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From Cell Biology to Tissue Engineering

Review

The importance of physical activity in osteoporosis. From the molecular pathways to the clinical evidence

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Summary. Osteoporosis is a very common bone disorder characterized by low bone mass and signs of deterioration, responsible for bone fragility typical in this pathology. The risk factors for the onset of osteoporosis are many and different from each other. Some of them cannot be modified, such as age, hereditary diseases and endocrine diseases. Others are modifiable, so that prevention is an advisable tool to reduce the incidence of osteoporosis. Among preventive tools, physical activity is certainly a valid instrument of prevention, in fact physical activity contributes to a healthy energy balance and increases muscle mass and bone mass. In the present narrative review, we wanted to pay attention to the possible influence of physical activity on the pathophysiological molecular pathways of osteoporosis and to the use of different exercise training in treatment of osteoporosis. From the literature analyzed, in relation to the effects of physical activity on bone metabolism, it is shown that exercise acts on molecular pathways of bone remodeling involving all cellular types of bone tissue. In relation to clinical trials adopted in patients with osteoporosis, it is evident that a multi-component training, including aerobic activity and other types of training (resistance and/or strength exercises), is the best kind of exercise in improving bone mass and bone metabolism in older adults and especially osteopoenic and osteoporotic women. With regard to whole-body-vibration training, it seems to be a valid alternative to current methods due to its greater adaptability to patients. In conclusion, physical activity, whatever the adopted training, always has beneficial effects on patients suffering from osteoporosis, and not only on bone homeostasis but on the whole skeletal muscle system.

Key words: Osteoporosis, Aerobic training, Resistance exercise, Strength exercise, Whole-body-vibration training

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Introduction

Bone tissue is a dynamic tissue, characterized by a continuous turnover throughout life. It is reduced as a consequence of several physiological events and is substituted with new bone tissue through the complex mechanism of bone remodeling (Musumeci et al., 2013a). In bone remodeling, osteoblasts produce the receptor activator of nuclear factor kappa B ligand (RANKL), macrophage colony-stimulating factor (M-CSF) and osteoprotegerin (OPG), which, as is well known, are the most important regulators of bone remodeling (Fig. 1). M-CSF and RANKL induce the proliferation and differentiation of mature osteoclasts (Lerner, 2006). OPG inhibits osteoclast differentiation by its binding to RANKL and thereby blocks binding between RANKL and RANK receptor present on the osteoclast precursor (Lerner, 2006). The osteoclast activity is also regulated by growth factors and cytokines such as tumor necrosis factor (TNF-α), the interleukin cytokines (IL-1, IL-6, IL-7), transforming growth factor (TGF-β), vascular endothelial growth factor (VEGF), platelet-derived growth factor (PDGF) and fibroblast growth factor (FGF) (Lerner, 2006).

During childhood and in early life, the amount of newly formed bone tissue is superior to that of reduced bone, consequently bone density and its strength reaches a maximum at around 30 years (Gerber et al., 2003). Afterwards, the body degrades more bone tissue than it forms new (Gerber et al., 2003). If, after 30 years of age, the degradation of the bone tissue occurs too quickly or if the density of bone mass is low, osteoporosis can appear (Rizzoli, 2014). Osteoporosis is a very common bone disorder characterized by weakening of the bones, which may cause bone fractures even after simple falls or slight injuries (Musumeci et al., 2011). In osteoporosis, the bone tissue shows low bone mass and signs of deterioration, responsible for bone fragility typical in this pathology (Lips and van Schoor, 2005; Pichler et al., 2013). Osteoporosis-related fractures are over 1 million every year in the USA and they will increase, in future years, by about 50% (Adachi et al., 2003; Pichler et al., 2013). Among the pathologies of the bone tissue, osteoporosis is the most common (Rizzoli, 2014) and affects both men and, particularly, women after menopause (Geusens, 2015). Osteoporosis can be divided into primary or secondary. Primary osteoporosis includes: idiopathic juvenile osteoporosis, a rare form that can affect adolescents and young adults, the cause of which is unclear (Khosla et al., 2008); post-menopausal osteoporosis which increases the risk up to 4 times (Cheng et al., 2009); senile osteoporosis, which can be caused by immobilization (Alexandre and Vico, 2011), low intake of micronutrients and hormones (Rizzoli, 2014), reduced function of the 1-α-hydroxylase (Kanis, 1999). Secondary osteoporosis is usually the consequence of medications such as glucocorticoids (Musumeci et al., 2013c), endocrine disorders, hematologic diseases, gastrointestinal disorders (e,g celiac disease), lifestyle factors, prolonged immobilization (Bonucci and Ballanti, 2014). The risk factors for the onset of osteoporosis are many and different from each other. Among them, some cannot be modified such as age, hereditary diseases (homo-

