

## Hypothesis

# A hypothesis about the role of exercise training intensities on bone turn over and muscle-bone cross talk in post-menopausal women: pH influences

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## Abstract

pH stress can be caused by menopause, poor nutrition, high protein intake, old age, prolonged strenuous and anaerobic exercise, anemia, diabetes, AIDS, and respiratory diseases. High calcium enters the bloodstream from the bones during the proton buffering due to metabolic acidosis, which the renal system excretes a significant amount of this calcium to eliminate the acidosis condition and regulate body pH. At the bone surface, this increase in hydrogen ions due to metabolic acidosis can destroy osteoblastic and strengthen osteoclast activity, which negative bone turnover and increases the amount of excreted calcium, thus accelerating the progress of osteoporosis. Due to the widespread prevalence of osteoporosis in postmenopausal women and the provision of various therapies such as medication, estrogen therapy, and proper diet, in recent studies, special attention has been paid to the role of endurance and resistance exercise to decrease osteoporosis or prevent the development of this disease. Also exercise training increases irisin secretion from muscle tissue, which this myokine has beneficial effects on other tissues especially on bone. Irisin increases osteocytic survival and production of sclerostin in bone tissue, which is associated with bone remodeling. However, exercise training in some intensity through metabolic mechanisms can increase pH stress and acidosis and may contribute to the development of osteoporosis in postmenopausal women. As a result, the hypothesis of different intensities of exercise and their induced acidosis stimuli in postmenopausal women should be considered.

**Key Words:** Menopause, pH stress, Exercise training intensities, Bone, Irisin

## Introduction

Maintaining a physiological pH is vital to the survival of body cells. One of the most important physical stresses that effects on cell homeostasis is the change in normal pH (Liu, Dan, Lu, & Pan, 2018). Increasing the pH value above 7 leads to alkalosis of the cell body and decreasing it below 7, cause's acidosis, which this value varies in different tissues. Various studies have shown higher harms of acidosis stress than alkalosis stress. For example, a decrease in blood pH may be due to a decrease in bicarbonate (HCO<sub>3</sub>, metabolic acidosis) or an increase in PCO<sub>2</sub> (respiratory acidosis) (Burger & Schaller, 2019). However, stimulation of metabolic acidosis is associated with an increase in the amount of protons and hydrogen ions (H<sup>+</sup>) in the body cells, which these phenomena not commonly seen in respiratory acidosis (Batlle, Chin-Theodorou, & Tucker, 2017). In addition, in the human body cells, H<sup>+</sup> is effective in stimulating acidosis through various oxidation reactions and other agent (Figure 1).

The presence of large concentrations of H<sup>+</sup> in the systemic bloodstream calls acidosis. Acidosis can cause serious damage to vital organs, especially the nervous system which can affect the control of the whole body, thus according to homeostasis, increase H<sup>+</sup> during metabolic acidosis must be cleared by a buffering system. One of the most important of which is the skeletal system or bone tissue, which during metabolic acidosis neutralizes the amount of H<sup>+</sup> with its key minerals, the most important of which is calcium (Liu et al., 2018). High calcium enters the bloodstream from the bones during the proton buffering due to metabolic acidosis, which the renal system excretes a significant amount of this calcium to regulate the pH and acidosis (Alexander, Cordat, Chambrey, Dimke, & Eladari, 2016). In the acidosis condition the activity of osteoclast is stimulated and the mineralization of the bone matrix is inhibited by the osteoblast (Figure 2). In addition, pH stress alters bone cell by influencing protein conformation and Transcription factors NFATc-1 and AP-1 (jun, Fos, ATF) and alters the structure of RANK / RANKL and genes expressed in osteoblasts, especially osteocalcin (Frick & Bushinsky, 2003; Lian & Stein, 2001; Roy, 2013; Spilmont et al., 2013). This process induces more bone resorption by increasing PGE<sub>2</sub> in osteoblast (Kato & Morita, 2013).

