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Review Article

Bioanthropological and Biomechanical Perspectives on Skeletal Senescence Variation

Sayf Muhammad Alaydrus[1] , Muhamad Andri Jauhari[2]

[1]Department of Anthropology, Faculty of Social and Political Sciences, Universitas Airlangga, Surabaya, Indonesia
[2]Department of Physics, Graduate School of Natural Sciences, Utrecht University, Utrecht, The Netherlands

Correspondence should be addressed to Sayf Muhammad Alaydrus, Department of Anthropology, Faculty of Social and Political Sciences, Universitas Airlangga, Jl. Airlangga 4-6, Airlangga, Gubeng, Surabaya 60286, Indonesia. email: sayf.muhammad.alaydrus-2021@fisip.unair.ac.id

ABSTRACT

Background: Senescence is the deterioration of the body's biological and physiological function throughout later life. Senescent populations are more prone to diseases. However, aside from osteoporosis, skeletal senescence is a less discussed topic in Indonesia. A global and national increase in the aging population indicates they will be a major group in society, raising the urgency of reviewing this matter. This study aims to comprehend the physiological and biomechanical mechanisms of skeletal senescence, as well as senescent variations in certain sex and population affinities.
Literature Review: Age-related skeletal cellular death and imbalance contributes to bone damage in elders. Senescence also affects skeletal biomechanics, expressed in increased bone porosity and brittleness. Stresses in aged bone risks straining above its elastic limit and causing fractures due to its inability to tolerate such stresses. The loss of sex hormones is related to skeletal senescence, especially in females, while the effects of testosterone on skeletal senescence are under-researched. Dietary change, estrogen replacement therapy, and calcitonin consumption are effective measures in reducing the effects of osteoporosis. Variations were found in the bone aging process in different populations, especially regarding bone mineral density loss in white, African-American, Asian, and Hispanic populations.
Conclusion: Specific population-based healthcare services in geriatrics and gerontology are highly suggested to ensure inclusive healthcare for every aged individual. Due to the minimal data about bone aging in Indonesia (other than osteoporosis), the authors encourage data procurement from the local populations to create more suitable medical guidelines for elders in Indonesia.

Keywords: Aging; Biological variation; Biomechanics; Inclusive health; Sex difference

INTRODUCTION

Aging is a natural process of growth and development that occurs in all living beings, including humans. After a certain age, a person's physical condition begins to decline in function. This process is known as "senescence." Many intrinsic and extrinsic factors are related to the acceleration of human senescence, such as genetics, hormones, skin type, nutrition, lifestyle, sunlight exposure, comorbid medications, and many more.[1–6]

Biological aging is closely related to cellular aging. Cells, as the main structures composing tissues and organs, slowly experience a loss in number and function. Cells lose their ability to repair or remodel themselves effectively, which is why older adults are more prone to illness. However, some individuals experience a slower aging process and may appear younger than their chronological age. The use of anti-aging products, a healthy lifestyle, and regular physical activity may contribute to this. However, it is important to note that a younger biological appearance does not necessarily equate to better physical fitness in older adults.[1,7–10]

Bone, like any other biological structure in the human body, is dynamic. At the molecular level, bone cells—osteoblasts and osteoclasts—continuously remodel the bone structure. Even without considering biological aging, human bone is a constantly dynamic structure. Humans

typically reach their peak height before gradually losing it due to changes in posture. Bone senescence plays a significant role in these changes, primarily through mechanisms such as bone density loss, decreased synovial fluid, and joint stiffness. All of these factors affect the bone's function within the musculoskeletal system, including its role in movement.[11–15]

These changes due to bone aging can be explicitly demonstrated through its biomechanical properties. The continuous remodeling of bone, coupled with senescent cells, leads to an increase in bone porosity from 4% to 12%. For older individuals, this can increase the bone porosity up to almost 50%, along with an approximate 40% reduction in ultimate strength. Ultimately, these increases affect an older person's ability to lift heavy objects.[16–19]

As mentioned previously, age-related functional decline can contribute to increased susceptibility to diseases. Several pathological cases, like osteoporosis, are considered inevitable for many elders. Other risks, such as bone fractures, also frequently occur. Several researchers have also stated that many diseases are closely related to senescence.[20–23] Therefore, a literature review on skeletal senescence and age-related pathologies is necessary.