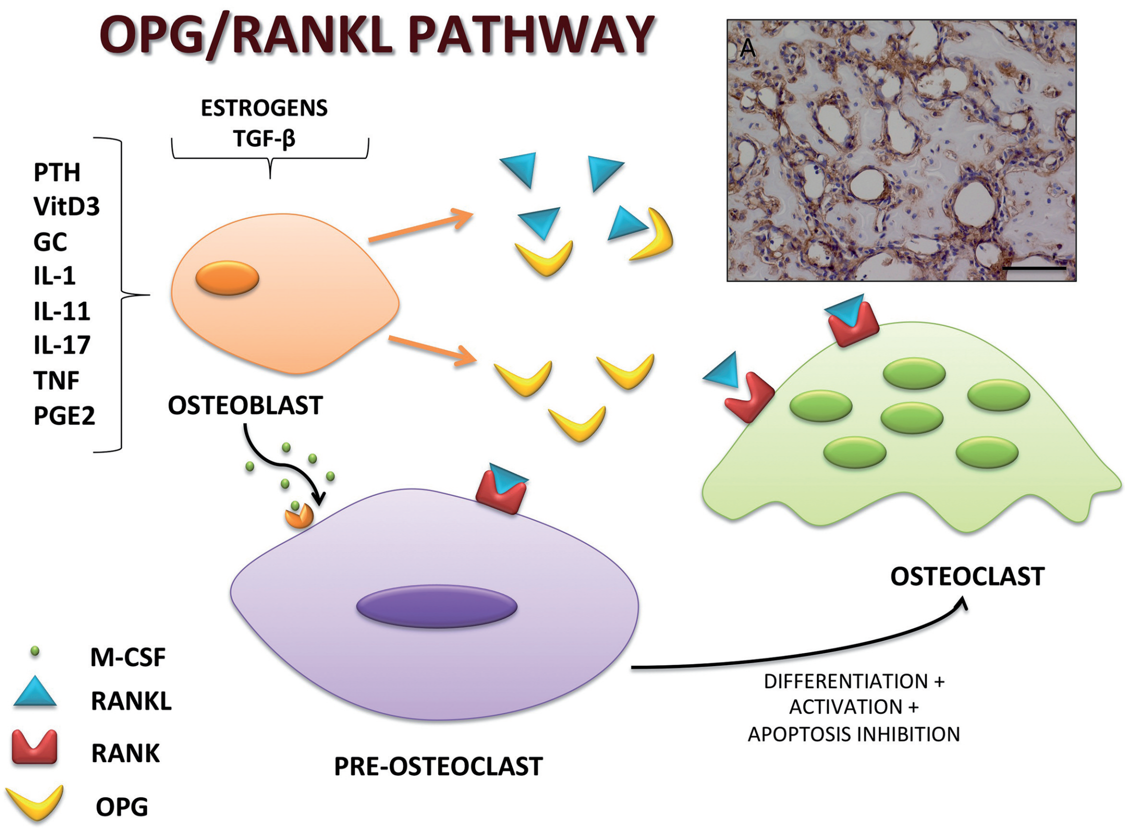

Fig. 1. OPG/RANKL pathway in bone remodeling. Osteoblasts produce RANKL, M-CSF OPG, regulators of the bone remodeling. M-CSF and RANKL induce the proliferation and differentiation of mature osteoclasts, respectively. OPG inhibits osteoclast differentiation binding to RANKL and, consequently, blocking binding between RANKL and RANK receptor present on the osteoclast precursor. Micrograph **(A)**, RANKL immunoexpression (IHC-P) of osteoblasts in normal trabecular bone. Scale bars: 100 µm.

cystinuria, osteogenesis imperfecta) (Hendrickx et al., 2015), endocrine diseases (Cushing's syndrome) (Tóth and Grossman, 2013), diabetes (Aiello et al., 2016) or other diseases such as rheumatoid arthritis and liver cirrhosis (Guañabens and Parés, 2011; Hoes et al., 2015; Musumeci, 2015; Trovato et al., 2016). Other risk factors are modifiable, among them lack of minerals in the diet, alcohol abuse, cigarette smoking, low body weight, use of drugs such as anticoagulants and antithrombin, physical inactivity (Rizzoli, 2014). With regard to modifiable risk factors, prevention is an advisable tool to reduce the incidence of osteoporosis (Ethgen et al., 2015). Among preventive tools, physical activity is certainly a valid instrument of prevention, in fact physical activity contributes to a healthy energy balance and increases muscle mass and bone mass (Pichler et al., 2013) and it also attenuates chronic disease conditions (Loreto et al., 2011; Pichler et al., 2013). In the present narrative review, we wanted to pay attention to some aspects of postmenopausal, senile and glucocorticoid-induced osteoporosis and particularly to the possible influence of physical activity on the pathophysiological molecular pathways of osteoporosis in order to support therapeutic applications of physical activity.

