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## Role of Serum Albumin in fracture healing

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### Abstract

Albumin is the most abundant plasma protein with molecular weight of 69 kd and it accounts for 55-60% measured in total serum protein, produced in liver. The multipotent progenitor cells of bone marrow differentiate into functional hepatocyte-like cells which expresses albumin. The 66kDa albumin protein is very prominent, and this protein component is present in the bone tissue as a major bone protein. The increase in IGF-I with fracture healing induce the production of albumin in the femoral-diaphyseal tissues and thus the osteoblastic proliferation takes place. The albumin also enhanced the bone calcium and DNA content that further promotes fracture healing, and its deficiency may be a significant determinant in healing process which may lead to fracture impairment. In this review we focused on the valuable significant role of albumin in fracture healing as well as the nonunion.

**Keywords:** Serum albumin, Fracture healing, Fracture nonunion, Fracture impairment.

### 1. Introduction

Human serum albumin is a multifunctional, non-glycosylated, negatively charged protein. Serum albumin level of  $\geq 3.5$  g/dl is widely accepted as normal [1]. The total body albumin content is 3.5-5.5 g/dl of which one third is intracompartmental (i.e. within the vessels) and remaining is extra compartmental (i.e. outside the vessels). The distribution of albumin outside vessels takes place in skin, muscles, gut, liver and in subcutaneous positions [2].

The fracture healing is a unique and complex physiological process that recapitulates embryonic skeletal formation. However, many factors are responsible for impaired fracture healing including poor nutritional of patients [3]. As the fracture healing process affected by multifactorial components, till now the problems of fracture nonunion are common and challenge for the treating surgeons [4-5]. However some studies reveals the association of fracture outcomes with serum albumin [6] and shows anabolic effect of albumin on bone components as well as fracture healing both in-vitro and in-vivo experiments [7, 8]. In this present review,

we have discussed the role of serum albumin in fracture healing.

### 2. Serum Albumin

Serum albumin consists of a simple amino acid chain with a quaternary helix-line structure. The center of this molecule has hydrophobic radicals which are binding sites for many ligands, while the outer part of this molecule is composed of hydrophilic ligands. Albumin is most abundant plasma protein, synthesized in liver and accounts for 55-60% of total serum protein [9]. Albumin synthesis is governed by a single copy gene lying on the long arm of chromosome 4, near the centromere at position q11.22 [10-12].

In humans, albumin synthesis takes place only in the liver [13]. Albumin is not stored by liver but it secreted into portal circulation as soon as it is manufactured. In healthy young adults the rate of synthesis is  $194 \text{ mg kg}^{-1} \text{ day}^{-1}$ , or about to 12-25 gm albumin  $\text{day}^{-1}$ . Total daily albumin degradation in adult is around  $14 \text{ g day}^{-1}$  or 5% of daily whole body turnover [14].

Albumin has the polypeptide chain of amino acid and having no change in the carbohydrate structure of the molecule, but there is a scarcity of tryptophane and methionine residues in it. The molecule is arranged in series of alpha helices and disulphide bonds [15]. Albumin is most important protein, it transport many small molecules such as bilirubin, calcium and magnesium, it combine with heavy metals and save our body from damage. It is a 69 kDa plasma protein (molecular radius =36 Å) with a variety of functions, including maintenance of plasma acid osmotic pressure, buffering of plasma acid base changes and functioning, fatty acids, phospholipids, ions and heavy metals [16].

The albumin molecule have an ellipsoidal shape (about 140 x 40 Å) and is composed of domains on the basis of amino acid sequence. The mature circulating molecule is arranged in series of  $\alpha$ -helices and pair of sub domains faces, each other to form a complete domain. These can in cylindrical structure with polar outer wall and hydrophilic internal core [17]. The tertiary structure of albumin crystal has been isolated by X-ray crystallography that resembles the heart shape. The shape of the molecule changes with the environmental conditions [18] and it regain their shape with the help of disulphide bonds and provide strength in physiological conditions [19]. The denaturation occurs only in dramatic and non-physiological changes in temperature, pH and ionic or chemical environment.

### 3. Serum Albumin in Fracture Healing

The fracture healing is a unique and complex physiological process of repair in which bone heals for the purpose to sustain and transfer the mechanical loads [20]. The process of fracture healing commonly occurs in four stages, i.e., the hematoma formation, fibrocartilaginous callus formation, bony callus formation and then the remodeling process [21].

Serum albumin is a well-known proliferative factor in cell culture having the ability to induce mesenchymal stem cell growth on the surface of bone allograft [9]. Hospitalized patient with albumin level of < 3.5 g/dl shows the effect to prolonged hospital stay, as well as their mortality rate. Later on Sabir et al., (2014) in a study also demonstrated that albumin level of < 3.5 g/dl was predictive of delay or impaired fracture healing [1]. Patients with low albumin level shows 4.6 times lesser recover rate. Study result shows that serum albumin level significantly enhances the proliferation of stem cells in bone [22].

Protein is important to solidarity of bones, organs, and body systems at all stages of life. Low

protein especially the albumin intake is strongly associated with poor functional outcomes after fracture [6]. Albumin is a major protein from femoral diaphyseal tissue and it has an anabolic effect on bone components. In an *in vitro* experiment, the addition of albumin causes markedly increase in calcium and DNA contents of the femoral-diaphyseal and diaphyseal tissues that mineralize the bone and make them hard [7]. Beside this, decreased albumin levels that also lead to the delayed wound healing [8].

