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A Compilation of Effects of Senescence on Bone Healing and the Treatment Plans Regarding Such Effects

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Abstract: **In modern times, Thailand, as well as most of the world, are developing into an increasingly aged society. The population of the elderly are taking up more of the percentile of the overall populations. As such, more care and attention should be taken to ensuring the wellbeing of this particular group of society. Senescence is a condition that naturally comes with aging, and it causes many complications in bone healing including but not limited to lower granulation tissue density, reduced vascular density, and heightened risks in non-union and other comorbidities independent of the initial wound. In accordance with the aforementioned conditions, there have been many studies regarding methods to aid in reducing such complications. Some studies aimed to improve treatment by reducing the risks of comorbidities, while other studies tested on subjects, like mice, to find ways to counter the effects of senescence directly. However, such studies are often limited by the sample size or the nature of its recipient itself which may prove difficult to translate the full degree of such studies to the general public. As such, it is advised that increased efforts be put into furthering these studies in the future.**

Keywords: **Senescence, bone healing, elderly, treatment of senescence.**

I. INTRODUCTION

A study reports 50% of women and 20% of men in the USA over the age of 50 years will experience an osteoporotic fracture[12], [15], [28].

As Thailand develops into an aging society, where the elderly, people aged 60 years and above, accounted for 10% of the population[42]. The need for innovative strategies to promote bone healing in elderly people becomes more urgent; however, previous approaches – including those based on growth factors, biomaterials, and cell therapies – have fallen short. This may be due to the bone tissue microenvironment – the surrounding cells, molecules and structures that support bone formation and repair – deteriorating, becoming stiffer, and displaying reduced metabolic activity with age[2].

It has now become more prevalent than ever to be informed of the effects senescence poses to one's health. Since failed or delayed healing can affect up to 10% of all fractures and can result from factors such as comminution, infection, tumor, and disrupted vascular supply [23], [33] causing casualties to a considerable number of the population.

The purpose of the paper is to compile an overview of bone fracture healing in the elderly and how it may be affected by senescence as one ages.

II. PROCESS OF BONE HEALING

There are two main modes of bone healing. The first type is primary bone healing which is dictated by absolute stability constructs that achieve a mechanical strain below 2%[4],[9],[11],[35],[40]. That is to say the bony fragments are reduced, aligned, and fixed under compression with no movement at the site of fracture [14], [26].

It is an intramembranous bone healing that occurs through Haversian remodeling.[4, 9,11,35,40]

Bone on one side of the cortex must connect with bone on the other side to reestablish mechanical and physical continuity[14],[20].

The other type is secondary bone healing which occurs in non-rigid fixation modalities such as braces, external fixation, plates in bridging mode, intramedullary nailing, ..etc. These fixation modalities achieve a mechanical strain between 2-10%. It consists of four steps: Hematoma formation, Granulation tissue formation, Bony callus formation, Bone remodeling [12],[40].

Immediately after fracture, in the hematoma phase, the fracture site experiences inflammation. Inflammation is the body's response to pathogens or tissue damage. During an inflammatory response, cells of the innate and adaptive immune systems are recruited and activated. These inflammatory factors have a direct effect on the differentiation and function of multiple bone cell types, including osteoblasts, osteoclasts, and osteocytes[2],[9], [15],[47].

Alongside this, The blood vessels supplying the bone and periosteum which were disrupted during the fracture, cause a hematoma to form at the fracture site, which is rich in hematopoietic cells. The hematoma clots and forms the temporary frame for subsequent healing[40].

Another key component in healing is granulation tissue at the injury site, which comprises fibroblasts, collagen, capillaries, and inflammatory cells. Bridging tissue gaps, supporting cell migration, and providing nutrients during healing through a capillary network that promotes healing are its main functions[24].