Since hormonal factors play a significant role in the aging process, it is also important to discuss how they affect human variations, particularly between the sexes. Biologically, both sexes have their own unique functions that require unique endocrines to stimulate these processes. For example, both primary and secondary puberty among males and females is stimulated by different hormones—males by testosterone and females by estrogen. It is important to note that while both sexes produce both hormones, the quantities differ significantly. This also relates to their susceptibility to bone loss.[23–27] It is both interesting and important to discuss the sex differences in skeletal aging, as understanding how bone ages in both sexes can provide insights into ensuring appropriate treatment.

Human biological variation does not only concern sex and age but also population affinity. The process of skeletal senescence also varies among populations. Medical guidance and procedures concerning bone diseases in senescent populations should adhere to this biological variation. Concerns have been raised about how the "one size fits all" rule is not pertinent in terms of senescence-related bone disease treatment. Reviewing the subtopic of human biological variations might give us insight into understanding the aging process in different population affinities.[28,29]

The study of human skeletal senescence has become a much more urgent issue, especially in Indonesia. According to the United Nations Department of Economic and Social Affairs Population Division, Indonesia's life expectancy is estimated to reach 75 years by 2050.[30] Here, many population censuses have recorded how the aging population is continuing to increase. As of 2023, 11.75% of the Indonesian population is categorized as elderly. This means that beginning now and in the near future, the aging population is and will continue to be a major part of the human population.[31] Considering how prone they are to physical and psychosocial problems, a more comprehensive understanding of their condition is urgently required in Indonesia since, according to demographic statistics, an increasing number of elderly individuals will require healthcare sooner or later. Due to the multidimensional aspects of aging, this review can be used as a reference to stimulate further studies in the fields of medicine (especially geriatrics, orthopedics, and traumatology), social sciences (especially social gerontology, anthropology, and sociology), sports sciences, and many other fields. All of these aspects will hopefully contribute to more successful, inclusive, and healthy aging for the elderly.[32,33]

A review of skeletal senescence is highly scarce in Indonesian search engines, hence the importance of raising this issue. This paper

aims to analyze how human skeletal elements age, and how population and sex differences affect skeletal senescence. This paper discusses how senescence affects the biomechanical properties and functions of bone. This paper also aims to describe several bone diseases and how age, and aging, contributes to them. After reading this paper, the reader will hopefully understand how bone ages and how aging affects bone. Hopefully, this paper will contribute and offer new and integrated perspectives, and stimulate research on bone biology and physiology, especially related to the aging process of human bone in various population settings. With new perspectives and stimulated research, it is hoped that the awareness of bone aging in the elderly population will rise and become a consideration for policymakers to create better health care in Indonesia. Thus, medical experts such as orthopedics, traumatologists, and radiologists, among others, can go on to provide better clinical services to elderly patients.

Just like any other research, this study has several limitations. The main limitation is how scarce the study of skeletal senescence is in Indonesia. Thus, it is difficult to specify the discussion to the Indonesian elderly population, among other undiscussed themes. The second limitation is the potential bias when it comes to the selection of articles for review, especially since this study is a narrative review that is not equipped with a rigid set of rules, unlike a systematic review. The third limitation is the bias when choosing the themes. The biomechanical properties reviewed in this paper are limited to the factors that affect bone density and the ultimate strength of the bone. Meanwhile, from the bioanthropological perspective, this paper will focus on discussing sex and population differences in terms of skeletal senescence. This means that other factors or variables, such as auxology, bone shape, genetic abnormality, and many other aspects are not discussed.