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Although bone has three general functions: structural support, protection of vital organs, and mineral storage, PH stress can reduce growth during puberty (Lemann Jr, Adams, Wilz, & Brenes, 2000) as well as increase bone resorption in old age, especially in women after menopause (Arnett, 2003; Meghji, Morrison, Henderson, & Arnett, 2001). Menopause is at risk factor for osteoporosis (Gambacciani, 2020; Huang et al., 2018). Also, exercise training is an agent that it can induce pH stress and acidosis (Robergs, Ghiasvand, & Parker, 2004; Sue, Wasserman, Moricca, & Casaburi, 1988). However, in postmenopausal women, there is conflicting debate about the relationship between pH stress and the intensity of physical activity, in terms of metabolic mechanisms and bone reversibility cycles. Physical activity has been reported to be an important factor in achieving maximal bone mass, but the mechanisms that affect bone metabolism due to exercise intensity and pH stress have not been fully understood. Therefore, the hypothesis of the present study is based on whether the pH stress caused by different training intensities is effective on bone reversibility in postmenopausal women.

## Hypothesis

The decrease in bone density, apart from aging, usually occurs due to inactive lifestyle (Kovvuru et al., 2020; McEntee, 2020). Studies have shown that mechanical stress induced by exercise is required to maintain optimal bone density (Benedetti, Furlini, Zati, & Letizia Mauro, 2018). However, exercise, especially strenuous exercise in aging, apart from mechanical stress, is able to impose a lot of negative stress on the calcium homeostasis and bone related hormones (Aly, Desouki, Abdel-Mottaleb, & Sweed). PH stress can increase at different exercise training intensities, and it causes metabolic acidosis (Chatel et al., 2017; Robergs et al., 2004; Wahl, Zinner, Achtzehn, Bloch, & Mester, 2010). It is stated that acidosis inhibits osteoblastic and stimulates osteoclastic activity (Bushinsky, 1995; Krieger, Sessler, & Bushinsky, 1992). This process in bone cells

, promotes bone turnover toward negative balance by increasing activation of osteoclast (Herrmann et al., 2007; Meghji et al., 2001; Yoon, 2018). In the post menopause women this acidosis and negative bone turnover is very harmful because apart from this stress, menopause causes osteoporosis (Lerner, 2006). In other words, the benefits of physical activity and exercise in preventing and reducing health risks in the elderly population have been confirmed, but its beneficial effects on the population of postmenopausal women need further investigation.

Based on increasing acidosis in some intensity of exercise training, it is not clear which exercise training are more valuable for postmenopausal women or how much exercise may be appropriate for this subjects. According to studies, different aerobic and strength exercise training can increase bone density (Armamento-Villareal et al., 2020; Beavers et al., 2017). But in postmenopausal women, walking is relatively ineffective in preventing a decrease in bone density (Jati et al., 2018; Sydora et al., 2020). Most studies that used load-bearing exercises in postmenopausal women, seems that this type of exercise have a natural increase in bone density due to mechanical loading (Kim & Lee, 2019; Watson et al., 2018). However, this study doesn't consider pH stress with anaerobic contraction and acidosis after resistance training. Different modality of exercise training in ageing women creates a variety of adaptation. It seems that that the amplitude of traction in exercise training (at different age) determines the amount of cell response. It has been show that began of exercise training in middle age and continued into old age, it had a positive effect on bone mass (Nishimura et al., 2018). While, this positive effects may not be obtained when the exercise program was started after mid-aged. However, the benefit of exercise was not limited by age (SMITH & RAAB, 1986). Another study, in female rats showed that young animals exercising on treadmills were directly affected by exercise stress by increased mineralization in the bone cortex (Iwamoto, Yeh, & Aloia, 1999; McDonald, Hegenauer, & Saltman, 1986). While in older subjects without bearing the weight on bones showed that it can have a systemic effect on bone density (Marques et al., 2011).

There are several important issues in consider of exercise training in ageing. One of them is the amount of load (mechanical stress) of exercise training and the other is related to the intensity of exercise used (biochemical stress and pH due to some exercise intensity). Higher-intensity weight-bearing exercise (i.e. jogging instead of walking or walking) put more strain on the bone and leads to metabolic acidosis, which may play a role in bone remodeling (Henderson et al., 1989). It seems that acute and chronic exercise (spatially in athlete) creates different response in bone to pH stress in ageing. Jacobson et al showed that ageing female athletes had similar bone mineral density in the radius and lumbar vertebrae to younger female athletes. As a result, the difference was not observed between older athletes and older non-athletes group

