The Links Between Osteoporosis and Sarcopenia in Women

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Highlights

1. Global aging will cause an increase in chronic diseases such as osteoporosis and sarcopenia.
2. The frequent coexistence of both diseases suggests cross talking between bone and muscle.
3. Different studies have shown that bone and muscle produce cytokines that affect the other.
4. The cellular senescence, with its production of cytokines, would be caused by musculoskeletal aging.
5. Improving lifestyles and decreasing senescent cells should be the therapeutic objective.

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26.1 Introduction

26.1.1 Epidemiology

A substantial and increased proportion of morbidity and mortality due to chronic disease occurs in people aged 60 years and older. Within the leading contributors to disease burden in older people are the diseases of the musculoskeletal system, being responsible for 7.5% of the total global burden [1]. There is an emphasis on maintaining an active lifestyle to reduce the risks of obesity, cardiovascular diseases, cancer, osteoporosis, and diabetes in older people. However, musculoskeletal conditions profoundly limit the ability of people to make these lifestyle changes.

In this group of diseases, osteoporosis and sarcopenia are two disorders that seriously impair the health of older women. Currently it is estimated that over 200 million people worldwide suffer from osteoporosis. Approximately 30% of all postmenopausal women have osteoporosis in the United States and in Europe. In the different Latin American countries, between 8 and 22% of women over 50 have osteoporosis at the level of the femoral neck [2]. At least 40% of these women will sustain one or more fragility fractures in their remaining lifetime. With modest assumptions concerning secular trends, the number of hip fractures could range between 7.3 and 21.3 million by 2050. The major demographic changes will occur in Asia [3]. The socioeconomic impact of hip fractures will increase markedly throughout the world, and there is an urgent need to develop preventive strategies, particularly in the developing countries.

Loss of muscle mass and strength, which in turn affects balance, gait, and overall ability to perform tasks of daily living, is hallmark sign of sarcopenia. Prevalence increased from 13–24% in persons under 70 years of age to >50% in persons over 80 years of age and was slightly greater in Hispanics than in non-Hispanic whites. Globally, with a conservative estimate of prevalence, sarcopenia affects >50 million people today and will affect >200 million in the next 40 years. Sarcopenia represents an impaired state of health with a high personal toll consisting in mobility disorders, increased risk of falls and fractures, impaired ability to perform daily activities, disabilities, loss of independence, and increased risk of death [4, 5].

26.1.2 Osteoporosis and Sarcopenia: Are They Two Different Diseases?

A growing evidence shows that osteoporosis and sarcopenia share many common pathways including the sensitivity to reduced anabolic hormone secretion, increased inflammatory cytokine activity, and anabolic or catabolic molecules released by the skeletal muscle or by the bone cells which affect the other tissue (i.e., myokines and osteokines). Studies using animal models in the setting of hind limb unloading or botulinum toxin (Botox) injection also reveal that muscle loss can induce bone loss. Moreover, muscle-derived factors such as irisin and leptin can inhibit bone loss induced by unloading [6]. Therefore, it is not surprising that, although osteoporosis

and sarcopenia are different nosological entities, the coexistence of both diseases in the same individual is not uncommon. The association of these two diseases has led to the development of the term "osteosarcopenia" to diagnose those patients suffering from both diseases. Actually, osteosarcopenia has been defined as the presence of sarcopenia and osteopenia or osteoporosis. Endocrine disorders, mainly diabetes, abnormal thyroid function and low levels of vitamin D, sex steroids, growth hormone (GH) and insulin-like growth factor-1 (IGF-1), malnutrition, obesity, and the use of corticosteroids are also associated with osteosarcopenia [7].

