

## **REPORT**

# **Osteocyte enhancement function of bisphosphonates in prosthetic replacement**

**Jun Yang<sup>1\*</sup>, Shangzeng Wang<sup>1</sup>, Qingliang Meng<sup>2</sup>, Yongqiang Sun<sup>1</sup> and A-fou Ran<sup>3</sup>**

<sup>1</sup>Joint Department of Henan Province Hospital of Traditional Chinese Medicine, Zhengzhou, China

<sup>2</sup>Rheumatism Bone Disease Department of Henan Province Hospital of Traditional Chinese Medicine, Zhengzhou, China

<sup>3</sup>Spinal Department of Henan Province Hospital of Traditional Chinese Medicine, Zhengzhou, China

---

**Abstract:** aseptic loosening after prosthetic replacement is the primary cause of shortened service life and lowered stability of prosthesis, and increased revision rate after joint replacement. Factors of causing the loosening of joint prosthesis include mechanical factors and biological factors. The mechanical effect of bisphosphonates (BP) is quite obvious, which can enhance osteocyte function, accelerate the generation of new bone and lower bone resorption activity of osteoclast and macrophage. In animal experiment and adjuvant therapy of patients after joint replacement, BP also shows up the functions of reducing osteolysis induced by wear debris, preventing stress shielding and interface fretting and enhancing bone density. This paper elaborated the mechanism of BP adjusting bone metabolism, and analyzed the action principle and the vital function of it in prosthetic replacement. It has proved that BP can effectively reduce the early peri-prosthesis bone absorption after total hip replacement and improve bone mass peri-prosthesis. It is currently the significant choice of preventing bone lose of peri-prosthesis after operation.

**Keywords:** BP, prosthetic replacement, cellular mechanism, adjuvant therapy

---

## **INTRODUCTION**

Prosthetic replacement is the effective therapy method of hip and knee joint lesion in terminal stage, such as rheumatoid arthritis, osteoarthritis, hip fracture in the elderly and femoral head necrosis. It has merits like relieve pain, maintain motion range and stability of joint, repair or not affect limb length, etc (Shujuan *et al.*, 2012). However, according to related literature report, in the complications after prosthetic replacement, aseptic loosening occupies three quarters of revision surgery, which has seriously impacted the expectation life of implanted prosthesis. Currently, many scholars in China have conducted researches on this field and obtained delightful results. In article Systematic Assessment on Bisphosphonates in Preventing Peri-prosthesis Bone Absorption Effect after Total Hip Replacement (Guang, 2012), Liang Guang from Guangxi Medical University had comprehensively collected peri-prosthesis bone absorption after total hip replacement. He also extracted relevant data and research quality, used Rev Man 5.1 for Meta analysis, and evaluated the effectiveness and security of using BP to prevent peri-prosthesis bone absorption after total hip replacement. In article The Influence of Osteoporosis on Long-term Aseptic Loosening of Artificial Joints (Yue and Zhiping, 2013), Ding Yue and Guan Zhiping discussed the effect of OP on forward aseptic loosening after prosthetic replacement

from aspects of the selection of operation methods, the mechanism of artificial joint forward aseptic loosening and the function of anti-OP drugs. In article Pathogenesis and Therapy Progress of Aseptic Loosening of Artificial Joint Prosthesis (Feng *et al.*, 2012), Liu Feng, Zhang Chao, Yao Zhenqiang, *et al* summarized the pathogenesis and therapy progress aseptic loosening of artificial joint prosthesis through correlated researches on the pathogenesis of aseptic loosening of artificial joint prosthesis and its prevention.

This paper summarized from the mechanism of BP regulating bone metabolism and the application progress of prosthetic replacement. Analysis on pharmacologic action of BP proved the significant function of BP in prosthetic replacement, which has provided theoretical direction and reference for related researches.

### ***Chemical structure of bp***

BP is artificially synthesized analogue of pyrophosphate, of which the P-O-P of pyrophosphate is replaced by P-C-P, and it is formed after chemical modification on the side chain R1 and R2 of atom C. R1 mainly combines with hydroxyapatite crystal, and R2 determines its biological activity. The type of side chain on atom C determines the intensity of BP (Zhang *et al.*, 2010). Currently, BP medicine has been developed for more than ten types and been put in clinical research. According to whether contain nitrogenous on side chain of R2, they are divided into non-nitrogenous BP (like etidronate, clodronate) and

---

\*Corresponding author: e-mail: yjjuny@163.com

nitrogenous BP (like alendronate, risedronate and zoledronate).