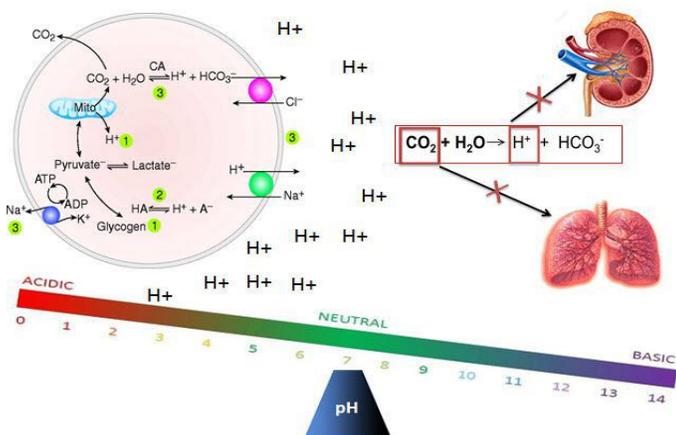


Figure1. Increase of H<sup>+</sup> in the human body through different oxide reactions and reduction in pH stress stimulation.

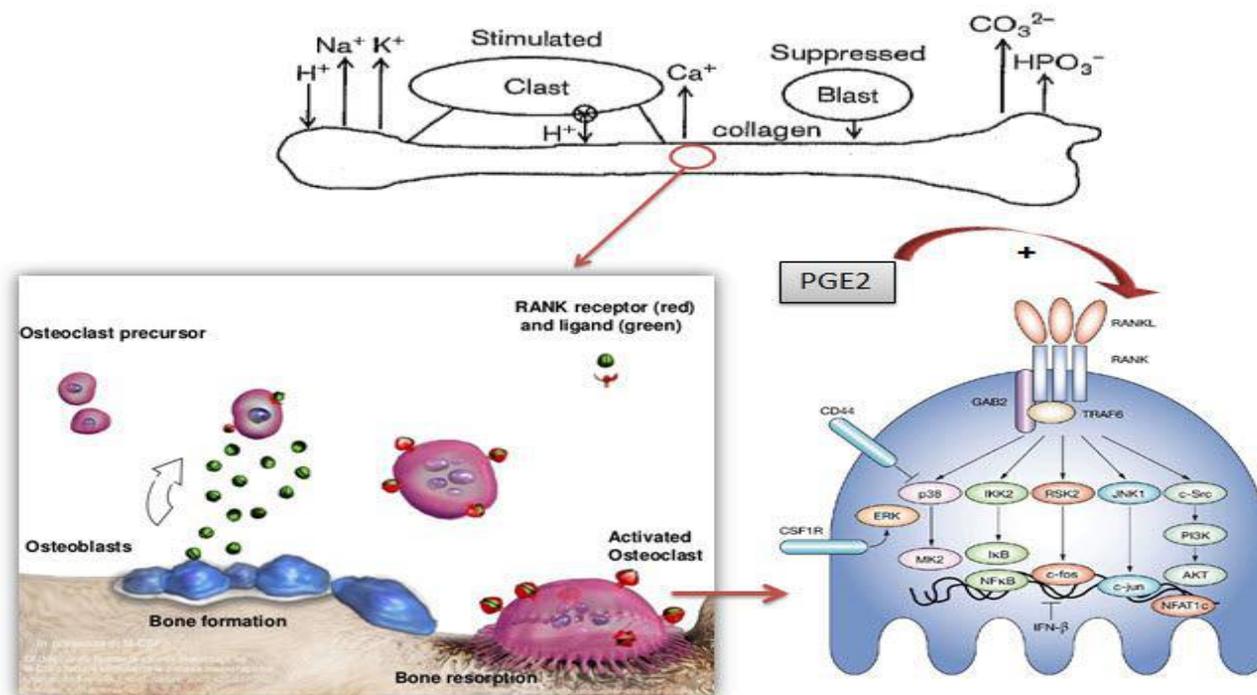


Figure 2. Schematic of the effect of metabolic acidosis on bone.

(Jacobson, Beaver, Grubb, Taft, & Talmage, 1984). This study supports the idea that exercise may be especially important in the postmenopausal years. Talmage et al. showed that in non-athlete women, radius bone density decreases with age after approximately 47 to 52 years, but no changes were observed in female athletes (Talmage, Stinnett, Landwehr, Vincent, & McCartney, 1986). Nelson et al. show that postmenopausal women with endurance training had similar bone density in the radius and vertebrae compare to women who were sedentary (NELSON, MEREDITH, DAWSON-HUGHES, & EVANS, 1988). These changes can be attributed to weight loss from exercise or even pH stress due to intensity of exercise training. Athletes participating in aerobic non-weight-bearing sports such as cycling and swimming usually had lower BMDs than other participants in resistance and impact exercise.

