

## REVIEWS

## ARTICOLE DE SINTEZĂ

# Exercise, osteoprotegerin and bone metabolism

## Efortul fizic, osteoprotegerina și metabolismul osos

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### Abstract

Osteoprotegerin (OPG) is a member of the tumor necrosis factor superfamily and acts as a decoy soluble receptor for the receptor activator of nuclear factor  $\kappa$ B (RANK) ligand (RANKL). It thus prevents RANKL binding to its receptor RANK and the activation of osteoclastogenesis and osteoclast-induced bone loss. Physical exercise is known to have a favorable effect on bone mass. The aim of this article is to analyze the studies which evaluated the modifications of circulating OPG and RANKL in relation to different types of exercise and to bone turnover markers. The results of these studies indicate a positive effect of physical exercise on bone mass that is not accompanied by significant modifications of OPG and RANKL, in the majority of these studies. The increase of OPG levels found in long-distance runners suggests a role of OPG as a mediator of mechanical loading in humans. In conclusion, the role of OPG and RANKL in relation to physical exercise and bone metabolism is not yet clear, in view of the existing literature data.

**Key words:** exercise, osteoprotegerin, RANKL, bone mass.

### Rezumat

Osteoprotegerina (OPG) este un membru al superfamiliei factorului de necroză tumorală și acționează ca un fals receptor solubil pentru RANKL - ligantul receptorului activator al factorului nuclear  $\kappa$ B (RANK). Ea împiedică astfel legarea RANKL de receptorul său RANK și, în consecință, activarea osteoclastogenezei și a reducerii masei osoase. Exercițiul fizic are un rol favorabil cunoscut asupra masei osoase. Scopul acestui articol a fost de a analiza studiile care au evaluat modificările nivelurilor OPG și ale RANKL în relație cu diferite programe de exerciții fizice și cu markerii ”turn-overului” osos. Rezultatele indică un efect favorabil al exercițiului fizic asupra masei osoase, modificările concentrațiilor OPG și RANKL fiind nesemnificative, în majoritatea cazurilor. Nivelurile crescute ale OPG constatate la alergătorii de cursă lungă (maraton) sugerează un posibil rol de mediator al OPG la nivel osos, în contextul încărcării mecanice. În concluzie, rolul OPG și al RANKL în relația dintre efortul fizic și metabolismul osos este încă neclar, în lumina datelor existente în prezent în literatură.

**Cuvinte cheie:** efort fizic, osteoprotegerina, RANKL, masa osoasă.

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### Introduction

Osteoprotegerin (OPG) is an important molecule for both bone metabolism and vascular wall pathology and it has also been involved in carcinogenesis and central thermoregulation. It has been associated with both osteoporosis and vascular atherosclerosis and calcification (Simonet et al., 1997; Caidahl et al., 2010). OPG protects against osteoporosis, inhibiting osteoclastogenesis (Simonet et al., 1997; Schoppet et al., 2002). The precise role of OPG at the level of the arterial wall is still a subject of debate, because animal studies indicate a possible protective vascular role and human studies link OPG with an increased cardiovascular risk (Schoppet et al., 2002).

Physical exercise has a protective action on bones, stimulating bone formation (Borer et al., 2005; Yang et al., 2014).

OPG is mainly produced by bones, but is also secreted by other numerous tissues including the cardiovascular structures (heart, arteries and veins), lungs, kidneys, hematopoietic and immune cells (Simonet et al., 1997; Schoppet et al., 2002). OPG is a member of the tumor necrosis factor receptor superfamily and it acts as a soluble decoy receptor for the receptor activator of nuclear factor  $\kappa$ B-ligand (RANKL), blocking RANK activation (Yasuda et al., 1998). The synthesis of OPG is stimulated by several cytokines, such as TNF, interleukin (IL)-1, IL-18, transforming growth factor (TGF), bone morphogenetic

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proteins, and steroid hormones (Schoppet et al., 2002; Brandstrom et al., 2001). Some other molecules such as glucocorticoids, parathyroid hormone and prostaglandin E2 are known to inhibit OPG production (Yasuda et al., 1998; Vidal et al., 1998). RANKL (receptor activator of nuclear factor-kappa B ligand) is produced by osteoblastic lineage cells and activated T cells and stimulates osteoclast formation, differentiation and activation leading to bone resorption (Lacey et al., 1998).