### **Cellular mechanism of bp regulating bone metabolism**

#### **BP on osteoblast**

In recent years, one research found that alendronate and risedronate can effectively enhance the potency of forming osteoblast-like cell. In this experiment, different concentrations of BP were applied to osteoblast. Results showed that alkaline phosphatase activities increased, the genetic expression of bone morphogenetic protein-2, I collagen and osteocalcin increased. It was thought that besides the function of inhibiting bone resorption of osteoclast, BP also can promote the proliferation and differentiation of osteoblast, of which the mechanism might be related to BP inducing Ca<sup>2+</sup> internal flow to activate the signal conditioning kinase outside cell.

Other research result (Maurizio *et al.*, 2011). proved that BP-type medicine can not only strengthen the osteogenesis of adult bone marrow stroma stem cells, promote the proliferation and differentiation of BMSC, but also can effectively inhibit the apoptosis of osteoblast no matter in vivo experiment or in vitro experiment.

#### **BP on osteoclast**

Function of BP on osteoclast distinguishes nitrogenous and non-nitrogenous. The former that combines with osteoclast can inhibit the synthesis of intermediate products pyrophosphoric acid synthetase by mevalonic acid synthetic route in the process of cholesterol synthesis, such as FPP and GGPP. FPP and GGPP participate in prenylation modification after small GTP enzymatic translation. Only prenylation GTP enzyme matter can located on the cell membrane, thus to have osteoclast obtain the bone resorption needed structure and function. BP indirectly inhibits the prenylation of small GTP through inhibiting mevalonic acid, which has osteoclast lose ruga and destroys the formation of actin, thus induce the apoptosis of osteoclast. However, the principle of the latter is that ammonia tRNA synthetase catalyze the non-nitrogenous BP, thus to have it combine with the ATP molecule of osteoclast to form ATP analogue. BP maintains comparatively local high concentration on bone surface, which disturb osteoclast to receive bone resorption signal from bone matrix, so as to directly lower its activity and inhibit the differentiation and gathering of osteoclast. In later period of bone remodeling, these analogues accumulate in quantity, which inhibit the activity of ATP-dependent enzyme, influence function of osteoclast and induce the apoptosis of osteoclast.

#### **BP on macro phagocyte**

When macro phagocyte migrating and gathering to peri-prosthesis, it can obtain excitation by swallowing a large number of wear debris generated after long-term abrasion of artificial joint, then secrete mass of inflammatory factors and induce the osteolysis in peri-joint. However,

the existing experiments also proved that BP can lower activity of macrophage, weaken migration and gather ability of macrophage, thus to induce them apoptosis and lessen local inflammatory reaction and its negative influence on osteoblast.

#### **BP on prosthetic replacement**

##### **Application of BP in the therapy after experimental prosthetic replacement**

With the in-depth research of BP action mechanism, an increasing number of scholars are trying to research and apply BP so as to prevent the prosthetic loosening of joint replacement. In previous experiments, through establishing bone adaptation model after arthroplasty, scholars (Laura *et al.*, 2011) discovered that compared with model without using BP, BP could apparently lower the incidence rate of bone lose after arthroplasty. The incidence rate lowered 42% in one year, which has slowed down bone remodeling to a large extent. Other scholars once divided 12 sheep, which had experienced one-side bone cement artificial femoral head replacement into two groups. They found that compared with zoledronate group, bone density after operation of control group was significantly reduced. Observe from tectology, the lacuna ratio of cortical bone area, thickness and osteocyte fill in zoledronate group were all apparently higher than that in control group. It is suggest that BP can be used to prevent osteoporosis caused by stress shielding after joint replacement and aseptic loosening caused by it.

##### **Research progress of BP on adjuvant therapy after joint replacement**

With the constant excavation of medical scientific research, the application of BP in adjuvant therapy after joint replacement gradually show its significance, which has win the favor of scholars from many countries.

Large-scale retrospective researches by Thillemann, *et al* (Thillemann *et al.*, 2010) have incorporated 16145 patients with osteoporotic who had experienced initial total hip replacement, of which 632 cases experienced revision. They found that long-term usage of BP after initial replacement could lower revision rate, but the revision rate caused by deep infection relatively increased. Prieto-Alhambra, *et al* (Daniel *et al.*, 2011) conducted follow-up visit on 41995 patients, of which 1912 cases were patients with BP treatment, the other were in control group. Results showed that BP has significant protective effect on the survival of prosthesis. Duration from post joint replacement to revision in treatment group has increased by one times than that in control group. Duration from post hip replacement to revision in treatment group has increased by 70% than that in control group.