The prevalence of osteosarcopenia varies with age, sex, and country. A study of community-dwelling Chinese elders older than age 65 found prevalence of osteoporosis-sarcopenia in 10.4% of men and 15.1% of women [8]. Studies in Australian persons with previous history of falls reported that 40% of this high-risk population had osteopenia-sarcopenia. Being a female; having a history of osteoarthritis, oophorectomy, or cancer; and impaired mobility were risk factors for osteosarcopenia in this Australian cohort [9]. Data presented by Campodónico in the Congress of the Argentine Association of Menopause in 2016 shows that osteosarcopenia is found in 9.7% of Chilean women between 35 and 69 years. Although the prevalence of osteosarcopenia may be different in each study group, its diagnosis has significant clinical implications. Patients with osteosarcopenia are more susceptible to occurrence of fragility fracture, poor quality of life, and higher mortality [10].

26.2 Pathophysiology

26.2.1 Role of Cytokines

The biological explanation of the association of low bone mass with sarcopenia is not based solely on the anatomical proximity of the muscle to the bone, but could be based on the cross talk between both organs. Muscle produces cytokines, called myokines, such as myostatin, transforming growth factor beta β, activin, interleukin-6, and monocyte chemoattractant protein-1 (MCP-1) which have a negative influence on bone metabolism. On the other hand, bone produces other cytokines such as sclerostin that decreases muscle mass. Osteosarcopenia would be produced by the interaction of these cytokines with aging, genetic factors, lifestyles, and chronic diseases (Fig. 26.1) [11].

26.2.2 A New Actor: Cellular Senescence

The paradigm of the pathophysiology of osteosarcopenia shown in Fig. 26.1 could be complemented with the concepts of cellular senescence described more than 40 years ago. Fibroblasts in cultures initially undergo rapid division; but afterwards, they lose their capacity for duplication. However, they remain viable in a senescent state for many weeks. Later, cellular senescence was understood as an irreversible arrest of the growth that occurs when the cells undergo aggressions that may be
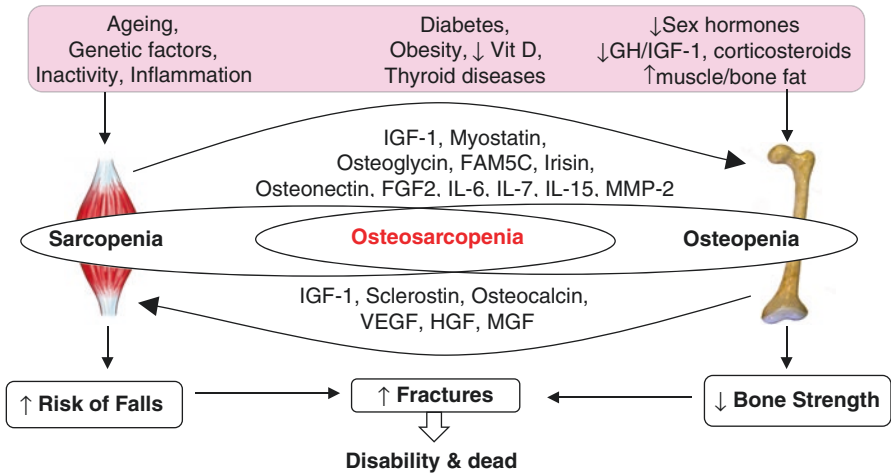
Fig. 26.1 Pathophysiology of osteosarcopenia. *FAM5C* family with sequence similarity 5, member C, *FGF2* fibroblast growth factor 2, *GH* growth hormone, *HGF* hepatocyte growth factor, *IGF-1* insulin-like growth factor 1, *IL* interleukin, *MGF* mechano-growth factor, *MMP-2* matrix metallopeptidase 2, *VEGF* vascular endothelial growth factor, *Vit D* vitamin D. (Modified with permission from: Hirschfeld HP, Kinsella R, Duque G. Osteoporos Int 2017; 28:2781–90)

oncogenic. Therefore, cellular senescence is an important mechanism to prevent the proliferation of potential cancer cells [12].

