BMD in the single hormone therapy group.

In the 2004 study by Ettinger et al, the effects of teriparatide on BMD were examined through administration of a continuous 18-month treatment of teriparatide (20 μg) on osteoporotic women who had taken alendronate or ralozifene earlier.[17] This study enrolled a total of 59 postmenopausal women, aged 60–87 years, who had BMD T-scores of 2 or less and had taken prior alendronate or raloxifene for 18–36 months. All subjects were given calcium 1000 mg and vitamin D 400 IU daily. After 18 months of treatment, lumber spine BMD in subjects with prior alendronate increased by only 4.1%, as opposed to a 10.2% increase in the subjects with prior raloxifene. In addition, the total hip BMD in the subjects with prior raloxifene rose by 1.8% ($p < 0.05$), whereas there was no improvement in the alendronate group. This study proved that teriparatide can increase BMD in patients with prior raloxifene, but a preceding alendronate treatment may compromise the effects of a following teriparatide on BMD.

According to recent subgroup analyses from the EUROFORS clinical study, a daily teriparatide 20 μg treatment for 2 years induced a remarkable increase in BMD and bone-formation markers in postmenopausal, osteoporotic women, with or without prior antiresorptive agents.[18]

4. Clinical studies on men with osteoporosis

In their randomized, double-blind, controlled clinical study in 2003, Orwoll et al examined the osteogenic effect of teriparatide on BMD and bone turnover markers in male patients with osteoporosis.[19] A total of 437 male subjects were randomized to receive

a daily treatment of teriparatide 20 μg, teriparatide 40 μg, or placebo. The results showed that after 3 months of intervention, teriparatide 20 μg and 40 μg increased lumbar spine BMD by 5.9% and 9% ($p < 0.001$), respectively. Femoral neck BMD was also increased by 1.5% and 2.9% in the teriparatide 20 μg and 40 μg groups, respectively ($p < 0.001$), whereas there was no change in radius BMD. These effects were not influenced by gonadal status, age, baseline BMD, body surface area, smoking or drinking.

4.1. Combination or sequential therapy

Kaufman et al observed 355 of the subjects from the above clinical study by Orwoll et al through 30 months of post-treatment follow-up.[20] They found that although BMD gradually decreased after discontinuation of teriparatide, lumbar spine and total hip BMD at 30-month follow-up was still significantly higher than that before treatment ($p \leq 0.001$). The addition of antiresorptive agents not only prevented the drop in BMD but further increased BMD.

In line with the findings in combination therapies on female osteoporotic patients, a study on male osteoporotic patients has shown that teriparatide and alendronate not only failed to work in synergy as a combination therapy, but the effects of teriparatide on BMD might be compromised. In a clinical study of 83 men,[21] the subjects were randomly placed into three treatment groups: alendronate 10 mg daily, teriparatide 40 μg daily, and a combination of both agents. Male subjects receiving teriparatide alone showed a much more significant increase in lumbar spine BMD, compared to that in other groups. A similar increase was observed in femoral neck BMD. Through some mechanism that has yet to be fully explained, alendronate seems to impede teriparatide's osteogenic effects.

Although Kaufman et al did not focus on fracture prevention, they compared the lateral thoracic lumbar radiographs of 279 subjects at an 18-month follow-up with pretreatment baseline and found that teriparatide lowered the risks for vertebral fracture by 51% ($p = 0.07$, nonsignificant) and significantly reduced the incidence of moderate or severe fracture by 83% ($p = 0.01$), compared to placebo.

5. Clinical studies on glucocorticoid-induced osteoporosis

In a randomized, double-blind, controlled clinical trial study, the effects of teriparatide and alendronate on male and female patients with glucocorticoid-induced osteoporosis were examined.[22] A total of 428 osteoporotic patients who had long-term use of glucocorticoid (prednisone equivalent 5 μg daily) were randomized; 214 received teriparatide 20 μg plus oral placebo daily, and 214 received 10 mg alendronate plus placebo injection daily. The primary endpoint was set as the change in lumbar spine BMD. Both groups showed significant rise in lumbar spine BMD, while the group receiving 18 months of teriparatide had a twofold higher increase in BMD than that of the alendronate group ($7.2\% \pm 0.7\%$ vs. $3.4\% \pm 0.7\%$; $p < 0.001$). Between-group difference was first noted in the sixth month and continued to exist through to the end of the study.

In addition, assessments at 12 and 18 months showed increase in total hip BMD in both groups. However, the teriparatide group demonstrated a significantly larger rise than that of the alendronate group ($p < 0.001$).

Despite a lack of research with primary endpoints set as bone fractures prevention in patients with glucocorticoid-induced osteoporosis, the above clinical trial by Saag et al found that the incidence of new vertebral fracture in the teriparatide group was lower than that in the alendronate group (0.6% *vs.* 6.1%, $p = 0.004$). However, the two groups showed no difference in the incidence of non-vertebral fractures (5.6% vs. 3.7%, $p = 0.36$).