In recent years, the latest research found that 4mg zoledronate of single vein was applied to patients that

experienced non-bone cement total hip replacement. After 2 years, the displacement degree of artificial acetabulum and prosthesis stem reduced to lowest. It proved that BP also has the function of increasing the stability of prosthesis and preventing the early interface fretting of prosthesis.

## CONCLUSION

The aseptic loosening of joint prosthesis has become the main reason of the forward failure of prosthetic replacement. Through sort summary of various experimental results and main points, this paper proved that BP can promote the proliferation and differentiation of osteoblast and strengthen bone marrow stroma stem cells. In addition, BP can also affect the function of osteoclast, induce its apoptosis and reduce the activity of macrophage. BP still can inhibit the release of peri-prosthesis inflammatory factors and reduce local inflammatory reaction (Naoyuki *et al.*, 2011; Trevisan *et al.*, 2010). In the adjuvant therapy of animal experiment and joint replacement, they also proved that BP can reduce the osteolysis induced by wear debris, prevent stress shielding and interface fretting, increase bone density and improve clinical index. It can be said that BP-type medicine is expected to become an important assistance of clinical prevention and treatment of the aseptic loosening of joint prosthesis, which has pointed out explicit orientation for future development of medical science in this field.

## REFERENCES

- Daniel PA, M Kassim J, Andrew J, David M, Andy C, Cyrus C and Nigel KA (2011). Association Between Bisphosphonate Use and Implant Survival after Primary Total Arthroplasty of the Knee or Hip: Population Based Retrospective Cohort Study. *BMJ*, **343**: d7222.
- Feng L, Chao Z and Zhenqiang Y (2012). Pathogenesis and therapy progress of aseptic loosening of artificial joint prosthesis. *Chin. J. of Tissue Eng. Res., (CJTER)*, **16**(26): 4886-4891.
- Guang L (2012). Systematic assessment on bisphosphonates in preventing peri-prosthesis bone absorption effect after total hip replacement. *Nanning. Guangxi. Medi. Univer.*, **5**:
- Laura PW, Muhammad M, David J, Gillian H, Nadia G, Peter A, Daniel W, Peter W and Andreas L (2011). Bisphosphonate Use and the Risk of Subtrochanteric or Femoral Shaft Fractures in Older Women. *JAMA Feb.*, **305**(8): 783-789.
- Maurizio M, Eugenio Q, Laura Q, Antonella G, Antonio O, Antonio M and Giuseppe R (2011). Ibandronate and Periprosthetic Bone Mass: New therapeutic approach in periprosthetic loosening prevention. *Clini. Cases in Min. and Bone Meta.*, **8**(1): 55-56.
- Naoyuki I, Yutaka I, Naomi K, Takashi I, Yohei Y and Tomoyuki S (2011). A comparison of the effects of alendronate and alfacalcidol on bone mineral density around the femoral implant and in the lumbar spine after total hip arthroplasty. *J. of Bone & Joint Surg. Am.*, **93**(13): 1203-1209.
- Shujuan X, Liu Z and Weihong P (2012). Zoledronic acid promotes osseo integration of dental implant. *J. of Medi. Post.*, **25**(1): 76-79.
- Thillemann TM, Pedersen AB, Mehnert F, Johnsen SP and Søballe K (2010). Postoperative use of bisphosphonates and risk of revision after primary total hip arthroplasty: A nationwide population-based study. *Bone*, **46**(4): 946-951.
- Trevisan C, Ortolani SP, Isaia G, Agnese L, Dallari D, Grappiolo G, Cherubini R, Massari L and Bianchi G (2010). Decreased periprosthetic bone loss in patients treated with clodronate: A 1-year randomized controlled study. *Calci. Tissue Inter.*, **86**(6): 436-446.
- Yue D and Zhiping G (2013). The influence of osteoporosis on long-term aseptic loosening of artificial joints. *Chin. J. of Joint Surg. (Electr. Version)*, **27**(1): 112-116.
- Zhang L, Jia TH, Chong ACM, Bai L, Yu H, Gong W, Wooley PH and Yang SY (2010). Cell-based osteoprotegerin therapy for debris-induced aseptic prosthetic loosening on a murine model. *Gene. Ther.*, **17**(10): 1262-1269.