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Review Article

Bioanthropological and Biomechanical Perspectives on Skeletal Senescence Variation: A Literature Review

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ABSTRACT

Background: Senescence is the deterioration of the body's biological and physiological function throughout later life. Senescent populations are more prone to diseases, though other than osteoporosis, skeletal senescence is a less discussed topic in Indonesia. Furthermore, a global and national increase in the aging population showed that they will be a major group in society, thus raising the urgency to review this matter. This study aims to comprehend the physiological and biomechanical mechanisms of skeletal senescence, as well as senescent variations in a certain sex or population affinity.
Literature Review: Age-related skeletal cellular death and imbalance contribute to bone damage in elders. Senescence also affects skeletal biomechanics, expressed in increased bone porosity and brittleness. Stresses in aged bone risk straining above its elastic limit and causing fractures due to its inability to tolerate stresses. The loss of sex hormones is related to skeletal senescence, especially in females, though the effects of testosterone on skeletal senescence are underresearched. 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.
Summary: Specific population-based healthcare services in geriatrics and gerontology are highly suggested to ensure inclusive healthcare for every aged individual. Due to the minimum data about bone aging in Indonesia (other than osteoporosis), the authors encourage data procurement on 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 existing and growing from time to time that occurs in living beings, including humans. After a certain age, a person's physical condition shall begin to decline in function. This process is called "senescence". Many intrinsic and extrinsic factors are related to the acceleration of human senescence, such as genetics, hormonal, skin type, nutrition intake, lifestyle, sunlight exposure, comorbid medication, and many more.[1–6]

Biological aging is closely related to cellular aging. Cells, as the main structure that composes tissues and organs, will slowly experience loss in number and function. The cells will lose their effectiveness to repair or remodel themselves, hence the reason behind elders' proneness to illnesses, though some elders remain to "slow" the process—possibly appearing younger than some. The use of anti-aging products, a healthy lifestyle, and constant physical activity stimulus may be the factors behind such a thing. It is important to note, however, that younger biological appearance among elders does not equal fitness.[1,7–10]

The bone, like any other biological structure in the human body, is dynamic. On a molecular level, the bone cells—namely the osteoblasts and osteoclasts—are continuously remodeling the bone structure. Even without bringing biological aging into the equation, the

human bone is a constantly dynamic structure. Age-wise, humans will grow to their peak height before losing it due to the changing of posture. Senescence of the bone plays a huge factor in these changes, namely through the mechanisms of bone density loss, decrease in synovial lubricants, and joint stiffness. All of the aforementioned factors affect how the bone functions as a part of the musculoskeletal system, such as in creating movements.[11–15]

All these changes due to bone aging can be shown explicitly by its biomechanical properties. The continuous remodeling of bone coupled with senescent cells made the increase of bone porosity from 4%-12%. For elderly individuals, this might lead to an increase in bone porosity of up to almost 50%, along with an approximately 40% reduction in ultimate strength. Ultimately, these increases affect how an elderly ability to lift heavy objects.[16–19]

Related to their loss of function, it is previously mentioned that old age and the process of being older might contribute to being prone to diseases. Several pathological cases, like osteoporosis, are considered inevitable for many elders. Other risks, such as bone fractures, also frequently occur in elderly people. Several researchers also stated that many diseases are in fact closely related to senescence.[20–23] Therefore, a literature review on skeletal senescence and age-related pathologies is urgently needed right now.

Since hormonal factors play a huge part in the aging process, it is also important to discuss how they affect human variations, namely the sexes. Why the sexes? Biologically, both sexes have their own unique function that requires unique endocrines to stimulate the process. For example, both primary and secondary puberty amongst males and females are stimulated by different hormones—the males by testosterone and the females by estrogen. It is important to note, however, that even though both sexes are not exclusive to producing a certain hormone, the quantity of hormones produced is quite different. This also relates to their susceptibility to bone loss.[23–27] It is interesting and important to discuss how males and females differ in terms of skeletal aging, since understanding how both sexes' bone age might give us an insight into how to ensure the treatment needed.