RANK is the specific receptor of RANKL and is expressed in different cells such as osteoclasts, activated T cells and myeloid-derived dendritic cells (Schoppet et al., 2002; Nakagawa et al., 1998). RANKL activates its receptor RANK on osteoclasts, stimulating osteoclastogenesis (Yasuda et al., 1998; Schoppet et al., 2002). OPG acts as a soluble receptor of RANKL and prevents RANK activation, consequently inhibiting osteoclastogenesis and osteoclast activation (Yasuda et al., 1998; Caidahl et al., 2010). OPG also neutralizes the effect of TNF-related apoptosis inducing ligand (TRAIL), inhibiting the proapoptotic pathways (Yasuda et al., 1998; Caidahl et al., 2010).

RANKL and OPG are also involved in vascular calcification. It has been shown that OPG knockout mice develop osteoporosis and calcification of the media of aorta and renal arteries (Bucay et al., 1998). This was the first evidence that the RANK/OPG system may be involved in both osteoporosis and vascular calcification. Clinical and epidemiological studies underline the association of vascular calcification and cardiovascular complications in postmenopausal and elderly women with osteoporosis (Caidahl et al., 2010; Kado et al., 2000; Browner et al., 2001). The role of OPG in cardiovascular disease is still a subject of debate because experimental studies indicate a protective vascular role, while clinical and epidemiological research shows an association between increased OPG concentrations and cardiovascular diseases and mortality (Lieb et al., 2010; Nybo & Rasmussen, 2002).

OPG has been associated in many clinical studies with systemic inflammation and its markers, C reactive protein (CRP), fibrinogen, and the erythrocyte sedimentation rate (Libby, 2002). It has been suggested that OPG is a marker of inflammation because besides its association with inflammatory conditions and mediators, it is downregulated by anti-inflammatory molecules such as immunosuppressants and anti-TNF medications (Ziolkowska et al., 2002; Hofbauer et al., 2001; Hamerman, 2005).

Systemic inflammation is also involved in osteoporosis and it may be one of the links between atherosclerosis and bone loss. Many of the circulating inflammatory markers characteristic of atherosclerosis may interfere with bone metabolism and stimulate osteoblastic release of factors that stimulate osteoclastogenesis (Hamerman, 2005). Even though OPG inhibits the activation of osteoclasts, elevated circulating levels have been found in postmenopausal women with osteoporosis compared to matched controls. One possible explanation supports the hypothesis that the increase in OPG levels may be a compensatory mechanism for enhanced RANKL osteoclastic bone resorption (Hamerman, 2005).

Data regarding the effect of exercise on OPG levels are sparse. The aim of this article is to analyze the literature data evaluating the effects of physical exercise on circulating OPG and its correlation with the bone remodeling process.

### Physical exercise and circulating OPG

Exercise has been reported to have favorable effects in both osteoporosis and cardiovascular disease. The precise mechanism by which physical exercise influences bone metabolism is not elucidated. Literature data support the hypothesis that bone mass is influenced principally by the increased mechanical strain because athletes practicing sports that generate high weight bearing or impact loading have a higher body mass density in comparison with athletes who practice sports with lower mechanical solicitations (Morel et al., 2001; Herrmann & Herrmann, 2004; Hinton et al., 2006). In addition, exercise may cause hormonal and bone metabolism changes, with the involvement of molecules responsible for bone turnover such as osteocalcin and the osteoprotegerin/RANK/RANKL axis (Maïmoun & Sultan, 2009; Herrmann & Herrmann, 2004; Hinton et al., 2006).