LITERATURE REVIEW

Skeletal Senescence and Remodeling

Bone formation and resorption are dynamic and constant processes, collectively termed bone remodeling. Figure 1 illustrates the five steps of this process. Overall, bone remodeling is complex, controlled by local and systemic factors, and is carried out by multiple cell types that interact through cytokines, cell contacts, and matrix elaboration. The bone cells discussed in this review are osteocytes, osteoblasts, osteoclasts, and bone marrow mesenchymal stem cells—all of which contribute to bone remodeling. Like any other part of the human body, bone structure and bone cells are affected by aging. Aging bone cells may incur several changes in characteristics and function compared to their normal state.[12,34,35]

Osteocytes are the longest-lived bone cells, with a natural lifespan of approximately 25 years. Several studies have shown that osteocytes are still subject to aging. Senescent osteocytes may lead to several malfunctions, such as bone loss, microfractures, and osteoporosis. Osteocyte death also signifies a decline in bone strength due to its role in regulating bone vascularity and hydration. Sex hormone deficiency, loss of mechanical strain, and glucocorticoid excess contribute significantly to osteocyte death.[12,13,15,34,35,37,38]

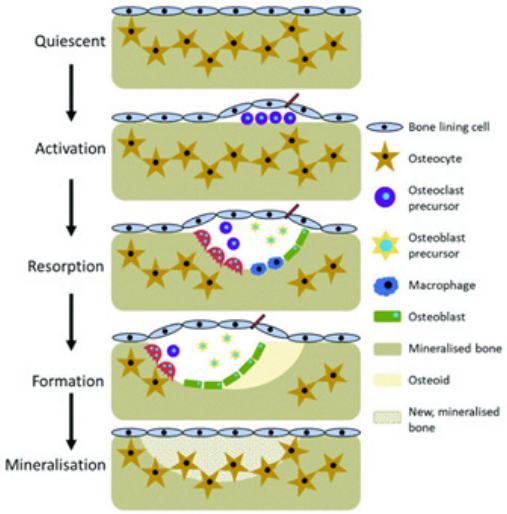

Figure 1. Five stages of bone remodeling.[36]

Autophagy failure and nuclear pore leakiness are the most likely causes of age-related osteocyte death. Autophagy, a process conducted by lysosomes, is highly functional in cellular recycling and defending cells from stressful stimuli. Autophagy failure may lead to the decrease and death of long-lived postmitotic cells in many organs, such as the brain, heart, muscles, and kidneys. Autophagy failure is also closely related to degenerative neurological diseases, cancer, and heart failure. Therefore, it is very likely that osteocytes may be affected by autophagy failure as well, resulting in an increased rate of osteocyte death throughout senescence. Nuclear pore complexes (NPCs) are channels of nucleoproteins that serve as a physical barrier within the nuclear envelope. NPCs are known for their function in regulating the movement of cytoplasmic proteins to the DNA and selectively transporting newly-synthesized mRNAs from the nucleus to the cytoplasm and ribosomes. Similar to autophagy, aging also causes NPCs to decline in postmitotic cells due to the oxidative damage of nucleoporins. Since oxidative stress induces osteocyte death, it is very likely that nuclear pore leakage contributes to the demise of osteocytes.[12,35]

Aging also affects osteoblasts, one of the cells responsible for bone formation and the mineralization of its matrix. Unlike osteocytes, osteoblasts only last for a few months, and many of them (60–80%) die by apoptosis at the site of resorption. With aging, osteoblasts experience a significant change in function. A decrease in mineralization optimality, differentiation capacity, and cell activity are commonly observed traits of senescent osteoblasts. Senescent osteoblasts are also not as responsive to stimuli from hormones. In relation to bone pathology, a previous experiment on mice showed that senescent osteoblasts increase the risk of bone tumor formation and metastasis.[13,15,35,37,39]