However, it has become evident that senescence involves more than a simple cessation of cell growth. These senescent cells stop their growth, thus contributing to the depletion of stem cell proliferation and cell aging. In addition to their capacity to suppress tumorigenesis, cell senescence could also promote chronic inflammation associated with aging. Several common molecular pathways have been identified that are associated with both aging and low-grade inflammation. Senescent cells have an altered secretion pattern SASP that comprises a complex mix of factors including cytokines, growth factors, chemokines, matrix metalloproteinases, telomere shortening, and decondensation of pericentromeric satellite DNA (Fig. 26.2). SASP has been related with inflammation that leads to cellular transformation and chronical diseases [13].

In bone, cellular senescence has been studied in animals and human beings. For example, in mice p16Ink4a expression, a senescence marker was significantly higher with aging in osteoblasts, osteocytes B cells, T cells, and myeloid cells. Furthermore, in vivo quantification of senescence-associated distension of satellites (SADS), i.e., large-scale unraveling of pericentromeric satellite DNA, revealed significantly more senescent osteocytes in old compared with young bone cortices [14]. The same study analyzed a panel of 36 established SASP factors (p16INK4a, p16 cyclin-dependent kinase inhibitor 4A, multiple tumor suppressor 1, p21, p51, etc.) in bone biopsies from women, which found that 12 SASP factors were significantly higher in the bone from old subjects compared with young ones.
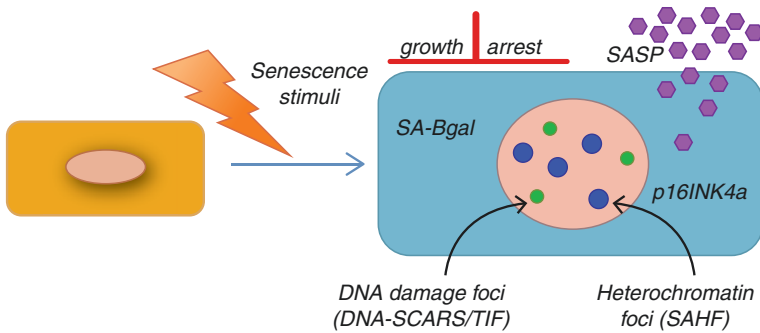
Fig. 26.2 Hallmarks of cellular senescence. *DNA-SCARS* DNA segments with chromatin altera-
tions reinforcing senescence, *p16INK4a* tumor suppressor protein, *SA-Bgal* senescence-associated
beta-galactosidase, *SAHF* senescence-associated heterochromatin foci, *SASP* senescence-
associated secretory phenotype. (Copy with permission from Rodier F, Campisi J. Four faces of
cellular senescence. J Cell Bio 2011; 192:547–56)

In the muscle, stem cell (satellite cells) function is essential for organismal
homeostasis, providing a renewable source of cells to repair damaged tissues.
Regeneration of skeletal muscle relies on a population of stem cells, which are
impaired in very old individuals undergoing sarcopenia. Aged satellite cells lose the
repression of locus, which switches stem cell reversible quiescence into a pre-
senescent state; upon regenerative or proliferative pressure, these cells undergo
accelerated senescence [15].

Therefore, as in the bone, in the muscle there are markers of cellular senescence
in the elderly. We could conclude by pointing out that pathologically the central
process that joins osteoporosis with sarcopenia is aging, which in the light of cur-
rent knowledge would be determined by cellular senescence. It could even be sug-
gested that the processes that have been described separately for both diseases,
which involve a series of cellular mechanisms mediated by biochemical mediators
of cellular metabolism, would be mere intermediaries of a central process that is
cellular senescence. In the next few years, we expect to have the answers to these
questions.