Bone remodeling in osteoporosis

Post-menopausal osteoporosis

The most common type of osteoporosis is one which is established at menopause, due to reduced estrogen production, required for growth, development and maintenance of bone tissue (Yuan et al., 2016). The post-menopausal reduction of estrogen implies that osteoclasts remove bone tissue excessively without the latter being replaced adequately by the activity of osteoblasts (McNamara, 2010). Osteoblasts and osteoclasts respond to estrogen by the two receptors ERα e ERβ that play a role in β-Catenin nuclear entry in response to mechanical strain in osteoblasts (Yuan et al., 2016). The binding of estrogen to ERα and ERβ on osteoclasts has an inhibitory effect on the latter and in particular on the formation of mature osteoclasts, and there is also an increase in their apoptosis (McNamara, 2010). The decrease of estrogen at menopause leads to an increase of hematopoietic progenitors of osteoclasts, which increase in number. There is also detected an inhibition of osteoclast apoptosis, and all this results in an increase in bone resorption (McNamara, 2010). It is also true that according to some studies, the regulation of osteoclast activity by estrogen is mediated by the presence of osteoblasts (Michael et al., 2005). Because osteoblasts and osteocytes have receptors for estrogen, menopause reduction of estrogen also affects their regular activity (McNamara, 2010). In the absence of estrogen, osteoblasts respond less effectively to mechanical stimuli in vitro (Jessop et al. 2004; Musumeci, 2016). In addition, estrogen deficiency induces apoptosis of osteoblasts (Kousteni et al., 2001) and alters the osteocytes network (Knothe Tate et al., 2004), thereby affecting the mechanical properties of bone tissue (Tatsumi et al., 2007). Many studies suggest that post-menopausal osteoporosis is due to alterations in levels of RANKL, M-CSF and OPG (Ikeda et al., 2001; Eghbali-Fatourechi et al., 2003). In addition, altered expression of TNF-α, IL-1, IL-6, IL-7, TGF-b, VEGF, PDGF and FGF results in post-menopausal osteoporosis (Zheng et al., 1997; Weitzmann et al., 2002; Sato et al., 2007).

Glucocorticoid-induced osteoporosis

The most common form of secondary osteoporosis is glucocorticoid-induced osteoporosis. Glucocorticoids (GC) have an anti-inflammatory function and are mainly used in inflammatory rheumatic diseases such as osteoarthritis (Musumeci et al., 2013b), rheumatoid arthritis, polymyalgia rheumatica, and respiratory diseases such as asthma (Briot and Roux, 2015). Data from the literature show that inflammation and inflammatory diseases have a negative effect on bone remodeling (Harre et al., 2012; Chen et al., 2013), in fact the differentiation of osteoclasts can be regulated by lymphocytes and fibroblasts during the inflammatory process or in deficiency of estrogen (Charatcharoenwitthaya et al., 2007). Even if GCs have an anti-inflammatory function, the prolonged use of GCs increases the risk of bone loss and of fractures (Roux, 2011), and the negative effect of GCs on bone remodeling is independent of inflammation, as shown in some studies (Ton et al., 2005). GCs increase the expression of RANKL and decrease the expression of OPG, thus resulting in an increase in bone resorption (Swanson et al., 2006). Although the use of GCs results in an increase in bone resorption, GCs mainly determine a decrease in the number of osteoblasts, osteocytes and in their activity, thus inducing a reduction in bone formation (Lane et al., 2006). GCs also determine changes in bone matrix surrounding the bone lacunae, decreasing the viability of osteocytes (Lane et al., 2006), and increasing apoptosis of osteocytes and osteoblasts through caspase 3 (Liu et al., 2004; Musumeci et al., 2013b). The osteoblastic activity also decreases as a result of an indirect effect due to the decrease of GH, IGF1 and IGF2 caused by GCs. Other indirect effects of GCs on bone tissue concern calcium metabolism, and in fact they decrease its gastrointestinal absorption and promote its renal loss. Furthermore, GCs reduce the production of sex hormones inducing hypogonadism, which in turn induces an increase in bone resorption (Canalis et al., 2007) (Fig. 2).