Osteoclasts are short-lived, blood-generating bone cells, existing for approximately 2–4 weeks before dying by apoptosis. Several cellular changes in osteoclast expression are age-related, namely in the RANKL/RANK/OPG and M-CSF of bone marrow cells. A previous study showed that senescent osteoclasts in mice produced sclerostin, which might indicate a weakened ability to remodel in aged bone.[35,37]

Bone marrow mesenchymal stem cells (BSMCs) are a group of significantly functioning stem cells. Also known for their pluripotency, BSMCs' abilities include self-renewal and self-differentiation into osteogenic, adipogenic, and chondrogenic lineages. Changes caused by aging include decreasing proliferative capacity and increasing adipogenesis. Consequently, the decreasing amount of osteoblasts will create an imbalance in the bone. The excessive amount of marrow adipocytes with no osteoblasts to balance them may result in bone loss.[35,40–42]

Biomechanics of the Aging Bone

Bone is one of the most dynamic tissues in the human body, existing in a constant state of flux as both a material and a structure. This dynamic nature affects how bone handles loads. The study of how bone handles loads can be explained through the lens of biomechanics. The biomechanical properties of bone describe the relationship between the forces (F), or loads, applied to the bone or bone specimen, and the resulting deformations. The forces applied to bones have several possible origins including external forces—such as the impact of catching a ball or ground reaction force during running—and internal forces created by muscle interactions or ligament tensions. Bone resistance developed in response to applied forces is known as stress (σ). It represents local force intensity with dimensions of force per unit area ($\sigma = F/A$) and has the pascal (Pa) as its unit in the International System of Units (SI): 1 Pa = 1 N/m^2. The deformation of bone due to stress is usually represented as strain (ε), defined as the ratio of the change in a specific dimension (such as length) of the bone to the original value of that dimension ($\varepsilon = \Delta l/l$) and is non-dimensional.[43–45]

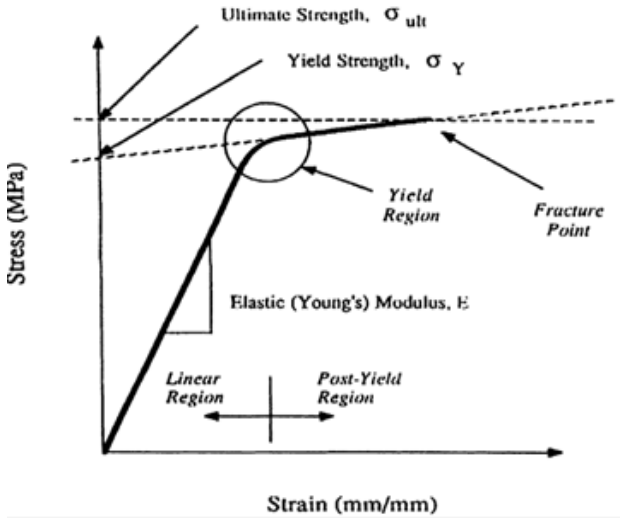

Figure 2. Stress-strain curve of a bone under tension.[6]

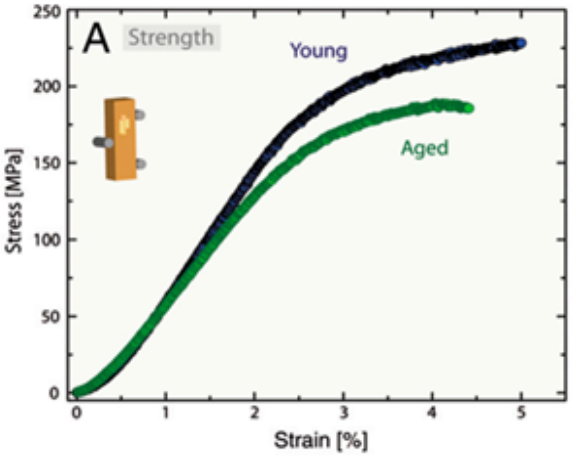

Figure 3. Stress-strain curve comparison between young and aged individuals.[17]

