The “Diamond Concept” of normal fracture healing

The “diamond concept” described by Giannoudis is a requirement for a successful bone healing [14]. The fundamental constituents of bone healing are: the osteogenic cells that initiate and repair, an osteo-conductive scaffold upon which new bone can be created and osteo-inductive growth factors like bone morphogenetic proteins (BMPs) that differentiate the stem cells along the bone repair pathway. Mechanical stability is a fourth crucial element, which must be given the same importance. This conceptual framework is completed by two most significant parameters for the healing process: vascularity at the site of the fracture and biology of the host [15]. The progression of fracture healing can be compromised by many physiological, pathological or environmental factors. A recent large case-control study has shown that factors like diabetes, NSAID use or high energy trauma are more likely to result in fracture-healing complications regardless of fracture site [16]. Aging, smoking and inflammatory conditions also increase the risk of delayed union or non-union [17,18].

Fracture healing, osteoporosis and aging

Osteoporotic bone differs from normal bone in its reduced bone mass and deterioration of its architecture leading to bone fragility and an increased fracture risk. This is a consequence of the imbalance in bone formation and bone resorption. Osteoporosis is potentially harmful for fracture treatment: the compromised bone strength affects anchorage of the implants and at the fracture site, the impaired bone ingrowths and late remodeling could impair the strength of the callus and the bony union [19]. Few studies have investigated the effects of osteoporosis itself on bone healing. It has been assumed that bone healing did not seem to change between normal and osteoporotic bone but the process is delayed.

Animal studies have been conducted on ovariectomized rodent animal model with a tibia or femur osteotomy [20]. Despite some contradictory results, more studies support a delay in ossification, a decrease of 20% to 40% in callus area, and a reduction around 20% in BMD. Mechanical properties of the callus were also disrupted, with decreased strength, decreased peak failure load and decreased bending stiffness. The architecture was modified with thinning and disruption of the trabeculae and a decrease in connectivity [21]. Clinical data are even more controversial. The failure rates of fixation in patients with osteoporosis range from 10% to 25% [22]. Despite significant effect in several clinical studies, there is so far no high level of evidence that osteoporosis per se increases the incidence of fracture non-union [2,23]. Cohorts of patients are heterogeneous, randomized studies comparing osteoporotic patients versus non-osteoporotic are missing.

Osteoporosis is closely linked with aging. Fracture healing in elderly is compromised by the decline of capacity of bone formation [17]. The loss of osteoblasts in the aging skeleton has been attributed to a decrease in the number of mesenchymal stem cells (MSCs) and their ability to differentiate in progenitors towards the osteoblastic lineage [24]. Due to the augmentation of the life expectancy the absolute number of fragility fracture and its corollary, the absolute number of delayed or non-union increase and the consequences are an augmentation of the mortality and morbidity in this population. The main determinants for deficient fracture healing can be divided in biological and surgical factors [22] (Fig. 3).

The treatment of fragility fracture in elderly remains challenging for the orthopaedic surgeon. The poor quality of bone and the frequent fracture comminution make fixation of osteoporotic fracture difficult despite the development of new fixation devices like locked plating or locked intra medullary nailing, both having revolutionized the fracture fixation in weak bone [25]. Augmentation with cement or bone substitutes may fill the bone void or enhance the strength of the fixation. As in hip fracture, where the indications of joint replacement have been well described for a long time, some complex epiphyseal fractures (shoulder, elbow, knee), may benefit from primary prosthetic replacement. This option of replacement instead of fixation in comminuted articular fracture of the shoulder, the knee or the elbow has faster and better functional results in very elderly people compared with a mechanically poor fracture fixation [26].

Influence of anti-osteoporosis medications

The anti-osteoporosis drugs have been shown either to reduce bone resorption or stimulate bone formation in order to prevent fractures and to increase bone strength. The different classes of drugs, anti-resorptive bone forming or dual-effect agents have been investigated in preclinical and clinical studies to evaluate how they could influence the early stages of fracture healing. So far there was no evidence that any anti-osteoporosis treatment has negative effect on initial union of fractures in animal model [27–29]. However, the investigations were conducted in a setting of an indirect healing process. Recently in a rodent model of rigid compression plate fixation of a tibial osteotomy, an inhibitory effect of bisphosphonates (BiPhs) has been shown on primary healing [30].

The clinical evidence of the current and new osteoporosis treatment on bone healing are reviewed below.

Anti-resorptive agents

Bisphosphonates are the most widely used medications to treat osteoporosis. Various studies have demonstrated no increased risk of non-union or of deleterious effect on fracture healing compared with a control group, independent of the post fracture timing of administration of zoledronic acid or risedronate in inter-trochanteric hip fracture [31] or risedronate in distal radius fractures. The same results were observed with denosumab, a receptor activator of nuclear factor kappa-B ligand (RANKL) inhibitor, in the post-hoc analysis of a phase 2 clinical trial [32].

Bone forming agents

The impact of parathyroid hormone (PTH) peptides on bone repair has strong evidence in preclinical studies and there is a