26.3   Diagnosis of Osteoporosis and/or Sarcopenia

The study of bone mass should be performed with double-photon bone densitome-
try. The World Health Organization has defined a number of threshold values (mea-
surements) for osteoporosis. The reference measurement is derived from bone
density measurements in a population of healthy young adults (*T*-score).
Osteoporosis is diagnosed when a person's bone mineral density is equal to or more
than 2.5 standard deviations below this reference measurement. Osteopenia is diag-
nosed when the measurement is between 1 and 2.5 standard deviations below the
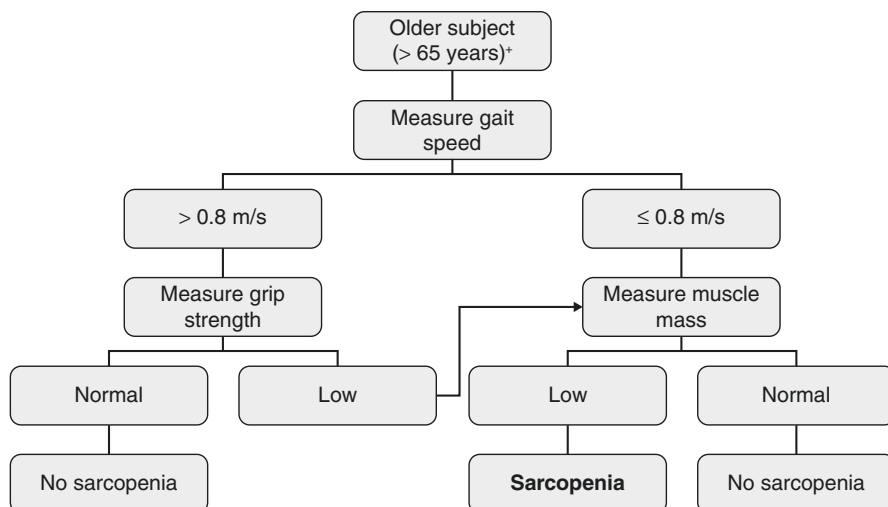young adult reference measurement.

Fig. 26.3 EWGSOP-suggested algorithm for sarcopenia case finding in older individuals. From: Cruz-Jentoft AJ, Baeyens JP, Bauer JM, Boirie Y, Cederholm T, Landi F, et al. Sarcopenia: European consensus on definition and diagnosis. Age and Ageing 2010; 39, 412–23

Sarcopenia is the loss of muscle mass, strength, and function related to aging. The European Working Group on Sarcopenia in Older People (EWGSOP) developed a practical clinical definition and consensus diagnostic criteria for age-related sarcopenia (Fig. 26.3) [16].

The diagnosis of osteosarcopenia includes the presence of osteopenia/osteoporosis and sarcopenia in the same patient.

26.4 Treatment of Osteoporosis and/or Sarcopenia

26.4.1 Treatment Today

At present, the available therapeutic options to treat osteoporosis are mostly limited either to decreasing bone resorption or to increasing bone formation, and both approaches could be associated with serious side effects. Although estrogen replacement therapy is now rarely used for the prevention or treatment of osteoporosis, it continues to be a valid alternative, especially in women with climacteric symptoms. Additional pharmacological options have been developed, including a selective estrogen receptor modulator (raloxifene), bisphosphonates (alendronate, risedronate, ibandronate, and zoledronic acid), a human monoclonal antibody to receptor activator of nuclear factor κ-B ligand (RANKL, denosumab), and the parathyroid hormone. The new preparation of conjugated estrogens/bazedoxifene has been approved by the US Food and Drug Administration to prevent postmenopausal osteoporosis. However, the suspension of these treatments may cause loss of bone

gain obtained with the treatment. This has led to the search for new therapeutic options, without having achieved to date a therapy that satisfies the expectations of physicians and patients. In addition to the mentioned pharmacological options, a diet with an adequate supply of proteins, calcium, and fruits is necessary. Physical activity and the maintenance of adequate levels of vitamin D are essential measures [17].