Protein also plays a significant role in mineralization of bones. Albumin, transferrin  $\alpha$ 1-antichymotrypsin,  $\alpha$ -HS glycoprotein, soluble fibronectin, haptoglobin, serum cholinestrate and hemopexin, are amongst the plasma proteins that accumulate in bones in detectable amount of these  $\alpha$ 2-HS glycoprotein is thought to have a role in regulation of matrix minerilaztion of bones, this is making the bone hard. The nutritional status of patients with simple diaphyseal tibial fractures shows insignificant relative risk in relation to fracture healing, but serum albumin shows positive interrelationship with the bone healing progression of the fracture. Fracture impairment leads to prolonged disability, associated with substantial pain and put extra burden on the patient [23]. There are also other key players, as growth factors cytokines, uncounted nutrients, inflammatory antioxidants, amino acids, bone break down cells. The cytokine brings the repair cells into the fracture gap, which instantly begins to differentiate into specialized cells that build new bone cells, osteoclasts and new cartilage chondroclast. In the next few months, these cells begin repair process, settling down new bone matrix and cartilage. At this initial stage, osteoclast cells dissolves and recycle bone debris. The reparative stage starts after 2-3 months of the fracture. Within this stage, proteins produced by the osteoblasts and chondroblasts begin to combined and thus forming what is known as a soft callus. This soft, new bone substance converts into a hard callus as the bone weaves together after 6-12 weeks. The final step of fracture repair is known as the remodeling phase. At this stage the callus begins to mature and remodel itself. The woven bone is remodeled into stronger lamellar bone by the orchestrated action of both osteoblast and osteoclasts cells [24].

An experiment performed on adult rat by albumin coated allograft which reveals the colonization of cells at the site of altered gap in mid shaft of femur. The altered bone shows the interposition of a spacer in the osteotomy for four weeks which resulted in compromised healing and nonunion. Albumin coated graft shows its efficacy that enhance bone healing [19,20]. The serum albumin, which is a well-known proliferative factor

in cell culture, has the ability to induce mesenchymal stem cell growth on the surface of bone allografts [3]. Since it is obvious that the proliferation of bone-forming cells is the rate-limiting factor in graft remodelling, one may postulate that serum addition to bone substitutes may improve the colonization of the graft by host cells. In this study the serum albumin coating of bone grafts represent that it may be enough to improve graft integration in a compromised bone-healing model [25].

Fracture impairment problems are more common amongst males because they have a higher incidence of high energy trauma [26]. In pediatrics bones the already ongoing growth process [27] provides an osteogenic environment in which many of the processes in conduct to healing are already in progress at the time of the fracture. In the skeletally matured individuals growth process has already ceased with significant impact on fracture repair process [28].

The albumin is produced from femoral-diaphyseal tissues in response to fracture healing [29]. Fracture healing increases IGF-I, TGF- $\beta$ 1, osteocalcin and 66 kDa protein molecules in the femoral diaphyseal tissues. Especially 66-kDa protein, this protein is present in the bone tissues as a major bone protein and is greatly released in the culture medium of femoral-diaphyseal tissues at the fracture site [30]. This protein plays an important role in the fracture healing process. After study we perceive that a 66-kDa protein is identical to albumin which is produced by femoral tissues and it has an anabolic effect on bone components in the femoral-diaphyseal and metaphyseal tissues.

During fracture repair, a number of growth factors, cytokines and their allied receptors are released around the fracture site [31]. Many of these proteins are normally expressed in skeletal tissue, and few of them are released from associated inflammatory cells at the site of injury. As we were already discussed, 66-kDa albumin protein is very prominent, and plays very significant role in healing process. The hepatocyte growth factor also induces differentiation of bone marrow cells [32]. The multipotent progenitor cells of bone marrow differentiate into functional hepatocyte-like cells which expresses albumin [33]. The production of albumin in the femoral-diaphyseal tissues with fracture healing is notably stimulated in the presence of acexamate, zinc, IGF-I, and PTH, which are bone formation-stimulating factors. Especially, the increase in IGF-I with fracture healing may induce the production of albumin in the femoral-diaphyseal tissues. The albumin performs a pathophysiological functions in fracture repair in collaboration with IGF-I. It stimulates bone formation and osteoblastic

proliferation in bone tissues. The cellular mechanism by which albumin has its anabolic effect on bone metabolism remains to be elucidated. The current discovery that albumin has a stimulatory effect on bone calcium and DNA content, may support the view that albumin plays an important role in promoting fracture repair [34].

#### 4. Future perspective

Serum albumin is essential for fracture healing, so it may be targeted as a therapeutic biomarker. The albumin is extensively used clinically to address the healing problems as well as nonunion along with many other complications which may reduce the potential of healing (i.e. hypoproteinemia, fetal erythroblastosis etc.). This will contribute to a new paradigm for treatment in different situations. Also the author recommend early interference in those cases with low albumin level by IV infusion of albumin supplements or early (primary) bone graft, so that the healing process will be properly achieve within the optimal time frame. Moreover, albumin also has a significant role in biotechnological and biopharmaceutical applications, including O<sub>2</sub> transport and nanodelivery of drugs. All these specific functions of albumin make it very promising for future use as a biomarker.

**Conflicts Of Interest:** None

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