To define the mechanical or material properties of bone, the shape and size of the bone must be accounted for by establishing these properties. This allows for a true understanding of bone purely as a material, independent of any particular shape or length. The material properties are also defined as "stress-strain properties" because they can be observed from the stress-strain curve. Considering the definitions of "stress" and "strain," the stress-strain curves of a material will be the same for different shapes and sizes of said material. Figure 2 shows a stress-strain curve for a bone specimen under compression and tension in longitudinal and transverse orientations.[44,46,47]

Figure 2 shows a linear region in the stress-strain curve. The slope of this linear region defines the "elastic" or "Young's modulus" of the bone. When the bone begins to yield, it reaches its elastic limit. At the point where the slope becomes constant again, the bone attains its yield strength. With the further application of stress, the curve extends into the post-yield or plastic region until the fracture point is reached. The term "ultimate strength of the bone" is used to define the maximum stress a bone can handle before fracturing.[44,48]

Age-related degradation in bone mechanical properties is accompanied by subtle but significant changes in porosity.[46] The porosity in cortical bone increases from about 4% in young, healthy bone to around 12% at age 60. In elderly individuals, bone porosity can reach almost 50%. The increased surface area of cortical bone provides more surface area for receiving signals to initiate remodeling, further accelerating cortical bone loss with age.[16]

Increases in intracortical porosity result in higher strains, which are directly related to decreases in Young's modulus throughout human bone aging.[17,49–52] The Young's modulus of human bone decreases by about 2% per decade.[16] An example of such decreases is shown in Figure 3, where the constant slope of a young person is steeper than that of an aged person, and the steeper slope indicates a higher Young's modulus.[46,53]

An elderly person has more senescent cells, and they begin to accumulate in their tissues, including bones. Cellular senescence damages the bone remodeling ability by impairing bone formation. This is shown by current studies, which demonstrate a decrease in bone load strength due to aging correlated with cell senescence.[15,54] Senescent cells in bone tissue cause a higher rate of bone resorption than bone formation, which leads to lower bone mineral density. However, the occupied volume or space of the bone remains the same. Hence, bone formation leaves small spaces between the bone tissues. These small spaces make the bone porous, increasing bone porosity.[55,56] As the bone becomes

more porous, the bonding strength of the bone material decreases due to the empty spaces. Weaker bonding means easier breakage, resulting in the weaker ultimate strength of the bone and lower Young's modulus.[57,58]

Another effect of bone aging is bone brittleness. A material is called brittle if, when subjected to stress, it fractures with little elastic deformation and without significant plastic deformation.[59] The increased brittleness that occurs with age is related to changes in the collagen and collagen-mineral interface. Non-enzymatic glycation forms intra-molecular collagen bonds known as advanced glycation end-products (AGEs). Because AGEs are formed in the presence of sugars, they accumulate in the collagenous tissues of people with diabetes and are considered to be one cause of skeletal fragility found in this condition. AGEs are also produced by oxidation reactions and form naturally as collagen ages. Proteins with long half-lives, such as collagen, can accumulate substantial amounts of AGEs. Therefore, unlike enzymatically mediated cross-links, AGEs accumulate naturally in bone with age. AGE accumulation may decrease collagen's ability to deform by as much as 25% and cause increased brittleness. It reduces the capacity of aged bone to resist fracture. The brittleness of bone affects its ultimate strength, which can be observed in Figure 3. The ultimate strength of a young person lies in the 200–250 MPa range, while an aged person's ultimate strength lies in the 150–200 MPa range, representing a 20–40% reduction in ultimate strength.[17–19]