Human biological variation does not only concern sex and age but also population affinity. The process of skeletal senescence also varies among populations. Therefore, 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 an insight into how to understand the aging process in different population affinities.[28,29]

The study on human skeletal senescence became a much more urgent issue, especially in Indonesia. According to the Population Division of the United Nations Department of Economic and Social Affairs report, it is estimated that Indonesia's life expectancy will reach 75 years in 2050.[30] In Indonesia, many population censuses have recorded how the aging population continues to increase. As of 2023, 11.75% of the Indonesian population can be 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 their proneness to physical and psychosocial problems, a more comprehensive understanding of their condition is urgently required in Indonesia since according to the demographical statistics, an increasing number of elderlies 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 a more successful, inclusive, and healthy aging for the elderly.[32,33]

A review on skeletal senescence is highly scarce in Indonesian search engines, hence the importance of raising this issue. This paper aims to discuss and analyze how human skeletal elements age as well as how population and sex differences affect skeletal senescence. This paper also discusses how senescence affects the biomechanical properties and functions of the bone. This paper also aims to describe several bone diseases and how age or 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, offer new and integrated perspectives, and stimulate the research of bone biology and physiology, especially related to the aging process of the human bone in various population settings. With new perspectives and stimulated research, hopefully, the awareness of bone aging in the elderly population will rise and become a consideration for the policymakers to make better health care in Indonesia. Thus, medical experts such as orthopedics, traumatologists, and (but not limited to) radiologists could provide better clinical services to the elderly patients.

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

REVIEW

Skeletal Senescence and Remodeling

Bone formation and resorption are dynamic and constant processes. Such a process is called bone remodeling. Figure 1 illustrates how the bone remodeling process happens in five steps. Overall, it is a complex process that is controlled by local and systemic factors and carried out by multiple types of cells that interact through cytokines, cell contacts, and matrix elaboration. The bone cells that will be discussed in this review are osteocytes, osteoblasts, osteoclasts, and bone marrow mesenchymal stem cells—all contribute to bone remodeling. The bone structure and bone cells, like any other part of the human body, are also affected by aging. Aging bone cells might cause several changes in characteristics and function in comparison to their normal state.[12,34,35]

Osteocytes are the longest-lived bone cells. Its natural lifespan is approximately 25 years. However, several studies showed that osteocytes are also subject to aging. Senescent osteocytes might lead to several malfunctions, such as bone loss, microfractures, and osteoporosis. Osteocyte death also means the decline of bone strength due to its demise in regulating bone vascularity and hydration. Sex hormone deficiency, loss of mechanical strains, and glucocorticoid excess are highly contributive to osteocyte death.[12,13,15,34,35,37,38]

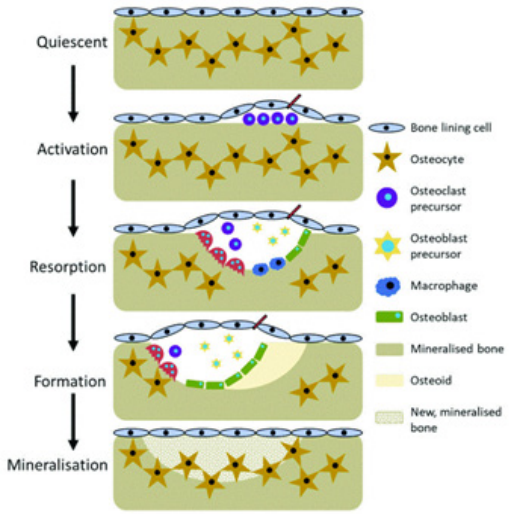

Figure 1. Five stages of bone remodeling.[36]