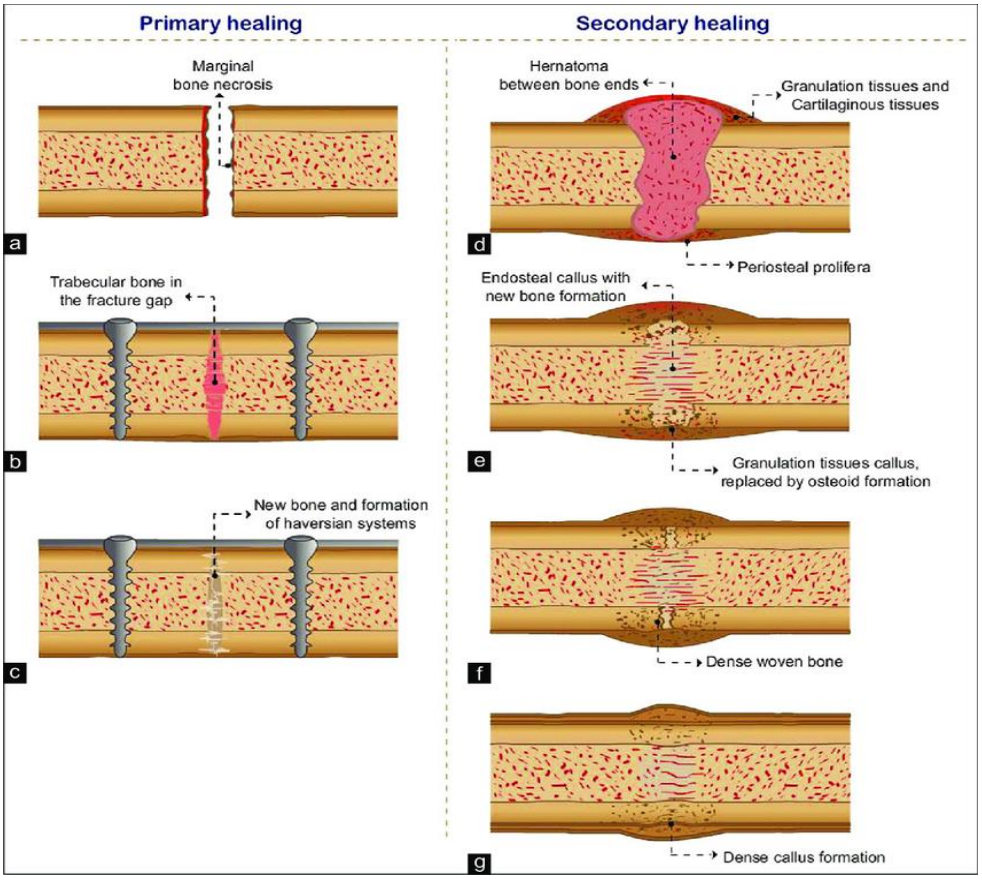

Fig.1 A diagram illustrating primary bone healing and secondary bone healing[49].

III. EFFECTS OF SENESCENCE IN BONE HEALING

Aging contributes as one of the risk factors for fracture and in the presence of a BMD score, the risk of

fractures will be higher for elderly[17],[23],[27]. With rising age, fracture repair slows down, and the risk of non-union increases among many other crucial processes. Furthermore, the inflammatory response of the immune response is influenced by aging, which manifests in an increase in the inflammatory status[25],[47].

Elderly patients, as Marvel Idowu found, had significantly lower granulation tissue density, reduced vascular density compared to younger patients at 3 weeks post-fracture. Collagen deposition was also significantly lower in the elderly group at 6 weeks, resulting in prolonged healing time compared to younger patients[25].

Many older patients suffer delayed healing secondary to reduced vascularization, decreased collagen synthesis, and lost immune function. Healing is often further complicated by comorbidities, specifically diabetes and cardiovascular conditions, which inhibit tissue regeneration and blood flow. However, the observed progression of granulation tissue over time also shows ongoing inflammation[24].

Patients with osteoporosis and comorbidities (such as diabetes) are also commonly elderly and are predisposed to impaired healing and increased infection risk, as mentioned by (Sobh et al, 2022) [24],[41].

IV. CURRENT TREATMENTS REGARDING SENESCENCE IN BONE HEALING

Below are several studies that have conducted research in various treatments focusing on countering the effects on bone healing following senescence.

Emerging evidence suggests that targeting metabolic pathways and rejuvenating the bone microenvironment could unlock the regenerative potential of aged tissues. However, this has been limited by a lack of studies on mice that are old enough to accurately reflect the decline seen in elderly humans[39].

The incidence of distal femoral fractures (DFF) in the elderly is increasing, mainly because of the growing aged population[7],[16],[34], [36]. In this age group, surgical treatment is frequently complicated by previous surgery and femoral implants,[3],[34], [36], [39] and also age-related deterioration of bone quality that will affect osteosynthesis stability[1],[8],[34], [38],[44]. Anatomical distal femoral locking plates are standard treatment, as they also can be used for peri-implant fixation.When applied as a long bridging plate, biomechanical advantages include lower incidence of loss of fixation,[22],[34],[44] more flexibility, and better capability to withstand permanent deformation[6],[10],[31],[34],[48].

