EVOLUTION AND HEALING OF FRAGILITY FRACTURES OF THE PROXIMAL FEMUR

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ABSTRACT

After a traumatic fracture a physiological process begins to heal the fracture. The steps of the process are inflammation, granulation, formation of fibrous callus and finally bone. There are many factors that may influence the healing of the fracture: adequate blood supply, good contact between bone fragments, good stability of the fracture, general health, age, smoking, related pathology, use of drugs, etc. In elderly patients the variations in bone structure and healing processes have a negative influence on fracture healing. Fragility fractures require careful placement of the implants to reduce the risk of failure of osteosynthesis. Appropriate surgical devices and facilitation factors must be used to allow bone healing.

***Key words**: Femur, Osteoporosis, Fracture, Healing.*

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Introduction

Fragility fractures of the proximal femur are a significant social problem, considering the high frequency among senior citizens and the mortality rate related to such fractures[1,2]. They are typical of the age group for whom healing is negatively influenced by variations in bone structure and healing processes. Surgical treatment includes the use of prostheses or other surgical devices (screws, nails) chosen by the surgeon on the basis of the characteristics of the specific fracture and the patient's general clinical condition. Medical treatment also helps healing by promoting the formation of new bone and by reducing bone re-absorption, thereby stimulating bone healing and decreasing the risk of new fractures. Nowadays treatment is attempted as soon as possible to reduce the risk of complications related to delayed healing and prolonged hospitalization. The goal of this study is to clarify the physiological steps and processes of healing of fractures of the proximal femur and possible treatments to accelerate healing.

Generality

There are usually four healing phases following a traumatic bone fracture[3,4,5].

• ***Inflammatory phas***e (1-7 days): immediately after the trauma the surfaces of the fracture bleed and a hematoma forms as a result of the rupture of the intra-bone vessels, periosteal and the surrounding center. The bone near the margins of the fracture necrotizes, and the coagulate is infiltrated by leukocytes, macrophages, mastocytes, and fibroblasts to remove the necrotic bone.

• ***Fibrous callus phase*** (2-3 weeks): the coagulate hardens due to the presence of collagen fiber and vasal elements; there is a proliferation of bone progenitor cells (preosteocytes), and osteoblasts of the cambial layer of the periosteum and the endosteum; osteoblasts and condroblasts of mesenchymal origin also appear. There is also the formation of fibrous callus composed of osteoid, cartilage and collagen (hardening of the hematoma and formation of osteogenic and condrogenic tissue).

• ***Osseous callus phase*** (1-4 months): mineralization of the osteoid and cartilage of the external fibrous callus, periostal, and endostal, through their transformation in primitive bone. Hence there is a re-absorption of dead bone and the formation of new bone tissue.

• ***Remodeling phase*** may last a few months to years. The activity of osteoblasts and osteoclasts slowly transforms primitively formed bone into mature lamellar bone, having true haversian systems. This phase leads to the consolidation of the fracture[6,7].

Consolidation of the fragility fracture

The consolidation of a fracture under physiological conditions normally occurs within a certain period called normal consolidation time and which is from 15-20 days (e.g. greenwood fracture of a child's clavicle), to a maximum of 5-6 months (e.g. middle-third or lower tibia in the adult), according to the three variables that influence healing time: skeletal location, type of fracture, and patient's age[8]. The physiological healing processes are modified in some bone pathologies, especially osteoporosis. Under physiological conditions the process of bone remodeling where the bone is continually formed as a result of the osteoblasts, equals the bone that is gradually reabsorbed by the osteoclasts.

Under pathological conditions, in contrast, the action of the osteoclasts is predominant over the osteoblasts with the consequent increase in the reabsorption of bone, a general increase in bone turnover, and deleterious effects both on the quantity and quality of bone, leading to the extreme condition of fragile fracture[9,10]. Structural bone variations which we previously described negatively influence the healing of these fractures, especially in primitive osteoporosis[11].

Compromise of the healing process in primitive osteoporosis

In post-menopausal osteoporosis the estrogen deficit is responsible for an increase of the activity in osteoclasts, and hence an increase in bone turnover, which negatively influences all phases of fracture healing, especially the final phases of mineralization and remodeling[12].

In senile osteoporosis there are several problems related to skeletal fragility that can negatively influence fracture healing:

• ***Cellular senescence***, in which the mesenchymal cells no longer mature due to the reduced expression of the RUNX-2/, Cbfal and Osx genes[13]. There is also an increase in differentiation of the multipotent (MSCs) cell progenitor in the adipose tissue and a reduction in osteogenesis.

• ***Nutritional deficiency and malabsorption*** of nutrients and important hormones for bone metabolism (vitamin D, phosphorus, potassium, magnesium, calcium, vitamin K, vitamin B, proteins, etc.). Specifically, the deficiency in minerals and vitamin D cause reduced mineralization of the callus bone and hence the bone neoformation; vitamin K deficiency causes reduced enzyme activation of osteocalcin, which decreases the ability to bind with the hydroxyapatite crystals; the deficiency in B vitamins (B6 and B12) may alter the three-dimensional conformation of the bone matrix; protein deficiency contributes to sarcopenia in elderly patients[14].