Autophagy failure and nuclear pore leakiness are most likely the cause of age-related osteocyte death. Autophagy is a process conducted by lysosomes and is highly functional in cellular recycling and defending the cells from stressful stimuli. Autophagy failure might lead to the decrease and death of long-lived postmitotic cells in many organs, such as the brain, heart, muscle, and kidney. Autophagy failure is also closely related to degenerative neurological diseases, cancer, and heart failure. Therefore, it is very likely that osteocytes might be affected by autophagy failure as well, resulting in an increased rate of osteocyte death throughout senescence. Nuclear pore complexes (NPCs), on the other hand, are channels of nucleoproteins that serve as a physical barrier within the nuclear envelope. NPCs are known for their function to regulate the movement of cytoplasmic proteins to the DNA and selectively transport 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 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 affected osteoblasts, one of the cells responsible for bone formation and mineralization of its matrix. Unlike the osteocyte, osteoblast only lasts for a few months and many of them (60-80%) will die by apoptosis at the site of resorption. With aging, osteoblasts experience a significant change in function. The decrease of mineralization optimality, differentiation capacity, and cell activity are commonly observed traits of senescent osteoblasts. Senescent osteoblasts are also not as responsive to stimuli given by 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 osteoclasts' expression are age-related, namely in the RANKL/RANK/OPG and M-CSF of the 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, the BSMCs' abilities include self-renewal and self-differentiation into osteogenic, adipogenic, and chondrogenic lineages. Changes caused by aging are decreasing proliferative capacity and increasing adipogenesis. In consequence, the decreasing amount of osteoblasts will make the bone unbalanced. 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

The bone is one of the most dynamic tissues in the human body. It is in a constant state of flux as a material as well as a structure. These affect how a bone handles a load. The study of how a bone handles a load can be explained through the lens of biomechanics. Biomechanical properties of the bone describe the relationship between forces (F), or loads, applied to the bone or bone specimen and the deformations that result from these applied forces. 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 interactions of muscle or tensions of the ligament. Bone resistance developed as a response to the applied forces is known as stress (σ). It represents local force intensity with dimensions of force per unit area ($\sigma = F/A$) and has pascal (Pa): 1 Pa = $1N/m^2$ unit in the International System of Units (SI). The deformation of bone due to stress is usually represented as the strain (ε) defined as the ratio of the change of specific dimension (such as length) of bone, with the original value of such dimension ($\varepsilon = \Delta l / l$) and is non-dimensional.[43–45]

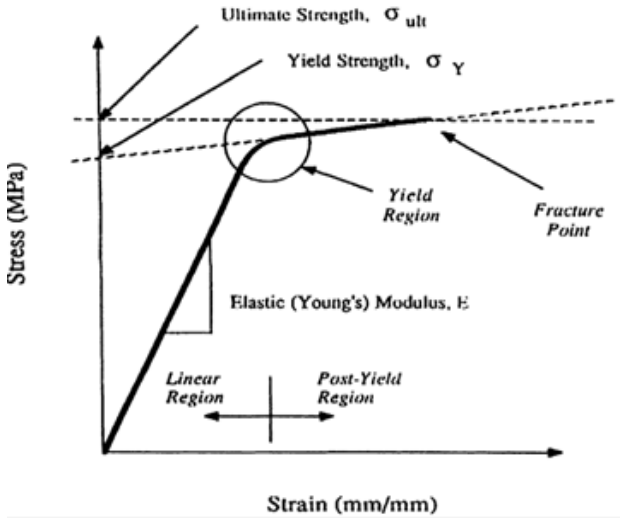

Figure 2. Stress-strain curve of a bone under tension.[6]

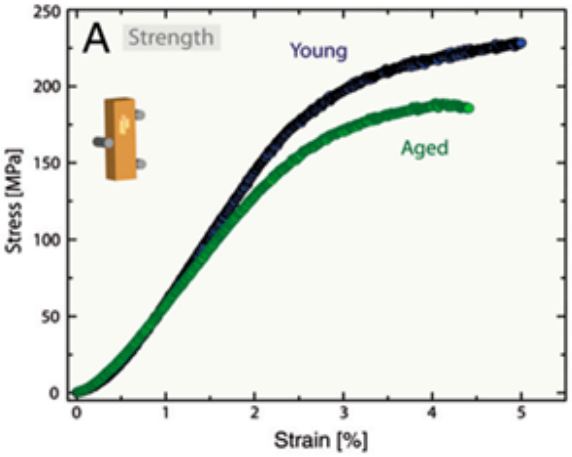

Figure 3. Stress-strain curve comparison between young and aged individuals.[17]