Although fracture subsidence of the metaphyseal fragment or even cut-out of the osteosynthesis is common in osteoporotic bone in other locations such as hip and proximal humerus,[13],[19],[30],[34],[38] it has not been perceived as a problem in DFF. In DFF, metaphyseal migration and cut-outs have been studied mainly in experimental models[21],[32],[34], [45]. Thus, this study by (Martin et al, 2024) aims to increase the knowledge of secondary displacement in a strictly bridging plate fixation in elderly patients with osteoporotic bone.

They found that no correlation was found between the degree of general BMD or BMI and secondary displacements. Restricted weight-bearing for 8 weeks did not prevent the fracture from secondary displacements; interestingly, there was a significantly larger femoral shortening in the restricted weight-bearing group at 52 weeks. In addition, a nonsignificant increase in mechanical adverse events, such as cut-outs, was seen in the restricted weight-bearing group. The benefits of restricted weight-bearing in the elderly should be questioned [34].

The bone cement technique, also known as cementation or cemented fixation, represents a remarkable advancement in orthopedic surgery, significantly improving patient outcomes in joint arthroplasty, fracture management, and revision surgeries. The technique, as Lecai et al. found, was associated with accelerated clinical healing time, reduced time spent in bed after surgery, and improved postoperative pain relief and functional recovery during the early postoperative periods The cemented fixation method has provided excellent stability and promoted successful long-term outcomes for patients, especially the elderly [18],[46].

Clinical studies evaluating the efficacy of bone cement in pelvic fragility fractures have shown promising results,with improved pain relief, early mobilization, and enhanced functional recovery observed in many cases [18],[37],[43]. However, the initial benefits observed may diminish over time. Lecai et al. encouraged repetition of the study with a larger sample size.

There are no FDA-approved drugs to enhance fracture healing in the elderly, nor are the molecular mechanisms that delay fracture healing in aged individuals well studied[5],[29], which leads to a group of researchers to study the potentials of senolytic drugs.

Jiatong et al. reports using primary senescence cells (SCs) and mesenchymal progenitor cells (MPCs) derived from fracture callus. They found that aged mice had a significantly higher number of SCs in callus than did young mice or in non-fractured bones of aged mice. The senolytic drugs were found to enhance fracture healing in the aged mice, which prevented the

inhibitory effects of aged SCs on MPCs and promoted fracture healing in aged mice. Thus, fracture injury triggers significant senescence of cells in the callus tissue of aged mice, leading to inhibition of MPC growth and fracture repair. Senolytic drugs represent a promising therapy for enhancing fracture repair in the elderly by eliminating SCs, which Jiatong et al. have identified as a molecular inhibitor of repair[29].

V. DISCUSSION

Many articles regarding effects of senescence agreed that bone fragility becomes more prominent as one ages which increases the risk of osteoporosis. Additionally, the presence of SCs inhibits inflammation which is a significant process in bone healing. Thus, slowing down the recovery process in elderly patients. More prominently, the weakened immune system and reduced vascularization brought about by senescence increases the risk of comorbidities independent of the initial fracture, thereby further jeopardizing recovery rates and also increasing infection risks in the wound.

Consequently, studies regarding treatments of the elderly may be inclined to focus primarily on preventing such complications in the first place. Although there were also studies which experimented on treating the senescence itself by way of senolytic drugs or rejuvenating bone microenvironment, the progresses in such studies were limited to mice.

In this regard, it is advisable that further efforts in studying methods with which to counter senescence should be prioritized.

VI. CONCLUSION

Senescence, characterized by the presence of senescence cells and impaired recovery in bodily functions, affects the recovery processes of bone via the presence of inhibitors to crucial components in the healing and reduction in immunity which causes comorbidities independent from the initial wound. Due to these risks, the elderly patients which are predisposed to senescence often possess impaired healing, the effects of which greatly increase the likelihood to develop these morbidities.

In response, there are a breadth of studies which focus their efforts in managing and minigating the effects of senescence on the bone. Studies regarding this topic follow a pattern of dichotomy, one of which is prevention of comorbidities, while another is focusing on contravention of the effects of senescence directly. The studies on both ends of the dichotomy each lack the sufficient quantity and depth to revolutionize the current data regarding the healing of bone fractures in the elderly. It is recommended to increase further efforts to study the relationship between bone healing and the effects of senescence.

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