It is important to note that when exercise is performed in obese women for a long time, the beneficial role of mechanical stress due to weight loss in bone were eliminated and therefore other stresses should be considered in this hypothesis. Various mechanisms can be considered to investigate the role of exercise intensity, pH stress in women, especially after menopause. In addition to the metabolic benefits, endurance exercise at a variety of VO<sub>2</sub>maxes that include long sessions (increase duration of exercise), can induce respiratory and metabolic acidosis during fatigue, which can have the negative effect on bone metabolism (Bushinsky & Ori, 1993). Also, if intensity and duration of exercise training increased, it causes releasing catabolic hormones such as cortisol and then proteolysis in elderly people (Simmons, Miles, Gerich, & Haymond, 1984). It is stated that

at menopause period, there is a decrease in key female hormones such as estrogen, which this decrease also causes an increase in cortisol (McInnes et al., 2012). It has been show that both levels of exogenous or endogenous glucocorticoids reduce bone mineral density (Kumar, 2001).

The mechanism by which glucocorticoids reduce bone density is multifactorial (Perez, Oster, Katz, & Vaamonde, 1979). There is also evidence in both human and animal studies that metabolic acidosis stimulates increased cortisol production. Chronic metabolic acidosis can increase cortisol production, and both acidosis and cortisol can cause osteopenia (Kukreja, Bowser, Hargis, Henderson, & Williams, 1976; Weger, Kotanko, Weger, Deutschmann, & Skrabal, 2000). Also, Krieger et al. (2002) showed that cortisol inhibits the induction of bone resorption due to acidosis (Krieger, Frick, & Bushinsky, 2002). Studies on the effects of cortisol from both menopause and acidosis on bone destruction and osteoporosis in menopausal women has been limited. It is stated that, women have approximately 20% less aerobic capacity and less oxygen carrying capacity in their blood. Because this reason their response to exercise training is difference and it can cause acidosis. They also have metabolic differences than men in lipids metabolism at rest and during exercise training (Wilmore, Costill, & Kenney, 1994). These factors can be effective in inducing pH stress. Therefore, all these cases should be considered in exercise training prescription spatially in menopause women. For example, jogging may be a simply exercise for middle-aged, but for some postmenopausal women it can be too intense.

Different intensities of exercise training can be effective in inducing

pH stress. It is stated that in menopause women's, cycling (low intensity) can be recommended to improve general health and create a positive effect along with other strengthening physical activities and weight bearing (Moreira et al., 2014). In simple weight bearing activities such as walking, eliminating the intensity of exercise usually reduces the amount of stress caused by exercise. PH stress is usually stimulated at high training intensities (age-dependent), but in simple walking activity the amount of pressure on the metabolic systems is not high enough to stimulate metabolic acidosis. Studies have also measured the effect of walking activity on bone tissue, measuring only mechanical stress and the amount of load on bone mass. They showed that promoting and sustaining walking could improve thigh BMD in postmenopausal women without having any effect on spinal BMD. Although it had positive and significant effects on BMD of the femur neck, it should be noted that the effects of quick walking alone are not enough to stimulate spinal BMD in postmenopausal women. Proton release also occurs during ATP hydrolysis when an exercise becomes intense, the rate of ATP hydrolysis is not matched by the transfer of protons, inorganic phosphate, and ADP can't enter the mitochondria. Consequently, increase in ATP dependence on glycolysis. Under these conditions, the release of cytosolic protons from glycolysis and hydrolysis of ATP increases. Cell buffering capacity limited and as a result acidosis develops (Robergs, 2001). That this agent can cause stress in postmenopausal women.