To define the mechanical or material properties of the bone, the shape and size of the bone must be accounted for by establishing these properties. One can achieve a true understanding of the bone purely as a material and not one that is dependent on some twisted 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 definition of "stress" and "strain", the stress-strain curves of a material will be the same for different shapes and sizes of such a material. Figure 2 shows a stress-strain curve for a bone specimen under compression and tension in a longitudinal and transverse orientation.[44,46,47]

Also in Figure 2, there is a linear region of the stress-strain curve. The slope of the 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 postyield or plastic region until the fracture point is reached. The term "ultimate strength of the bone" is used to define the maximum stress that a bone can handle before fracturing itself.[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 the young healthy bone to around 12% at age 60 years. In elderly individuals, the bone's porosity is up to almost 50%. The increased surface area of the cortical bone provides more surface-to-receiving signals for remodeling to be initiated and thus further accelerates cortical bone loss with age.[16]

The increases in intracortical porosity present higher strains, which is directly related to decreases in Young's modulus throughout human bone age.[17,49–52] The Young's modulus of a 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 an aged person and the steeper slope means a higher Young's modulus.[46,53]

An elderly person has more senescent cells and it starts to accumulate in their tissues, including bones. Cell senescence damages bone remodeling ability by impairing the formation of bone. This is shown by the current studies, which decrease bone load strength due to aging correlation with cell senescence.[15,54] Senescent cells in bone tissues 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, the bone formation leaves small spaces between the bone tissues. These small spaces make bone porous, increasing bone porosity.[55,56] As the bone becomes more porous, the bonding strength of bone material decreases due to the empty space between them.

Weaker bonding means easier to break, thus 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 to the collagen and collagen-mineral interface. Non-enzymatic glycation forms intra-molecular collage 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 that is found in this condition. However, 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 the enzymatically-mediated crosslinks, AGEs accumulate naturally in bone with age. With aging, 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 of the bone. The ultimate strength of older bone is less due to AGE accumulation, 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 or 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 persons as they age and can be measured by T-score—an individual with lesser than -2.5 T-score indicates a higher rate of bone fragility and is thus diagnosable as osteoporosis.[60] This disruption will last consistently throughout life, thus making elders—especially elder females—more susceptible to osteoporosis-related fractures. The cause of osteoporosis is dependent on its type: type 1 osteoporosis is caused by hormonal changes, especially post-menopause; type 2 osteoporosis is caused by misuse of vitamin D by the body; and finally, secondary osteoporosis is mostly caused by steroid medication, myeloma, bone metastasis, hormonal changes, alcohol consumption, cigarette smoking, and hypogonadism, among many other extraskeletal factors.[15,20,61]

In Indonesia, around 22-55% of elderly females are diagnosed with osteoporosis. Approximately, around 30% of 60-70-year-old females are currently living with osteoporosis.[20] In females, osteoporosis is worsened by not only hormonal changes but also senescence. Males, on the other hand, usually suffer osteoporosis due to senescence alone. This is related to the fact that females will eventually experience 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 is proven in many previous studies. Even though it is called the "female or male sex hormone", both hormones are not mutually exclusive to each sex. Instead, every sex has a combination of those hormones. The difference is observable in their amount, where testosterone values are significantly higher in males, and vice versa in females and estrogen. The loss of estrogen and testosterone do occur in aging males and females, and both affect the bone in similar yet different manners—estrogen loss is more rapid in females, while testosterone loss in males is not as rapid. It is important to note, however, that bone loss in males is not as commonly researched in comparison to females. The relationship between testosterone and its relation to bone remodeling shall 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, the existence of estrogen is proven to be able to slow down bone mass loss, hence defending the matrix from fractures. During and