Exercise also has anti-inflammatory effects because contracting muscles release cytokines with anti-inflammatory actions (Mattush et al., 2000). Even if intense physical exercise determines muscular injuries and a local inflammatory reaction, regular exercise has anti-oxidative and anti-inflammatory effects (Pinto et al., 2012).

During the last 10-15 years, various studies have focused on the effect of physical activity on the OPG/RANKL/RANK system, but the results are conflicting. Studies include various populations and different types and periods of physical activities, and it is difficult to compare and extrapolate their results. We included in this analysis prospective studies that evaluated the effect of different types of physical activity on bone formation markers such as osteocalcin and bone alkaline phosphatase and on bone resorption markers including C-terminal cross-links of type I collagen in correlation with the OPG/RANK/RANKL system and body mass density (BMD). These studies are listed in Table I.

#### *Resistance training studies*

In a study that included forty healthy women (aged 45-60 years), the effects of two 12-week resistance training programs of different intensities (high intensity and low intensity) on bone turnover markers, BMD, OPG, and soluble receptor activator of nuclear factor kappa  $\beta$  ligand (soluble RANKL) were assessed (Karrarlan et al., 2010). The results indicate that both high intensity exercise and low intensity resistance training increased body mass density, with a more important effect for high intensity exercise. Changes in OPG were not significant and soluble RANKL decreased in all groups, suggesting that measures of these mediators may not be useful to predict body mass density or bone turnover status after resistance training exercise (Karrarlan et al., 2010).

In a study that included older women, the effects of a resistance training protocol and a moderate-impact aerobic training protocol (three times/week for 8 months) on bone mineral density (BMD), physical ability, serum OPG, and RANKL levels were compared (Marques et al., 2011).

After 8 months, only the resistance training group exhibited increases in BMD and improved body composition. Both types of exercise improved functional balance control strongly related to the risk of fall. These results were not accompanied by changes in OPG and RANKL levels or in the OPG/RANKL ratio (Marques et al., 2011).

In a group of elderly men and women, a combined exercise protocol (resistance and multicomponent weight-bearing impact exercise training) evaluated BMD at multiple sites, dynamic balance, muscle strength, serum levels of bone metabolism markers and inflammatory markers (Marques et al., 2013). The results suggest that these combined exercises reduce inflammation and increase BMD, balance, and lower-extremity muscle strength, despite having little effect on bone metabolism markers (Marques et al., 2013).

The acute effects of resistance training on pro-inflammatory and anti-inflammatory cytokines and OPG were tested in a study that included 24 sedentary middle-aged women divided into 2 groups with and without metabolic syndrome (Pereira et al., 2013). Women with metabolic syndrome had increased baseline pro-inflammatory cytokines and the acute resistance training did not induce an additional systemic response of OPG, pro- (TNF- $\alpha$ , IL-1- $\alpha$ , IL-6 and IL-12) and anti-inflammatory (IL-10) cytokines immediately and 60 min after exercise. The authors consider that submaximal resistance training is safe for patients with metabolic syndrome because no modification in pro-inflammatory cytokines was detected (Pereira et al., 2013).