• ***Vitamin D deficiency*** is very common in elderly patients due to malabsorption and/or reduced exposure to sunlight, which alters the structure and mineralization of the bone callus. In addition, a failure of vitamin D to bind with its receptor (VDR) may lead to sarcopenia[15,16,17].

• ***In sarcopenia*** there is a reduction in the number of muscle fibers, which is responsible for the reduced contribution in muscle stem cells with osteogenic capacity[18].

• ***Chronic systemic inflammation*** is directly correlated with bone metabolism. Post-menopausal estrogen deficiency and the increase in adipose tissue (liver, marrow, muscles) cause a massive production in pro-inflammatory cytokines, some of which (IL-1, IL-6) may increase osteoclastic activity, while others (IL-7, TNF-α) cause a reduction in osteoblastic activity[19,20].

There are also numerous metabolic changes that may negatively influence the structure and composition of callus in elderly patients.

• ***Disorganized positioning*** of the collagen fiber

• ***Decreased maturation*** of the cartilaginous callus

• ***Thin trabecular bone neoformation*** with extensive microporosity.

All of these factors result in an alteration of mechanical properties of bone hence in a prolonged fracture healing.

Fracture of the femur neck

The elderly population has a high frequency of femur neck fractures, so it is a significant public health problem, both in terms of social costs (quality of life declines after fractures, life expectancy is significantly shorter), and economic costs[21]. Fractures of the proximal femur are classified as medial or lateral on the basis of an anatomical distinction between the intercurrent relation of the level of the fracture and the distal insertion of the articular capsule of the hip. Medial fractures are intra-capsular and are divided into sub-capital (Fig. 1a) or mid-cervical (Fig. 1b). They are subdivided as Garden type I, II, III, or IV according to the degree of severity of separation and a worse prognosis (Fig. 2a,b,c,d). Lateral fractures are extra-capsular and are divided into basi cervical, petrochanteric and subtrochanteric fractures (Fig. 3c,d,e).

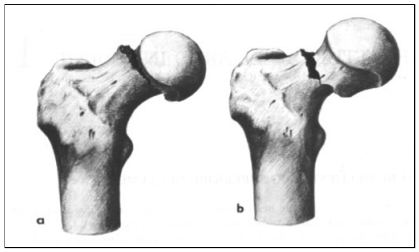

Fig 1: Medial fracture: a) subcapital, b) midcervical.

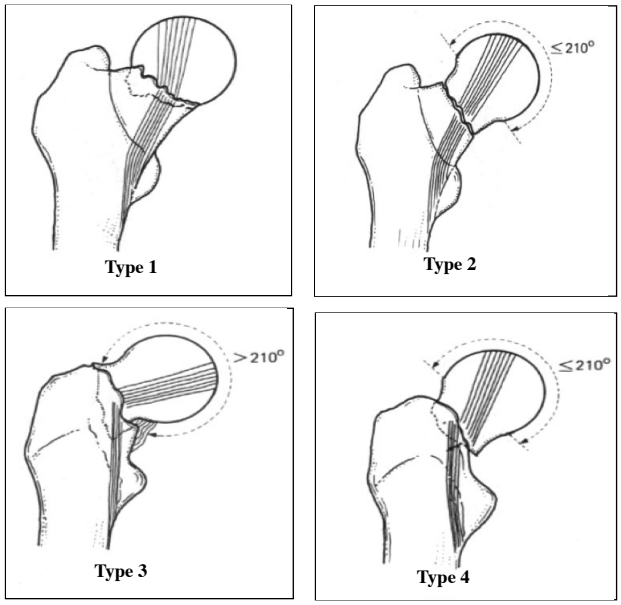

Fig 2 a-b-c-d: Garden classification.

The treatment of femur neck fractures consists of the attempts to restore the patient's functional autonomy, and prevent other general complications that interfere with healing and recovery. Effective surgery must take some fundamental factors into account to achieve good healing or adequate reduction of the fracture, choosing an appropriate surgical devices to improve the stability of the synthesis. Therapeutic alternatives depend on the type of fracture, which may require a prosthesis or osteosynthesis.

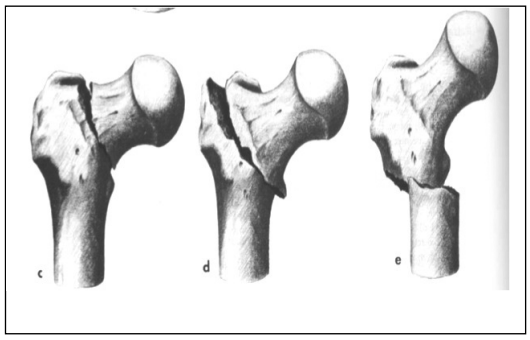

Fig 3: Lateral fracture: c) basicervical, d) pertrochanteric, e) subtrochanteric.