Senescence, Sex Hormones, and Osteoporosis

Osteoporosis is a bone pathology caused by a disruption in the bone resorption and formation process. Bone mass loss occurs in individuals as they age and can be measured by T-score—an individual with a T-score less than -2.5 indicates a higher rate of bone fragility, which is diagnosable as osteoporosis.[60] This disruption continues throughout life, making older adults—especially older females—more susceptible to osteoporosis-related fractures. The cause of osteoporosis depends on its type: type 1 osteoporosis is caused by hormonal changes, especially post-menopause, and type 2 osteoporosis is caused by the body's misuse of vitamin D. Secondary osteoporosis is mostly caused by steroid medication, myeloma, bone metastasis, hormonal changes, alcohol consumption, cigarette smoking, hypogonadism, and many other extraskeletal factors.[15,20,61]

In Indonesia, around 22–55% of elderly females are diagnosed with osteoporosis. Approximately 30% of 60–70-year-old females currently live with osteoporosis.[20] In females, osteoporosis is worsened not only by hormonal changes but also by senescence. Males, on the other hand, usually suffer from osteoporosis due to senescence alone. This relates to females experiencing menopause, while males continue to produce their sex hormones—proving once again that changes in sex hormones are a significant factor in osteoporosis.[24,27,62]

The significance of both male and female sex hormones in relation to aging has been proven in many previous studies. Even though they are called "female" or "male" sex hormones, both hormones are present in each sex. The difference is observable in their amounts, where testosterone values are significantly higher in males, and estrogen values are significantly higher in females. The loss of estrogen and testosterone does occur in aging males and females, and both affect bone in similar yet different ways. Estrogen loss is more rapid in females, while testosterone loss in males is not as rapid. It is important to note that bone loss in males is not as commonly researched compared to females. The relationship between testosterone and its relation to bone remodeling should be examined in further studies.[11,21,24,42,62]

Estrogen is a hormone that is substantial in the bone remodeling process. Due to its role in bone resorption, estrogen has been proven to slow bone mass loss, protecting the matrix from fractures. During and after menopause, females

lose much of their ability to produce estrogen. Pregnancy and breastfeeding might also decrease the amount of estrogen stored in the female body. Fetuses require their mother's calcium to stimulate bone formation, explaining the increase in calcium loss in female bone. The impact of such a phenomenon is an increase in bone resorption, which ultimately decreases bone quality. This is proven by the disproportionate rate of osteoporosis in females.[20,21,24,42,62] A previous study also discovered that greater hip fractures are more common in females than males.[23,63,64]

Osteoporosis can be considered a "silent killer" due to its lack of pre-fracture detection. There are several ways to prevent osteoporosis—or at least reduce its detrimental effects. Regulating one's diet and nutritional intake is one way to do it. The consumption of calcium and a vegetarian diet is proven to be more effective at preventing osteoporosis, especially in females. Since calcium is essential in bone remodeling, it is recommended to avoid alcohol consumption and smoking. Another way is to consistently stimulate the musculoskeletal system. A previous study stated that the musculoskeletal system of older adults who actively exercise is significantly healthier than those of the same age who do not exercise. The use of medication and therapy is also recommended in some cases, but this should be done under the supervision of a doctor or therapist. These methods might include estrogen replacement therapy (ERT), vitamin D therapy, and calcitonin consumption.[21,34,61,65-67]

Population Differences in Bone Aging

Variations in bone growth and bone aging exist across populations. As a result, incidences of bone fracture, osteoporosis, and other diseases related to bone growth in old age may vary from one population to another. Many studies have shown that the "one size fits all" approach is irrelevant in terms of bone health assessment and treatment. This notion demonstrates that variations in bone aging should be evaluated within populations as a means of adjusting for better healthcare services, especially for older patients who are more prone to bone diseases.[28]

One study compared bone mineral density in 65–78-year-old males from various populations, namely white, African American, Asian, Hispanic, Afro-Caribbean, Hong Kong Chinese, and South Korean males. After adjusting for age, this study found several interesting things. Afro-Caribbean and African-American males have higher whole-body bone mineral density levels compared to white Americans. The Asian populations (South Korean, Hong Kong Chinese, and Asian American) have relatively lower bone mineral density compared to white and African populations in nearly all bone sites. White American and Hispanic males are quite similar in terms of bone density.[68]