#### *Aerobic exercise training studies*

In overweight and obese men and women, the impact

**Table I**  
Studies evaluating the relationship between OPG, RANKL and physical exercise.

Studies	Subjects	Type of exercise	Outcome	Other results
Karaarslan et al., 2010 (30)	40 postmenopausal women (aged 45-60 years)	Resistance exercise for 12 weeks (comparison of three groups: high intensity exercise /low intensity exercise/ controls)	↓RANKL in all three groups ↔ OPG	↑ BMD ↑ osteocalcin
Marques et al., 2011	71 older women randomly assigned to 3 groups: resistance training/ aerobic exercise/ control group	Both types of exercise (resistance training and aerobic exercise) were performed 3 times/week, for 8 months	↔ OPG ↔ soluble RANKL ↔ OPG/RA NKL	Resistance exercise determined: ↑ BMD ↑ muscle strength
Marques et al., 2013	47 healthy older adults (women=24, men=23; mean age 68.2 years)	Exercise intervention: 32 weeks (60 min/session): resistance exercise training (2 days/week) at 75-80% of maximum plus a multicomponent weight-bearing impact exercise training (1 day/week)	↔OPG ↔RANKL	↑ dynamic balance ↑ muscle strength ↑ BMD ↔ osteocalcin ↔ CTX ↓ hs-CRP, ↓ IFN- $\gamma$ , ↔ TNF- $\alpha$
Pereira et al., 2013 (33)	24 women divided in 2 groups: with and without metabolic syndrome	Acute resistance training: 3 sets of 10 repetitions in the following exercises: machine leg press, leg extension, leg curl, chest press, lat front pull-down and machine shoulder press with 60% of 1 repetition maximum, followed by 15 repetitions of abdominal crunches. A rest interval of 1 min was allowed between sets of exercises	↔ OPG measured immediately and 60 min after training	↔ TNF- $\alpha$ , IL-1 $\alpha$ , IL-1 $\beta$ , IL-12, IL-6, IL-10 measured immediately and 60 min after training
Hinton et al., 2006	Overweight and obese men and women	6 weeks aerobic exercise (approximately 1675 kJ/d, walking or jogging at 60% maximum oxygen consumption) and energy restriction (reduced by approximately 3140 kJ/d)	↔ soluble RANKL	↑ osteocalcin, ↑ BAP ↔ CTX
Wieczorek-Baranowski et al., 2012	44 postmenopausal women: 27 participated in the training program, and 17 in the control group	Cycle-ergometer physical workout at a level of 70% to 80% of ventilatory threshold intensity for 8 weeks (40-minute sessions, 3 times per week)	↔OPG	↓ osteocalcin ↓ HOMA-IR ↓ waist-to-hip ratio ↔ CTX
Bergstrom et al., 2012	112 postmenopausal women aged 45-65 years randomized to either sedentary life (control) or physical activity (training)	Three fast 30-min walks and one or two 1-h aerobic training sessions per week for 1 year	↑ OPG	Non-significantly ↓ CTX ↓ BAP
Scott et al., 2010	11 recreationally active men, 10 endurance-trained men and 10 controls	An exhaustive treadmill run with determination of plasma parameters at baseline, during exercise and 1 to 4 days after exercise	↑ OPG after 20 min and remained elevated 1 day	↑ CTX for 4 days after training ↑ PTH for 4 days after training
Ziegler et al., 2005	31 long-distance runners	Running distances of either 15 or 42.195 km, respectively with evaluation before and immediately after the race	↓ soluble RANKL in both groups ↑ OPG only in runners covering 42.195 km	
Kersch-Schindl et al., 2009	18 runners (16 men and 2 women)	Spatathlon race 246 km Determinations of parameters at 15 min after the end of the race as well as three days after the race	↑ OPG ↑ RANKL Three days after the race	↑ CTX ↓ osteocalcin

Abbreviations: hs-CRP = hypersensitive C reactive protein; IFN- $\gamma$  = interferon- $\gamma$ ; TNF- $\alpha$  = tumor necrosis factor- $\alpha$ ; IL = interleukin; CTX = C-terminal telopeptide of collagen type I; BMD = body mass density; PTH = parathormone; HOMA-IR = Homeostasis Model Assessment-insulin resistance; ↑ increased; ↓ decreased; ↔ non-modified

of weight-bearing aerobic exercise training and diet-induced weight loss on bone turnover markers was investigated (Hinton et al., 2006). The subjects included in this study underwent 6 weeks of energy restriction (reduced by approximately 3140 kJ/d) and aerobic exercise (approximately 1675 kJ/d, walking or jogging at 60% maximum oxygen consumption) to induce a 5% reduction in body weight. After 6 weeks, bone formation markers, osteocalcin, and bone alkaline phosphatase, were significantly increased, and bone resorption markers, C-terminal cross-links of type I collagen and soluble RANKL, were unchanged. The authors concluded that weight-bearing aerobic exercise training may favorably affect the balance between bone resorption and bone formation during weight loss (Hinton et al., 2006).

