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*Short communication*

# Adiponectin: A new therapeutic option for periprosthetic osteolysis

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**Periprosthetic osteolysis is the most prevalent complication after total joint arthroplasty. It often results in aseptic loosening of the implant, which is required for revision surgery. Wear debris has been recognized as a key factor in the initiation and development of periprosthetic osteolysis, and yet there is no approved treatment available to it. Adiponectin is a hormone secreted by adipose tissue. Many researchers have reported that adiponectin can block osteoclastogenesis and promote osteoblast proliferation. We then hypothesize that adiponectin may play an efficient role in the therapy of periprosthetic osteolysis, which may offer new therapeutic options for the management of periprosthetic osteolysis after total joint arthroplasty.**

**Key words:** Adiponectin, periprosthetic osteolysis, wear debris.

## REVIEW OF PERIPROSTHETIC OSTEOLYSIS

Periprosthetic osteolysis is the presence of diffuse or localized areas of periprosthetic bone loss. It remains the leading complication of total joint arthroplasty (Pearle et al., 2007), often resulting in aseptic loosening of the implant, and ultimately requiring revision surgery (Greenfield et al., 2002).

Wear debris developed after total joint arthroplasty was recognized as a key factor in the initiation and development of periprosthetic osteolysis (Dumbleton et al., 2002; Wilkinson et al., 2005). It could be formed by the degradation products of any components of the prosthesis (such as metal, ceramic and polyethylene) as well as bone cement. Macrophages and osteoclast precursor cells are the primary targets of wear debris. The phagocytosis by macrophages is accompanied by the induction of proinflammatory mediators, including IL-6, IL-1β, PGE2, TNF-α, as well as up-regulate transcription factor NFκβ and downstream proinflammatory cytokines (Purdue et al ., 2007; Hallab et al., 2005; Schwarz et al., 2004; Ritchlin et al., 2004). These mediators can incite a complex cascade, which leads to osteoclast maturation and bone resorption.

Osteoclasts are multinucleated cells derived from circulating osteoclast precursor cells of the monocyte/macrophage lineage. It is believed that receptor activator of NF-kappa B ligand (RANKL) is the principal axis regulating the osteoclast generation and activation. RANKL binds to RANK expressed on the surface of osteoclast precursor cells, leading to recruitment and activation of osteoclasts (Hsu et al., 1999; Nicholson et al., 2000). Although, not occurring under normal conditions, there are reports showing that RANKL is derived from macrophages cells in the periprosthetic tissues of osteolysis patients (Haynes et al., 2001), on the other hand, the proinflammatory mediators secreted by macrophages phagocytosed wear debris can up-regulate the RANKL activity as well as accelerate the recruitment and activation of osteoclasts.

In addition, wear debris might also contribute to osteolysis by inhibiting bone formation. It has been shown that wear debris can decrease expression of collagen types I and III by osteoblasts (Vermes et al., 2000). There is also evidence that polymethylmethacrylate (PMMA) bone cement can reduce osteoblasts proliferation (Zambonin et al., 1998), and titanium can reduce osteoblasts viability by inducing apoptosis (Pioletti et al., 2002). These observations suggest that wear debris might inhibit osteoblasts formation and function.

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## DISCUSSION AND CONCLUSION

Adiponectin, an adipose-derived hormone, is specifically and highly expressed in adipose tissue and is present abundantly in plasma (Arita et al., 1999). It plays an important role in regulating insulin sensitivity, suppression of atherosclerosis, liver fibrosis and tumor growth (Combs et al., 2001; Berg et al., 2001). Adiponectin and its two related adiponectin receptor subtypes (AdipoR1 and AdipoR2) have been identified in osteoblasts (Shinoda et al., 2006; Oshima et al., 2005), indicating adiponectin's effect on bone metabolism.

Oshima et al. (2005) reported *in vitro* that adiponectin inhibits M-CSF-induced and RANKL-induced differentiation of mouse bone marrow macrophages and osteoclasts derived from human CD14-positive mononuclear cells, and also suppresses the bone-resorption activity of osteoclasts. Furthermore, adiponectin increases mRNA expression of alkaline phosphatase (ALP) and mineralization activity of mouse MC3T3-E1 osteoblasts. Yamaguchi et al. (2007) reported that adiponectin strongly blocks lipopolysaccharide/RANKL-mediated osteoclastogenesis. Luo et al. (2005) found that adiponectin promotes osteoblast proliferation and results in a dose and time-dependent increase in alkaline phosphatase (ALP) activity, osteocalcin and type I collagen production, as well as an increase in mineralized matrix. Suppression of AdipoR1 with small-interfering RNA (siRNA) abolishes the adiponectin-induced cell proliferation and ALP expression. Mitsui et al. (2011) demonstrated that elevation of the circulating adiponectin level increases bone mass by activating bone formation while normal osteoclast function is retained.

As mentioned previously, RANKL is the principal axis regulating the osteoclast generation and activation in wear debris induced periprosthetic osteolysis. Adiponectin inhibits RANKL-mediated osteoclast formation and suppresses bone-resorption activity of osteoclasts. It also promotes osteoblast proliferation and increases bone mass. Thus, we can hypothesize that adiponectin plays an important role in preventing the progression of periprosthetic osteolysis. Most likely, it can provide new therapeutic options for the management of periprosthetic osteolysis after total joint arthroplasty.

Although, there is only theoretical evidence suggesting that adiponectin may be beneficial in the treatment of periprosthetic osteolysis, the hypothesis gives us a novel perspective. In the future, more experiments and clinical researches should be performed to evaluate the exact effects of adiponectin on periprosthetic osteolysis.

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