Another study explored bone density in males and females from Black and white populations. They confirmed that Black males tend to have denser bones compared to white males. On the other hand, white and Black females have generally lower bone density.[69] The lower amount of bone mineral content in females, especially older females, is correlated with the higher energy expended for the reproductive stages, such as gestation and menstruation.[62,70]

The previous observation is further confirmed in another study. This study involved 80 Black males and females, and 80 white males and females. The variables of the participants were controlled for sex, age, bone age, pubertal stage, height, and weight. The study found that Black males and females have higher volumetric apparent bone mineral density in the trabecular bone of the vertebral body. No significant differences in bone mineral density were found in the femoral midshaft.[71]

In 2005, a scientist researched the correlation between type 2 diabetes and pelvic bone loss in 70–79-year-olds. Increased femoral neck bone loss was most prevalent in older, diabetic, white females compared to white males, Black males, and Black females. Significant changes in

bone loss were not observed in males and Black females with diabetes and normal glucose homeostasis. This explains the increased risk of bone fracture among older diabetic females, especially white females.[72]

A previous study compared the skeletal mass and bone mineral content of the radius in Black and white American females. This study reaffirmed previous studies that Black females experienced lower rates of bone fracture and osteoporosis. Due to having denser bones, the biomechanical integrity of Black females is maintained for a longer period. The larger muscle mass of Black females is attributable to this increased bone mass and resistance to osteoporosis and fracture.[73]

Another study explored how Black and white females differ in terms of bone loss rate during their menopausal stages. The study extracted data from 122 white and 121 African-American females. All females were measured at 6-month intervals over 3–4 years using single and dual photon absorptiometry of the upper extremity (compact bone) and vertebrae (spongy bone). Premenopausal females from both populations did not show significant differences in bone loss rate. However, bone loss speed variation was observed during the early menopausal stage. White females are more likely to lose bone mass during this stage compared to African-American females. After 5 years of the postmenopausal stage, the bone loss rate returned to being insignificantly different in tissue composition.[74]

According to the Third National Health and Nutrition Examination Survey (NHANES III), postmenopausal white females are more prone to osteoporosis (20%) compared to Hispanic females (10%) and African-American females (5%). For the male samples, the same conclusion can be drawn due to the relatively higher prevalence of osteoporosis in white males (4%) compared to Hispanic (2%) and African-American (3%) males.[75] Greater bone density in African-American people compared to white people might cause these discrepancies in osteoporosis prevalence. By calculating bone mineral apparent density, the bone size variable is adjusted, thus controlling for sex. By adjusting for bone size and sex, this study has proven that African-American people, on average, have higher bone density compared to white and Asian people.[76]

Other than research on Black and white populations, aging studies on the Hispanic population are also popular in the United States. Prior research has shown that the bone density of healthy, non-obese, Mexican-American older females is relatively higher than that of non-Hispanic whites. This might explain the lower rate of hip fractures in the Mexican-American population. This study also found that bone density variations between the two populations are independent variables, as they did not correlate to lean mass and fat mass.[77]

CONCLUSION

This review covered many aspects of how human bones age across different human characteristics, with the most common study topics concerning osteoporosis, bone loss, and bone fracture in white populations. This paper also discussed the dynamics of biomechanical properties, such as the decrease in bone density and ultimate strength, and their significant role in skeletal senescence mechanisms. After understanding how skeletal senescence mechanisms work differently in each human population, it is important that adjusted medical guidelines are provided to include a variety of treatments that work best for certain biological characteristics. Specific sex- and population-based healthcare services in geriatrics and gerontology are highly suggested to ensure inclusive healthcare for older adults from every population and sex. Due to the minimal data and research about bone aging in Indonesia (other than osteoporosis), the authors encourage data procurement on local populations to create or modify more suitable

medical guidelines for older adults and eldercare in Indonesia.

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CONFLICTS OF INTEREST

The authors declare that there are no conflicts of interest.

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