### Muscle-bone cross talk



It has been shown that Sclerostin produced by osteocytes (Van Bezooijen et al., 2004). Osteocytes also create from mature osteoblasts, that located in the bone matrix and make approximately 90% of bone cell composition (Bonewald, 2011). Evidence suggests that osteocytes can also increase bone formation in the presence of high blood calcium (Qing & Bonewald, 2009). One of the factors that can affect the activity of osteocytes is regular exercise that has no side effects. Physical activity not only targets bone cells but also increases the production of several hormone-like molecules from skeletal muscle called myokine (Pedersen & Febbraio, 2012). Several these myokines include interleukin-6 (IL-6) and irisin (Keller et al., 2001). It has been shown Irisin increase significantly in endurance exercise (Jedrychowski et al., 2015). Recent studies have shown that irisin injections can also affect bone regeneration. For example, irisin injections at very low doses have been shown to improve bone mineral density and resistance in the cerebral cortex (Colaiani et al., 2014). These effects were consistent with in vitro studies showing that irisin can increase osteoblast differentiation (Qiao et al., 2016). Recently, has been shown irisin act on bone integrin  $\alpha$ V receptors to enhance bone homeostasis and Sclerostin secretion. Therefore, increasing these factors all leads to improved bone regeneration. Based on this, it can be assumed that exercising by increasing irisin secretion can also improve bone metabolism during menopause, which prevents osteoporosis (Figure 3). Several studies have shown that insulin resistance may also occur due to acidosis or inflammation (Kobayashi, Maesato, Moriya, Ohtake, & Ikeda, 2005). Decreased irisin levels may be induced muscle insulin resistance in patients with CKD (Wen, Wang, Lin, & Hung, 2013).

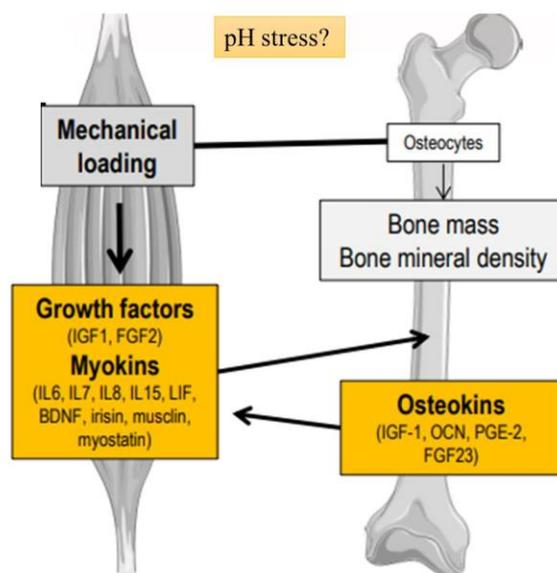


Figure 3. Exercise with muscle contraction and secretion of myokine irisin can cause cross-talk between muscle and bone, which ultimately enhances bone regeneration.

However, the fact that irisin improves glucose homeostasis and insulin resistance has been established in several studies (Boström, Wu, Jedrychowski, & Korde, 2012) but the association of acidosis with intramuscular irisin levels to control insulin resistance has not been established. If irisin is effective in controlling pH stress and regulating muscle acidosis, it can also improve insulin resistance and increase its secretion improve bone anabolism.

## Conclusion

Some studies have examined the beneficial effects of exercise on bone tissue in older men and women, and listed the benefits on bone metabolism. But our study assumes that high intensity and long-term exercise training can be effective in inducing acidosis and pH stress. It seems that resistance exercise training (lower load and high repeat in each set) apart from mechanical stress seems to have less effect on pH stress; therefore, less calcium excretion after resistance exercise can cause positive remodeling in bone mass and be effective in controlling osteoporosis caused by aging. Also muscle bone crosstalk can influence on bone remodeling and decrease adverse effects of pH in bone tissue. However, apart from the varying positive effects of exercise training in different age, the prescription of exercise training for post-menopausal woman need some caution that we certainly consider theses.

## What is already known on this subject?

Numerous studies have evaluated the role of pH stress on the destruction of bone turn over. Exercise by stimulating the secretion of Myokines and Osteokines can improve the homeostasis of these cells, but different intensities of exercise, especially anaerobic exercise can destroy cell homeostasis by destroying the pH.

## What this study adds?

It seems that although various exercises can destroy the bone turn over by expanding the pH, but Osteokines and Myokines such as irisin can neutralize this stress and have beneficial effects on bone metabolism in different exercise intensities in postmenopausal women.

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## Compliance with ethical standards

**Conflict of interest** The authors declare that they have no conflict of interest.

**Ethical approval** Not applicable.

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## Author contributions

Conceptualization: B.T., H.S.H.; Methodology: E.A., Z.F.; Software: E.A.; Validation: H.S.H., B.T.; Formal analysis: None.; Investigation: B.T., H.S.H., E.A.; Resources: Z.F.; Data curation: None.; Writing - original draft: B.T., H.S.H., E.A., Z.F.; Writing - review & editing: E.A., H.S.H.; Supervision: B.T.; Project administration: E.A.; Funding acquisition: H.S.H., Z.F.

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