In relation to sarcopenia, the main causes for the development of this disease are hormonal changes (reduced release of testosterone, estrogen, and growth hormone), nutritional deficiencies, chronic inflammation, and particularly a decrease in physical activity due to a sedentary lifestyle with advancing age. Therefore, treatment must first be focused on reversing these causes. A combination of exercise and high protein intake ($\geq$1.2 g/kg/day), with a relatively high content of animal protein and fractioned throughout the day, has the highest potential in improving different parameters of sarcopenia. In patients with sarcopenic obesity, we must add as an objective the achievement of moderate weight loss [18]. Potential medical treatments of sarcopenia are not evidence based and can be used in selected cases but not in all sarcopenic patients. They include androgenic hormones, estrogens, GH, and angiotensin-converting enzyme inhibitors. A meta-analysis of the estrogen-based treatments indicated that this therapy benefits strength [19]. This could explain why those women taking at least 80% of their hormonal prescriptions in the WHI study showed fewer falls compared with placebo [20]. There is evidence that both exercise training and vitamin D supplementation may benefit musculoskeletal health in older adults, and it is plausible that in combination their effects may be additive [21].

If we think that patients who have a musculoskeletal disease also have a high frequency of other comorbidities, it is not surprising that the elderly use many medications. If we add to this the fact that the elderly population is steadily increasing, we can understand why the use of polypharmacy in this age group has increased markedly in recent years. This is reflected in a study conducted in Scotland showing that between 1995 and 2010, the proportion of adults dispensed $\geq$5 drugs doubled to 20.8% [22]. Fundamentally, this is because current treatment strategies for all chronic age-related morbidities are disease-specific, with each drug targeting a single disease or condition, e.g., a statin for cardiovascular risk reduction, an antihyperglycemic agent for diabetes, a bisphosphonate for osteoporosis, etc. This inevitably leads to polypharmacy and the resultant problems related to adverse drug interactions and compliance.

26.4.2 Treatment in the Future

The paradigm of cellular senescence allows us to see chronic diseases as a single disease originated in the increase in the population of senescent cells and, therefore, think of a unique therapy for chronic diseases. Theoretically, the decrease in senescent cells or their biochemical mediators could stop the progression of chronic diseases such as osteoporosis and sarcopenia.

An option to decrease cellular senescence is to reduce senescent cells by activating a suicide gene with a drug. Baker using transgenic mice with accelerated aging, which permits inducible elimination of senescent cells (expressing p16Ink4a) upon administration of a synthetic drug (AP20187), showed that reduction of the senescent cell burden ameliorated multiple aging phenotypes in adipose tissue, skeletal muscle, and eyes. P16Ink4a found in these tissues contributes to the acquisition of age-related pathologies [23]. While initial studies used genetic approaches for the killing of senescent cells, recent approaches showed similar effects with both senolytic products (quercetin and dasatinib) and drugs that inhibit the production of the pro-inflammatory secretome of senescent cells (SASP) using a Janus kinase (JAK) inhibitor. The JAK pathway is activated in adipose tissue with aging and plays an important role in regulating inflammatory cytokines produced by senescent cells [24].

Farr et al. treated old mice with bone loss for 2–4 months, with three antiaging interventions, (activation of suicide gene, use of senolytic drugs, and use of SASP blocking drugs), similarly improving bone mass and microarchitecture in both trabecular and cortical bone [25]. On the other hand, the positive effect of estrogens on bone could be due to the decrease in cellular senescence and the increase in osteogenic differentiation. Oophorectomized rats express less special AT-rich sequence-binding protein 2 (SATB2), a protein that regulates cell differentiation in stem cells, which is associated with greater senescence and less osteogenic differentiation. The administration of E2 causes greater expression of SATB2, which is inhibited by blocking the estrogen receptor (ER-β). These results indicate that estrogen prevents osteoporosis by promoting cell differentiation and by inhibiting the senescence of stem cells through a RE-β/SATB2 pathway [26].