Senile osteoporosis

Although the most common form of senile osteoporosis is postmenopausal osteoporosis, whose pathophysiology has been discussed above, even males can be affected by this disease with a possible increase in falls and resulting fractures (Melton et al., 2000). Aging in itself can be the cause of osteoporosis, as a consequence of both hormonal alterations and osteoblast dysfunctions induced by age (D'Amelio and Isaia, 2015). In aging there is a reduction in bone formation due to reduced osteoblast activity. As is known, osteoblasts are differentiated from skeletal mesenchymal stem cells (MSCs) which, however, can also give rise to other cell lines such as adipocytes and chondrocytes (Sacchetti et al., 2007; Musumeci et al., 2014a). Studies on the pathophysiology of senile osteoporosis are controversial. In fact, according to some authors, aging reduces the number of MSCs able to differentiate into osteoblasts (Stolzing et al., 2008; Kuznetsov et al., 2009), on the contrary other authors do not reveal this scientific data (Stenderup et al., 2003; Zhou et al., 2008). According to other authors, during aging the number of MSCs is not reduced, but their ability to differentiate into osteoblasts is impaired, leading to decreased bone formation (Nishikawa et al., 2010). In addition, the aged osteoblast phenotype involves the release of inflammatory cytokines, proteases and growth factors that determine an increase in osteoclast activity, thus resulting in increased bone resorption (D'Amelio et al., 2011). Hypovitaminosis D, largely diffused in the elderly population (van Schoor et al., 2014), is considered a possible cause of senile osteoporosis (D'Amelio and Isaia, 2015), because its active form 1.25-dihydroxyvitamin D3, under physiological conditions, promotes the intestinal absorption of calcium maintaining the optimal calcium levels, thus promoting the mineralization of the bone tissue (Holick, 2006). On the other hand, a reduction of calcium leads to an increase of parathyroid hormone responsible for increased 1.25-dihydroxyvitamin D3 that, in order to ensure a proper level of calcium in the blood, stimulates osteoclast activity thus favoring bone resorption (Holick, 2006). Also, hormone levels alterations, especially sexual ones, during aging, are considered the causes of senile osteoporosis. In relation to women, we have already explained how the reduction in estrogen is directly involved in the onset of postmenopausal osteoporosis. With regard to men, many authors show that the decline in testosterone, but even more the bioavailability of estradiol, are responsible for the lower bone density and therefore for increased risk of fractures (Khosla, 2004; LeBlanc et al., 2009). Finally, in aging the expression of the enzyme 11 betahydroxysteroid dehydrogenase isozymes that converts cortisone to active cortisol in the bone is increased (Cooper et al., 2000) determining hypercortisolism and related

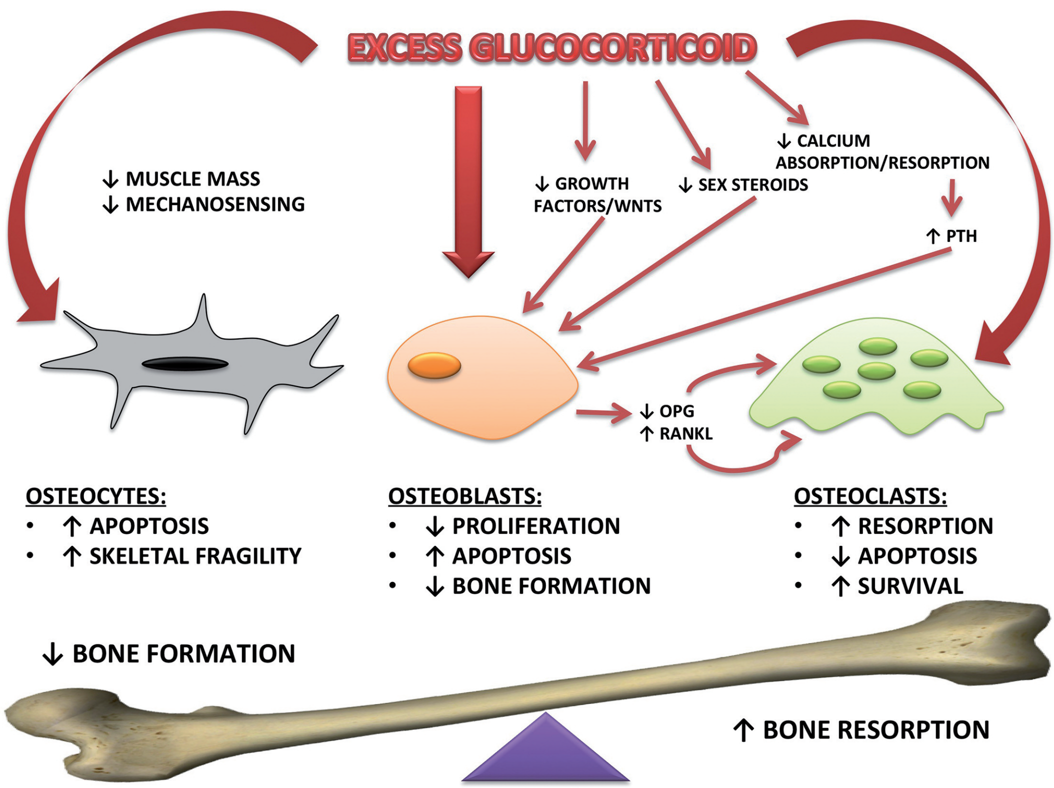

Fig. 2 Excess of glucocorticoids (GCs) in bone metabolism. Glucocorticoid excess leads to: increased RANKL, decreased OPG, increased osteoclasts differentiation, decreased proliferation of osteoblasts, increased apoptosis of both osteoblasts and osteocytes, changes in bone matrix, effects on production of GH, IGF1 and IGF2 and sex hormones, effects on calcium metabolism. All these effects induced by GC excess determine a decreased bone formation and an increased bone resorption.

consequences on homeostasis of bone tissue, as above described with regard to glucocorticoid-induced osteoporosis.