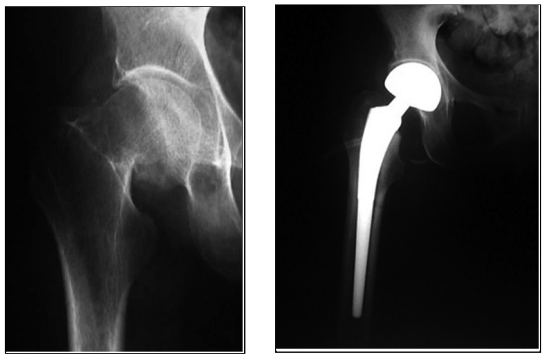

Fig 4 a-b: Medial fracture a) treated with bipolar hip prosthesis b).

Medial fractures have a poorer prognosis due to the vascularization of the head and the neck, and the consolidation and vitality of the head, so a prosthesis is more often necessary (Fig. 4). Lateral fractures have a better prognosis because they don't involve the articular capsula and its arterial circulation, so healing is possible through adequate reduction and synthesis. The choice depends on the characteristics of the fracture and the patient's general condition. Cannula screws and intramedullary nails are less invasive because doesn't cause the opening of the fracture (Fig. 5); instead screw-plate systems require more surgical exposure.

Sometimes the implants causes a modest seal of the bone, due to the presence of a broad diaphyseal canal, or a cavum profile in the epiphysial region. So it is important to ensure a good interface between bone and implants to reduce the risk of osteosynthesis failure. In such cases bone tissue

should be stimulated via autologue or allogenic bone transplant (demineralized bone matrice, etc.), or by using osteo-inducing factors (BMPs, PRP, MSCs, etc.).

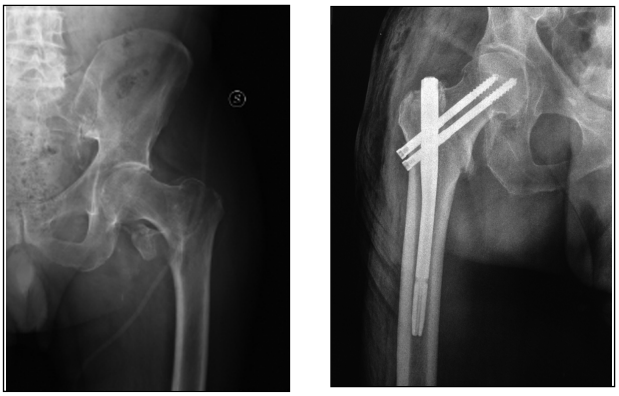

Fig 5 a-b: Pertrochanteric fracture a) treated with intramedullary nail b).

In addition, the stability of the implants can be improved by using augmentation factors (hydroxyapatite, calcium triphosphate, calcium phosphate cement)[23,24]. The goal of osteosynthesis in lateral fractures of the femur is to achieve a quick recovery of mobility even before the complete bone healing and the bearing is as a stimulus for bone callus formation[25]. Alongside surgical treatment of fragility fractures it is also important[22]. There used of drugs like bisphosphonates, parathormone (PTH 1-34), strontium ranelate, and more recently biological drugs (monoclonal antibodies); these drugs modify the processes of bone turnover on several levels:

• ***PTH (1-34)*** stimulates osteoblastic activity, which causes the adding of new bone on the trabecular and cortical surfaces[26],

• ***The bisphosphonates*** (alendronate, risedronate, clodronate) inhibit the action of the osteoclasts and therefore the re-absorption of bone, even though recent studies have evaluated the positive effects of the drug on the fracture healing process, and on the prosthesis osseointegration if used for a brief time in the immediate postoperative period[27,28];

• ***strontium ranelate*** is a dual action bone agent (DABA) as inhibits the production of osteoclasts and therefore the destruction of bone and at the same time stimulates the differentiation of osteoblasts and the production of new bone[29];

• ***biological therapy*** consists of the monoclonal antibodies of human origin (Denosumab) that inhibit the osteoclast activator (RANKL), thereby preventing the loss of bone mass[30];

Considering these factors it is clear that medical treatment is an important part of accelerating the healing of fractures of the proximal femur, in that the drugs improve the quality of the bone, cultivating osseointegration and the seal of the implants as well as good healing of the fracture.

Conclusions

The orthopedic surgeon has two challenges when treating a patient with a fragility fracture: choosing the most appropriate therapy for the actual fracture, and identifying the particular pathology of the fracture to prevent new fractures by using the best tools available against osteoporosis. The choice of surgical technique depends not only on the characteristics of the fracture, but also on the individual patient's factors such as age and general health. The preference should be for the least invasive techniques possible, for less risk of complications and the shortest surgical operations.

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