In postmenopausal women, 8 weeks of aerobic exercise were associated with a decrease in central adiposity, osteocalcin levels and insulin resistance, without a significant modification of OPG (Wieczorek-Baranowska et al., 2012).

Postmenopausal women have also been evaluated after a prolonged exercise program. In one study, 112 postmenopausal women (92 completed the study) were enrolled in an exercise program consisting of three fast 30-min walks and one or two 1-h aerobic training sessions per week over 1 year (Bergström et al., 2012). The bone turnover markers C-terminal telopeptide of collagen type I and bone alkaline phosphatase decreased in the training group versus controls, but the changes were small, while OPG increased significantly. The authors concluded that this kind of exercise induced an OPG-dependent inhibition of bone mass loss in postmenopausal women (Bergström et al., 2012).

#### *High intensity exercise studies*

Acute and intense exercise stimulates bone resorption but not bone formation. After strenuous running in recreationally active men and endurance-trained men, bone resorption but not bone formation was increased (Scott et al., 2010). Increased bone resorption may be caused by an increase in PTH, whereas elevated OPG was considered a compensatory response to increased bone resorption. These modifications are not influenced by the training status (Scott et al., 2010).

Long-distance running has been shown to have a favorable effect on bone mass. Ziegler et al. (Ziegler et al., 2005) determined plasma concentrations of OPG and soluble RANKL in 31 long-distance runners before and immediately after running distances of either 15 or 42.195 km, respectively. In both groups of endurance runners, a significant decrease of soluble RANKL was observed during the run, the extent of which was correlated with the running distance. An increase in OPG was observed only in runners covering the marathon distance of 42.195 km. The authors speculated that the known positive effect of long-distance running on the skeletal mass may be mediated by the OPG/RANKL system (Ziegler et al., 2005).

Even if regular physical exercise exerts a favorable effect on the skeleton, excessive physical exercise may have opposite effects. Osteocalcin, cross-linked-C-telopeptide of type I collagen, OPG, and RANKL were determined in 18 runners who participated in Spartathlon,

an annual ultramarathon race of 246 km. The results indicate increased bone resorption and suppressed bone formation (Kersch-Schindl et al., 2009) (Table I).

The results of these studies indicate that exercise, including both aerobic and resistance training, has favorable effects on bone mass. Even though aerobic exercise, especially walking, is preferred, it is considered that resistance training may be superior to aerobic exercise because peak load is the most important factor affecting bone mineral content (Kerr et al., 1996). Muscle contraction increases mechanical stress that enhances fluid forces, which stimulates biochemical mechanisms involved in osteogenesis (Atapattu et al., 2015). A combination of aerobic exercise (such as walking) and high impact exercise (jogging or stepping) is recommended for optimal benefits in elderly persons (Atapattu et al., 2015).

The great majority of studies have shown no significant modification of circulating OPG and RANKL. We cannot speculate any correlation between OPG and RANKL changes in these studies.

An increase in OPG was found after a prolonged aerobic exercise program for 1 year in postmenopausal women (Bergstrom et al., 2012) and after long-distance running in the marathon race (Ziegler et al., 2005), suggesting a possible implication of OPG in bone mass protection and a role of OPG as a mediator of mechanical loading in humans. Nevertheless, excessive physical exercise may have opposite effects with increased bone resorption (Kersch-Schindl et al., 2009). Acute and very intense exercise stimulated bone resorption but not bone formation, and the increase in OPG levels was considered a compensatory mechanism to increased bone resorption (Scott et al., 2010).

In conclusion, physical exercise induces favorable bone metabolic effects; the precise role of OPG and RANKL is not yet clear. There are important differences between studies regarding their exercise protocols, population, type and duration of exercises, time intervals between exercise programs and laboratory determinations. Moreover, as we mentioned before, there are very different sources of OPG and RANKL that could influence the circulating levels of these molecules. Further studies are necessary to elucidate the role of OPG and RANKL in the mechanism involved in the protective effect of exercise on bone metabolism.

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