Osteoporosis, remodeling bone and exercise

The treatment of osteoporosis is usually pharmacological even though drugs can usually have side effects. This last consideration leads to the need for alternative treatments such as physiotherapy and physical activity, that used appropriately and for long periods, reduce the risk of fractures due to even banal falls in patients with osteoporosis. In relation to physical activity as a treatment for osteoporosis, it must be primarily safe, given the high risk of falls in patients with functional deficits of the skeletal system (Weber-Rajek et al., 2015). In the literature there are a lot of studies on understanding the molecular mechanisms triggered by physical activity on the metabolism of bone tissue and its possible use as a prevention tool in chronic musculoskeletal diseases such as osteoporosis and osteoarthritis (Musumeci et al., 2013b, 2015). Since most of them, experimental and/or clinical trials, are based on the use of training programs including different types of physical activity, such as aerobic exercise and/or resistance exercise, it is difficult to analyze the influence of a specific type of physical activity on the molecular pathways of bone tissue metabolism. Furthermore, the training programs are very different from each other in the exercise time, intensity, and duration of the protocols. However, fundamental knowledge is provided by the many studies on the topic. In relation to changes of OPG levels due to exercise training, many authors highlighted, both in human and in animal models, the increased expression of OPG consequent to a training program. For example, in postmenopausal women, after a one-year training program composed of aerobic, strengthening exercises and stretching, an increase of OPG has been shown (Bergström et al., 2012). Also in men, both a protocol of plyometric jumping exercises (Kish et al., 2015) and an acute, weight-bearing endurance exercise determined an increase in OPG that seemed uninfluenced by the exercise intensity (Scott et al., 2011). In rats, resistance exercise increased trabecular bone formation and decreased bone reabsorption, leading to an increase in OPG/RANKL ratio (Fig. 3) and consequent inhibition of osteoclast differentiation (Notomi et al., 2014).

In several studies it has been demonstrated that exercise also promotes osteoblast differentiation and bone formation. In the study by Scott and coauthors on the effects of an acute, weight-bearing endurance exercise, the increase of OPG was accompanied by increased levels of some markers of bone formation,

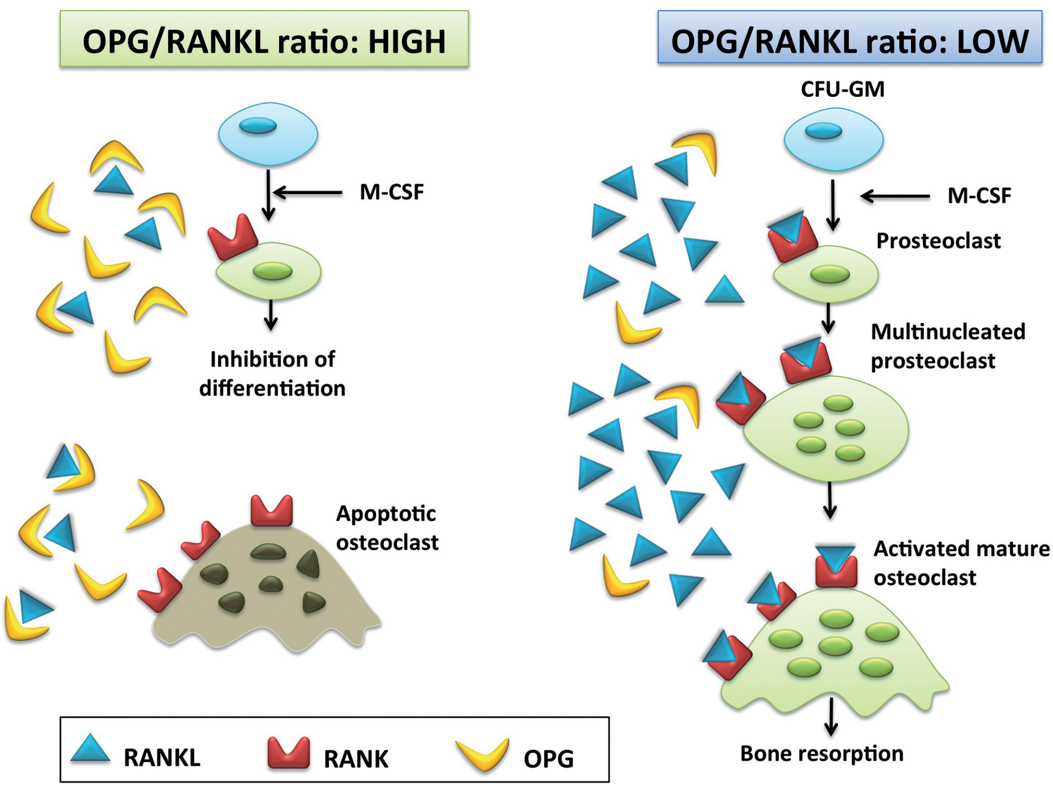

Fig. 3. OPG/RANKL ratio. A high OPG/RANKL ratio leads to inhibition of osteoclast differentiation, favoring bone formation. A low OPG/RANKL ratio promotes osteoclast differentiation, favoring bone resorption.