after menopause, females lose a lot of their ability to produce estrogen. Pregnancy and breastfeeding might also decrease the number of estrogens stored in the female body. Fetuses require their mother's calcium to stimulate bone formation, thus explaining the increase of calcium loss in the female bone. The impact of such a phenomenon is the increase of bone resorption which will ultimately decrease bone quality. This is proven by the disproportionate rate of osteoporosis in females.[20,21,24,42,62] A previous study also discovered the fact 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 in 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 elders who actively exercise is significantly healthier than those of the same age. The use of medication and therapy is also recommended in some cases, but they should be done under the doctor's or therapist's supervision. Those methods might include estrogen replacement therapy (ERT), vitamin D therapy, and calcitonin consumption.[21,34,61,65–67]

Population Differences in Bone Aging

Variation in bone growth and bone aging exists in populations. As a result, incidences of bone fracture, osteoporosis, or other diseases related to bone growth in old age might 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 proved that variations of bone aging should be evaluated within populations as a means of adjusting for better healthcare services, especially for senescent patients who are more prone to bone diseases.[28]

A previous study compared bone mineral density in 65-to-78-year-old males from various populations, namely white, African-American, Asian, Hispanic, Afro-Caribbean, Hong Kong Chinese, and South Korean males. After adjusting the age variable, this study found several interesting things. Afro-Caribbean and African-American males have a higher whole-body bone mineral density level in comparison to white Americans. The Asian populations (South Korean, Hong Kong Chinese, and Asian-American) have a relatively lower bone mineral density compared to white and African populations in nearly all bone sites. The 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 side, white and black females have a generally lower bone density.[69] The lower amount of bone mineral content in females, especially aged females, is correlated to the higher energy expedited for reproduction stages, such as gestation and menstruation.[62,70]

The previous narration 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 their sex, age, bone age, pubertal stage, height, and weight. The study found that black males and females have a 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-to-79-year-olds. Increased femoral neck bone loss was most prevalent in older, diabetic, white females in comparison to white males, black males, and black females. Significant change in bone loss was not observed in males and black females for participants 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 the 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. Black females's larger muscle mass is attributable to the increased bone mass and resistance to osteoporosis and fracture.[73]

Another study explored how black and white females differ in bone loss rate during their menopause stages. The study extracted the data from 122 white and 121 African-American females. All females were measured at 6-month intervals over 3-4 years by utilizing single and dual photon absorptiometry of the upper extremity (compact bone) and vertebrae (spongy bone). Pre-menopausal 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 post-menopausal stage, the bone loss rate returns to being insignificantly different in tissue composition.[74]

According to the Third National Health and Nutrition Examination Survey (NHANES III), post-menopausal 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 taken 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 the bone mineral apparent density, the bone size variable is adjusted, thus controlling the sex variable. By adjusting the bone size and sex variable, this study has proven that African-American people on average have higher bone density in comparison to white and Asian people.[76]

Other than research on black and white populations, aging studies on the Hispanic population were also popular in the United States. Prior research showed that healthy, non-obese Mexican-American elder females's bone density 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

The review dealt with many scopes to comprehend how human bones age within different human characteristics, with the most popular study topics concerning osteoporosis, bone loss, and bone fracture in white populations. Also, this paper discussed the dynamics of biomechanical properties, such as the decrease in bone density and ultimate strength, and its significant role in skeletal senescence mechanisms. After understanding how skeletal senescence mechanisms work differently in each human population, it is important that an adjusted medical guideline is provided to include a variation of treatments that works best on certain biological characteristics. Specific sex and population-based healthcare services in geriatrics and gerontology are highly suggested to ensure inclusive healthcare for elderlies from every population and sex. Due to the minimum 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 elders and eldercare in Indonesia.

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