Muscle repair and regeneration depends on a population of quiescent stem cells, called satellite cells, and is impaired in very old individuals with sarcopenia. Stem cell function is essential for organismal homeostasis, providing a renewable source of cells to repair damaged tissues. Old age causes an induction of p16INK4a in satellite cells, which translates into a senescent state, a condition in which there is a disorder in the regeneration of muscle fibers and tissue loss. Thus, cell senescence is causally implicated in the intrinsic defective regeneration of sarcopenic muscle. Interestingly, p16INK4a silencing induces rejuvenation of satellite cells, restoring regeneration in geriatric muscles. This suggests that genetic rejuvenation of satellite cells by preventing p16INK4a expression may be an effective way to prevent poor regeneration phenotypes in humans undergoing sarcopenia [14]. As previously mentioned, estrogen decreases cellular senescence, which would explain the results of the Women's Health Initiative Study that indicate that women who adequately complied with hormone therapy had fewer falls, which could reveal better muscle function [17]. The elimination of senescent cells or the inhibition of the production of their SASP (cytokines, metalloproteinase, etc.) in mice and even in humans has shown positive results not only in muscle and bone diseases but also in osteoarthritis, insulin resistance, atherosclerosis, cardiac function, and frailty. All this opens a wide range of possibilities for an eventual use in humans in the coming years [27].

26.5 Conclusion

There is an emphasis on maintaining an active lifestyle to reduce the impacts on obesity, cardiovascular conditions, cancer, osteoporosis, and diabetes in older people. However, musculoskeletal conditions profoundly limit the ability of people to make these lifestyle changes. Therefore, physicians must give special importance to musculoskeletal diseases and understand that they are framed within the problems of aging. Therefore, the presence of osteoporosis or osteopenia forces us to look for other comorbidities that occur with increasing age. Today we have specific therapies for each of them, but it is likely that in the next few years, all these diseases will be confined within the same paradigm, cellular senescence, and we will probably have therapies capable of changing the quality of life of the aging human being.

References

1. Prince MJ, Wu F, Guo Y, Gutierrez Robledo LM, O'Donnell M, Sullivan R, et al. The burden of disease in older people and implications for health policy and practice. Lancet. 2015;385(9967):549–62.
2. Riera-Espinoza G. Epidemiology of osteoporosis in Latin America 2008. Salud Publica Mex. 2009;51(Suppl 1):S52–5.
3. International Osteoporosis Foundation. One in three women over 50 will experience osteoporotic fractures. https://www.iofbonehealth.org/epidemiology. Accessed from 11 May 2018.
4. Baumgartner RN, Koehler KM, Gallagher D, Romero L, Heymsfield SB, Ross RR, et al. Epidemiology of sarcopenia among the elderly in New Mexico. Am J Epidemiol. 1998;147:755–63.
5. Cruz-Jentoft AJ, Landi F, Schneider SM, Zúñiga C, Arai H, Boirie Y, et al. Prevalence of and interventions for sarcopenia in ageing adults: a systematic review. Report of the International Sarcopenia Initiative (EWGSOP and IWGS). Age Ageing. 2014;43:748–59.
6. Bettis T, Kim BJ, Hamrick MW. Impact of muscle atrophy on bone metabolism and bone strength: implications for muscle-bone crosstalk with aging and disuse. Osteoporos Int. 2018;29(8):1713–20.
7. Hassan EB, Duque G. Osteosarcopenia: a new geriatric syndrome. Aust Fam Physician. 2017;46:849–53.
8. Wang YJ, Wang Y, Zhan JK, et al. Sarco-osteoporosis: prevalence and association with frailty in Chinese community-dwelling older adults. Int J Endocrinol. 2015;2015:482940.
9. Huo YR, Suriyaarachchi P, Gomez F, Curcio CL, Boersma D, Muir SW, et al. Phenotype of osteosarcopenia in older individuals with a history of falling. J Am Med Dir Assoc. 2015;16:290–5.
10. Yoo JI, Kim H, Ha YC, Kwon HB, Koo KH. Osteosarcopenia in patients with hip fracture is related with high mortality. J Korean Med Sci. 2018;33(4):e27.
11. Hirschfeld HP, Kinsella R, Duque G. Osteosarcopenia: where bone, muscle, and fat collide. Osteoporos Int. 2017;28:2781–90.
12. Rodier F, Campisi J. Four faces of cellular senescence. J Cell Bio. 2011;192:547–56.
13. Maciel-Barón LA, Morales-Rosales SL, Aquino-Cruz AA, Triana-Martínez F, Galván-Arzate S, Luna-López A, et al. Senescence associated secretory phenotype profile from primary lung mice fibroblasts depends on the senescence induction stimuli. Age (Dordr). 2016;38:26.