such as NH2-terminal propeptides of procollagen type 1 (P1NP), osteocalcin (OC) and bone alkaline phosphatase (ALP), and of parathyroid hormone (PTH), albumin-adjusted calcium (ACa), phosphate (PO4), and cortisol (Scott et al., 2011). The increase in serum markers of bone formation, ALP and Osteocalcin (OCL), in humans was shown after both acute plyometric jumping exercises (Kish et al., 2015) and long-term training, such as an 8-week jump training (Erickson and Vukovich, 2010) and an 8-week physical training program in women including aerobic, resistance, or combined aerobic and resistance exercises (Lester et al., 2009). Moreover, scientific data demonstrated that physical activity could promote bone formation inducing MSCs to differentiate towards osteoblasts. Maredziak and colleagues showed that endurance training, in mice, increased the total number of bone marrow MSCs, enhancing osteogenic differentiation and inhibiting the adipogenic potential of MSCs (Marędziak et al., 2015). Moreover, exercise promoted osteogenic differentiation in cultured MSCs from osteopenic adult female rats through increased production of nitric oxide (NO) which has a stimulatory effect on osteogenic differentiation of MSCs (Ocarino et al., 2008). In another animal model, exercise increased the number of mineralized nodules, and the expression of bone ALP and osteocalcin (OCL) in the MSCs (Hell et al., 2012).

Exercise can also influence the secretion of some hormones involved in bone formation, such as parathyroid hormone, prostaglandin E2 (PGE2) and estrogen (Yuan et al., 2015). In a mouse model study, Menuki and colleagues showed increased expression of PTH 1 Receptor due to climbing exercise, enhancing osteoblast differentiation from bone marrow mesenchymal stem cells (Menuki et al., 2008). Moreover, during exercise (a single bout of running on a treadmill) in male mice PTH release increased and PTH signaling enhanced, testifying a bone adaptation (Gardinier et al., 2015). PGE2 and estrogen may also increase in humans as a consequence of moderate exercise (Smith et al., 2013). In addition, exercise training could lower the PGE2 dose required to prevent ovariectomy-induced bone loss in old rats (Mo et al., 2002).

Moreover, some authors reported higher levels of anti-inflammatory cytokines such as IL-2 and IL-10, and lower levels of pro-inflammatory cytokines such as TNF-α and IL-6, as a consequence of moderate exercise, suggesting that exercise can also promote bone formation and inhibit bone resorption by OPG/RANKL/RANK-independent signaling pathways (Santos et al., 2012).

In addition to training programs, many studies support the effectiveness of the whole-body-vibration (WBV) training, and in particular its positive effects on bone turnover in osteoporosis, even if the literature data are controversial and often not uniform in methodology, so although the signs are positive, it is difficult to generalize on the role of whole-body-vibration training on osteoporosis pathophysiology (Musumeci et al., 2013b; Pichler et al., 2013). For example, some authors showed that a vertical sinusoidal WBV training (10 times for 60 s, with 60 s rest between the vibration sets) induced a hormonal response with an increase in testosterone and growth hormone levels and a decrease in cortisol concentration accompanied by an increase in neuromuscular effectiveness (Di Giminiani et al., 2014), and the combined effects on the endocrine system and neuromuscular one suggest its therapeutic approach for sarcopenia and possibly osteoporosis (Cardinale and Pope, 2003). Also, in animal models of postmenopausal osteoporosis (ovariectomized rats), different studies indicate that the method of safe and easily applicable vibration, in the form of a vibrating platform, is effective in preventing early post-ovariectomy bone loss and supports the idea of beneficial effects of passive physical loading on the preservation of bone in ovariectomized animals (Oxlund et al., 2003). Naghii and collaborators in a study on male rats subject to a vertical sinusoidal WVB training for 8 weeks, detected plasma levels of estradiol, IL-6 and vitamin D significantly higher in the experimental vibration group compared with the controls (Naghii et al., 2011). In a recent study of ours on rats affected by prednisolone-induced osteoporosis, we demonstrated that both treadmill exercise (12 weeks, five times a week for 30 minutes, with the treadmill inclined at 2° set at 10-speed m/min) and WBV exercise (30 minutes each day, 5 days per week, for 12 weeks) resulted in a decreased expression of RANKL and an increased expression of OPG in opposition, therefore, to the action of glucocorticoids in inducing osteoporosis, even if the best results were obtained when a combination of both trainings was used (Pichler et al., 2013). Anyway, due to the fact that the literature data are controversial and often not uniform in methodology, major clarifications are required to elucidate the relationships between biochemical factors, bone structure and parameters of the vibration training for osteoporosis.