6. Fracture healing

The large-scale, randomized, double-blind, controlled clinical trial conducted by Aspenberg et al in 2009 was the first to study the effects of teriparatide on fracture healing.[23] A total of 102 postmenopausal women with distal radial fracture were randomly placed into three experimental groups, each having 34 subjects, and a daily treatment of placebo, teriparatide 20 μg or teriparatide 40 μg was given. The interventions were initialized on the 10th day after the occurrence of fracture. Throughout the 8-week treatment cycle, follow-up X-ray radiography was performed every 2 weeks. The median time from the first day of fracture to the appearance of radiographic evidence of complete cortical bridging in three of four cortices was 9.1, 7.4, and 8.8 weeks for the placebo, teriparatide 20 μg and teriparatide 40 μg groups, respectively ($p = 0.015$). There was no statistically significant difference between the teriparatide 40 μg group and the placebo group ($p = 0.523$). In *post hoc* analyses, there was no significant difference between the teriparatide 20 μg group and the teriparatide 40 μg group either ($p = 0.053$). However, compared to the placebo, teriparatide 20 μg resulted in a shorter fracture healing time ($p = 0.006$). Although the primary endpoint that teriparatide 40 μg results in a shorter healing time compared to placebo was not met, the results suggested that teriparatide 20 μg had a tendency to shorten the median time of cortical bridging in three cortices.

Additionally, a number of case studies have shown that teriparatide tends to facilitate and quicken fracture healing. In the case report by Resmini et al on a 79-year-old woman with osteoporosis who was given teriparatide, they found significant healing of her left proximal humeral fracture after 25 days of treatment.[24] Bukata et al also conducted a study on 145 cases of vertebral or extremity fractures who received teriparatide 20 μg daily.[25] In their study, half of the subjects experienced delayed fracture healing prior to the treatment; of them, 88% were older patients or had other complications that put them in high-risk groups for surgery. Within the 12-week treatment of teriparatide 20 μg daily, 141 of the 145 subjects reported pain remission at the site of healing or fracture; 93% of them were confirmed with fracture healing. Fracture healing tended to be remarkably more active in locations with higher trabecular bone content, including vertebrae, sacral ala, and metadiaphyseal long bones, compared to diaphyseal bone fracture or fusion. Peichl et al have reported five older patients with pubic rami fractures, which generally require 12–16 more weeks to heal than does a common fracture. After PTH 1-84 treatment, it took only 8 weeks to observe pain remission and healing.[26] Although clinical trials and case studies to date have yet to fully prove the effect of teriparatide on fracture healing, a regular daily treatment of teriparatide 20 μg seems to be beneficial to fracture healing, particularly for high surgical risk populations such as the elderly and patients with complications.

Regarding the effect of teriparatide on chondrogenesis, animal studies on bone union and spinal fusion have discovered an increased cartilage formation at the fracture and fusion site in teriparatide-treated experimental groups, as opposed to the placebo-treated control groups. Kakar et al have proven that in teriparatide-treated rats, there was a threefold greater increase in chondrogenesis versus osteogenesis.[27] Similar findings have been reported by O'Loughlin et al in their study on chondrogenesis in spinal fusion using a rabbit animal model.[28] The increased chondrogenesis induced by teriparatide may further facilitate the formation of larger calluses at the fracture site. As the calluses and bone unions normally foster endochondral bone formation, it has been shown that teriparatide does not impede the chondrocyte differentiation in the calluses. While animal studies have indicated that teriparatide promotes chondrogenesis at fracture

and fusion sites, further evidence from human clinical trials is required.

7. Conclusions

Teriparatide has been proven to significantly reduce the risks for vertebral fractures in postmenopausal women with osteoporosis. Another important study has confirmed its ability to decrease the risks for nonvertebral fractures.[10] The drug has also been shown to be effective in increasing BMD in male patients with osteoporosis. It has been hypothesized that teriparatide, an osteogenic stimulator, and antiresorptive agents may work in synergy as a combination therapy, in light of their seemingly complementary mechanisms. However, literature on the combination of alendronate and teriparatide has found that the co-administration of the two agents is not more effective than a single application of teriparatide therapy, and alendronate may even suppress teriparatide's osteogenic effects. Upon discontinuation of teriparatide treatment, BMD tends to decrease gradually. Such a tendency may be countered by the use of antiresorptive agents following a complete teriparatide treatment cycle, which can further stabilize BMD. However, there is still a lack of literature on the duration of antiresorptive therapy after teriparatide. On the other hand, a prior use of bisphosphonates may compromise the osteogenic ability of the following teriparatide treatment.[17] Therefore, researchers have recommended that if there is a need to switch to teriparatide, a 6-month period or more is required between termination of bisphosphonate and initialization of teriparatide to prevent interference with the osteogenic effects of teriparatide.[29]

Several large-scale clinical trials have proven that teriparatide can facilitate osteogenesis in osteoporotic patients. Clinical studies have also suggested that this drug can be used as a growth factor to promote fracture healing and bone fusion. Other effects of teriparatide, including stimulation of bone healing and osteoconduction in porous joint replacement materials that may be extensively applied to orthopedic clinical practice, warrant further studies and confirmation.

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