14. Farr JN, Fraser DG, Wang H, Jaehn K, Ogrodnik MB, Weivoda MM, et al. Identification of senescent cells in the bone microenvironment. J Bone Miner Res. 2016;31:1920–9.

15. Sousa-Victor P, Perdiguero E, Muñoz-Cánoves P. Geroconversion of aged muscle stem cells under regenerative pressure. Cell Cycle. 2014;13:3183–90.

16. Cruz-Jentoft AJ, Baeyens JP, Bauer JM, Boirie Y, Cederholm T, Landi F, et al. Sarcopenia: European consensus on definition and diagnosis. Age Ageing. 2010;39:412–23.

17. Awasthi H, Mani D, Singh D, Gupta A. The underlying pathophysiology and therapeutic approaches for osteoporosis. Med Res Rev. 2018;38(6):2024–57.

18. Trouwborst I, Verreijen A, Memelink R, Massanet P, Boirie Y, Weijs P, et al. Exercise and nutrition strategies to counteract sarcopenic obesity. Nutrients. 2018;10(5):E605.

19. Greising SM, Baltgalvis KA, Lowe DA, Warren GL. Hormone therapy and skeletal muscle strength: a meta-analysis. J Gerontol A Biol Sci Med Sci. 2009;64:1071–81.

20. Bea JW, Zhao Q, Cauley JA, LaCroix AZ, Bassford T, Lewis CE, et al. Effect of hormone therapy on lean body mass, falls, and fractures: 6-year results from the Women's Health Initiative hormone trials. Menopause. 2011;18:44–52.

21. Antoniak AE, Greig CA. The effect of combined resistance exercise training and vitamin D3 supplementation on musculoskeletal health and function in older adults: a systematic review and meta-analysis. BMJ Open. 2017;7(7):e014619.

22. Guthrie B, Makubate B, Hernandez-Santiago V, Dreischulte T. The rising tide of polypharmacy and drug-drug interactions: population database analysis 1995-2010. BMC Med. 2015;13:74.

23. Baker DJ, Wijshake T, Tchkonia T, LeBrasseur NK, Childs BG, van de Sluis B, et al. Clearance of p16Ink4a-positive senescent cells delay aging-associated disorders. Nature. 2011;479:232–6.

24. Xu M, et al. JAK inhibition alleviates the cellular senescence-associated secretory phenotype and frailty in old age. Proc Natl Acad Sci U S A. 2015;112:301–10.

25. Farr JN, Xu M, Weivoda MM, Monroe DG, Fraser DG, Onken JL, et al. Targeting cellular senescence prevents age-related bone loss in mice. Nat Med. 2017;23:1072–9.

26. Wu G, Xu R, Zhang P, Xiao T, Fu Y, Zhang Y, et al. Estrogen regulates stemness and senescence of bone marrow stromal cells to prevent osteoporosis via ERβ-SATB2 pathway. J Cell Physiol. 2018;233:4194–204.

27. Dolivo D, Hernandez S, Dominko T. Cellular lifespan and senescence: a complex balance between multiple cellular pathways. BioEssays. 2016;38(Suppl 1):S33–44.