Physical training in clinical trials of osteoporosis

Aerobic exercise

Aerobic exercise is the most appropriate training for patients with osteoporosis, due to the bones' fragility and their often-advanced age that does not allow exercise of great physical impact. Data from the literature show that most of the clinical trials on the treatment of osteoporosis use aerobic training such as jogging, stair climbing, step training and, above all, walking. In particular, they measure the bone mineral density (BMD) and bone mineral content (BMC) as parameters to evaluate the effect of a specific training. In osteopenic postmenopausal women performing a training composed of walking combined with stepping at a moderate intensity for 24 weeks, the BMD of the lumbar spine and the femur increased 2.0% and 6.8% respectively (Chien et al., 2000). Moreover, in a longer aerobic training (22 months) including walking, jogging and stair climbing in postmenopausal patients, the BMC at lumbar spine increased 6,1% compared with the control group (Dalsky et al., 1988). BMD of senior athletes competing in running and swimming events compared with that of sedentary controls was higher among runners suggesting that moderate impact activities play a role in maintaining skeletal integrity with age (Velez et al., 2008). On the other hand, in a review by Martyn-St James and Carroll, it was shown that regular walking has no significant effect on preservation of BMD at the spine and at the radius in perimenopausal and postmenopausal women, whilst significant positive effects at femoral neck was evidenced (Martyn-St James and Carroll, 2008; Ma et al., 2013). However, even if aerobic training seems to be more appropriate to patients with osteoporosis, the global results are controversial perhaps due to the great variability in the protocols of the individual studies.

Resistance and/or strength exercise

Resistance, strength exercise and generally physical activities involving impact forces have better effects on bone metabolism even if these kinds of training are not always suitable for patients with osteoporosis, who are often elderly people usually with joint limitations, such as osteoarthritis (Musumeci et al., 2014b; Mobasheri et al., 2015), herniated discs, vertebral fractures and knee problems (Castrogiovanni and Musumeci, 2016). Nevertheless, from the clinical trials, it is evident that the BMD of patients undergoing these types of training improves or is at least preserved. Bocalini and coauthors demonstrated that 24 weeks of strength training (3 times/week) improved body composition parameters, increased muscular strength, and preserved BMD in postmenopausal women (Bocalini et al., 2009). In a clinical trial involving 59 postmenopausal women with osteoporosis or osteopenia, weight training exercise did not significantly improve bone mineral density in postmenopausal women, but in comparison to the control group, the results showed the importance of the weight training exercise for maintenance of bone health in postmenopausal women (de Matos et al., 2009). When the effect on BMD of two different schemes of loading in resistance training (different movement velocity) was explored, in 53 pretrained postmenopausal women, power training (explosive/4 s) seemed to be superior for maintaining BMD than strength training (4 s (concentric)/4 s) (von Stengel et al., 2007). Kerr and colleagues in a study conducted in 1996, examined the effect of a progressive resistance training program (1 year) on the bone mass of 56 postmenopausal women. Women were assigned to one of two resistance-training groups: a strength trained group (3x8 repetition maximum) or an endurance group (3x20 repetition maximum). The authors showed that postmenopausal bone mass could be significantly increased by a strength regimen that uses high-load low repetitions but not by an endurance regimen that uses low-load high repetitions, concluding that the peak load is more important than the number of loading cycles in increasing bone mass in early postmenopausal women (Kerr et al., 1996). In a meta-analysis on prevention and treatment of osteoporosis, Howe and colleagues verified a relatively small statistically significant, but possibly important, effect of exercise on bone density of postmenopausal women, and in particular the type of exercise that better benefits BMD was a no-impact high intensity resistance training, concluding that exercise has the potential to be a safe and effective way to prevent bone loss in postmenopausal women (Howe et al., 2011). Also with regard to resistance and/or strength training, the results of the different clinical trials are not all uniform, but they seem to better support the effects of this kind of training on bone metabolism.

Multi-component training

There are many literature data indicating that the best training for patients affected by osteoporosis or predisposed to this bone disorder consists of a combination of different types of physical exercise. An 8-month multi-component training with moderate-impact weight-bearing exercises reduced the potential risk factors for falls, improving muscle strength, balance, agility, and related fractures in older women (Tolomio et al., 2008; Marques et al., 2011). Moreover, a one-year multi-component community-based exercise program was effective for increasing BMD, independently of a calcium-vitamin D(3) supplement, which did not enhance the osteogenic response (Kukuljan et al., 2009). In post-menopausal women, ongoing hormone replacement therapy and performing physical therapy and gradually incorporated resistance and endurance training or home exercise (flexibility exercises) for 9 months, relatively vigorous exercise training, significantly increased lumbar spine BMD reducing fracture risk (Villareal et al., 2003). Finally, Karinkanta and colleagues showed that a combination of strength, balance, agility and jumping training for 1 year, prevented functional decline and bone fragility in women (70-78 years old), supporting the idea that it is possible to maintain good physical functioning by a multi-component exercise program and thus postpone the age-related functional problems (Karinkanta et al., 2007).

Whole-body-vibration training

Whole-body-vibration training (WBV) is a type of safe physical activity since this technique consists of performing specific exercises or maintaining a static position on a vibrating platform (Runge et al., 2000). In the literature there are many data and experiences of clinical trials in which WVB is used, particularly on patients suffering from postmenopausal osteoporosis. Iwamoto and colleagues suggest that WBV exercise using a Galileo machine appears to be useful in reducing chronic back pain, probably by relaxing the back muscles in post-menopausal osteoporotic women treated with alendronate (Iwamoto et al., 2005). The same authors confirmed their results in another randomized trial on 52 postmenopausal osteoporotic women treated with alendronate, in which they showed the benefit and safety of 6 months WBV training for improving their physical function (Iwamoto et al., 2012). Ruan and coauthors demonstrated that a treatment through a vibration platform, with a vibration frequency of 30 Hz, amplitude of 5 mm, for six months, appears to be useful in reducing chronic back pain and increasing the femoral neck and lumbar bone mineral density (BMD) in postmenopausal women with osteoporosis (Ruan et al., 2008). In a 1-year prospective, randomized trial of 70 postmenopausal women, Rubin and collaborators demonstrated that brief periods (<20 minutes) of a low-level (0.2g, 30 Hz) vibration applied during quiet standing can effectively inhibit bone loss in the spine and femur, particularly in those subjects with lower body mass (Rubin et al., 2004). Another study compared WBV training with coordination/balance training on neuromuscular function in 68 postmenopausal women with osteopenia or osteoporosis who may be at risk of falls and bone fracture, and the authors provide evidence that short-duration WBV exercise can have a greater impact on some aspects of neuromuscular function in post-menopausal women with low bone density than proprioceptive training (Stolzenberg et al., 2013). The majority of clinical trials suggest the utility of WBV training in improving bone mass, and so better outcomes in osteoporosis condition, in postmenopausal women, but few indications exist on the treatment by WBV of senile osteoporosis in men, so further studies are needed in order to confirm the same for the male sex. Anyway, from the above reported scientific data it is highlighted that low intensities and low amplitudes are more suitable for individuals with a higher risk of fractures such as patients with osteoporosis (Moreira et al., 2014). To date vibrating training is considered complementary to pharmacological and dietary treatments of osteoporosis.

Conclusion

From the literature analyzed in the present narrative review, some important knowledge appears, both on the importance of physical activity in the molecular mechanisms involved in bone metabolism and the different types of exercise training adoptable to prevent and treat osteoporosis. In relation to the effects of physical activity on bone metabolism, it is shown by many studies that exercise acts on molecular pathways of bone remodeling involving all cellular types of bone tissue, such as, for example, the stimulation of MSC osteogenic differentiation and the activities of osteoblasts and osteocytes. Furthermore, physical exercise inhibits osteoclastogenesis and bone resorption via OPG/RANKL, secreted by MSCs, osteoblasts, and osteocytes, and the pro-inflammatory cytokines. In relation to clinical trials adopted in patients with osteoporosis, there is a great variability in the training programs adopted in the many and different analyzed studies. With regard to aerobic training, the clinical trials point out that aerobic exercises are very suitable for elderly patients due to the low impact, but what emerges is that aerobic training is above all helpful in maintaining or slowing the loss of bone mass, whereas there is no significant improvement in BMD and bone parameters. From the clinical trials, it is much more evident that the BMD of patients undergoing resistance, strength exercise and generally physical activities involving impact forces, improves. The limit of this kind of training is that it is not always suitable for patients with osteoporosis, who are often elderly people. In order to improve BMD, bone parameters and metabolism, many clinical trials show that a multi-component training, including aerobic activity and other types of training (resistance and/or strength exercises) seems much more useful. This improves bone mass and bone metabolism in older adults and especially osteopoenic and osteoporotic women. Moreover, WBV training seems to be a valid alternative to current methods due to its greater adaptability to patients. It has similar effects to strength training and it also has other benefits, improving balance and, consequently, reducing the risk of falls. Such mechanical stimulation could therefore be a possible therapy in osteoporosis and in preservation of bone tissue as well as prevention of further bone damage. Further findings are needed to better understand the interactions between the molecular signals induced by physical activity and the pathways of bone metabolism in order to define the best treatment for the occurrence and progression of osteoporosis in medical therapy to preserve tissue function and prevent bone damage.

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