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Editorial

Fracture non-union: Who is at risk?

Fracture healing is a complex physiological process. It is regulated by cells, mediators and growth factors, with different phases of activity occurring over time, till normal bone formation is established [1]. Cellular recruitment, proliferation and differentiation under the guidance of signalling molecules with the involvement of extracellular matrix play an important role in creating the foundation for a successful bone healing response [2]. If any stage during these events is disturbed, it could lead to an impaired healing response expressed as delayed healing or nonunion of the fractured bone fragments [2]. The development of this devastating complication is frequently associated with loss of limb function, muscle atrophy, stiffness of the adjacent joints, diffuse limb osteopenia and systemic deterioration especially in the presence of infection [2]. More over the social economic and family implications can be immense [3,4]. As such strategies to predict early which patient might go on to develop fracture non-union are desirable. Risk factors or predicting models of an impaired bone repair process would allow early identification and treatment initiation to ensure a timely based successful healing outcome.

Clinicians managing patients with non-unions have made a number of observations related to potential risk factors that could be responsible for the failed internal physiological fracture healing response. In general terms, the identified parameters that have been implicated with a negative outcome have been divided into 4 categories: (a) Patient related factors, (b) Environmental factors, (c) Injury related factors and (d) Treatment modality related factors.

(A) Patient related factors

(1) Genetics

Different kinds of expressed signalling molecules and genes initiate and regulate the cascade of fracture healing and genetic variations within these molecules which have a role in fracture healing, and disturbed signalling pathways can be the reason for impaired bone formation [5,6].

Two single nucleotide polymorphisms (SNP) within the genes encoding for two known BMP inhibitory molecules (Noggin and Smad6) were found to be associated with a statistically significant greater risk of fracture non-union [7].

A significant association of a specific PDGF haplotype and non-unions, indicating that polymorphisms within the PDGF gene may represent a genetic risk factor for the development of non-unions has been reported also recently [8].

Another issue is the role of genes in the pathogenesis of fracture liability, some genes determine the risk of fracture. Genetic profiling can potentially improve the prognosis of fracture risk [9].

(2) Systemic disorders

Metabolically affected, Type-1 and Type-2 Diabetes Mellitus patients are more likely to have fracture healing complications. Inadequate insulin production causes reduced collagen production by osteoblasts [10]. Diabetic drugs such as thiazolidinediones have anti-osteogenic effects that may be a reason for impaired fracture healing [11]. Peripheral neuropathy and HbA1c levels >7% are significantly associated with bone healing complications [8]. Peripheral vasculopathy due to diabetes has also been associated with fracture healing impairment [12].

Obesity is a condition that can affect the health and condition of an individual. Obese people are predisposed to musculoskeletal injuries and have an increased complication rate. Difficulty in reducing the fracture (soft tissue over coverage) and difficulty in maintaining the stability after the fixation of the fracture due to overweight, can be the reasons for impaired fracture healing [13].

Osteoporosis is a prevalent metabolic bone disorder associated with an increased fracture risk particularly in the elderly. While the fragility is increased it has been reported that diminished bone quality does not influence the occurrence of nonunion [14]. The mechanical and biological factors involved in the healing process of bone are certainly affected by age and osteoporosis. In the elderly, alterations in bone metabolism and delay callus maturation can decelerate fracture healing [15]. More over biologically inactive periosteum, atherosclerosis and poor response to vascularization may negatively affect also fracture healing [16].

Elderly patients with osteoporosis may develop a compromised bone repair process due to mechanical instability after fixation of an osteoporotic bone, reduce availability of osteoprogenitor cells, and impaired influence and presence of signalling molecules [17–19]. Nevertheless, it is still an unsolved question whether fracture healing is impaired by osteoporosis [15].

Rheumatoid arthritis, malnutrition (metabolism requirements increase during fracture healing) [16]

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and pathological fractures are other systemic factors that could impair fracture healing.

(B) Environmental factors

(1) Smoking

Smoking cigarettes or tobacco usage or even inhalation of smoke has a negative effect on bone healing [20,21]. Nicotine is the major ingredient of tobacco, inhibiting the secretion of TNF-alpha by activating the cholinergic anti-inflammatory pathway [22]. In addition carbon monoxide (CO) may bind to haemoglobin and carboxy haemoglobin is formed in the pulmonary capillaries, this compound reduces the oxygen carrying capacity of blood, causing hypoxia of the peripheric tissue which may lead to impaired bone healing [23]. Nicotine also causes vasoconstriction leading to alteration of tissue perfusion and consequent hypoxia and ischaemia [16].

(2) Medication

Several pharmacological agents have been reported to be associated with fracture healing impairment. Corticosteroids (lead to osteoblast and osteocyte apoptosis and inhibition of osteoblastogenesis) [24,25], chemotherapeutic agents (affect neovasculogenesis, proper callus formation and host bone-allograft incorporation) [26–28], anticoagulants [29–32], aspirin [33], nonsteroidal anti-inflammatory drugs (NSAID) used for pain relief and inflammation, and drugs reducing osteoclastic activity have been all convicted to cause inhibition of fracture healing [29].

Antibiotics agents such as quinolones are thought to cause chondrocyte death and degeneration, having a detrimental effect on cartilage formation and maintenance. Ciprofloxacin [34], levofloxacin and trovafolxacin [35] decreased cellular proliferation and DNA synthesis. Gentamicin in high concentrations, decreases proliferation of osteoblastic progenitors interfering with normal bone healing [36]. Tetracycline with high doses impairs bone growth and maturation [37].

Anti-inflammatory action of NSAIDs is due to the inhibition of COX-2 [38]. After the occurrence of a fracture, local release of prostaglandins occurs and COX-2 plays a critical role in this phase and its induction in osteoblasts is essential for bone healing [39]. In vivo studies found no robust evidence to show a significant and appreciable patient harm resulting from the short-term use of NSAIDs following a fracture [40]. If used longer than 4 weeks, there is a correlation between non-unions and NSAIDs [41]. Administration of tenoxicam [42], Indometacin [43], ketorolac [44] have a negative effect on bone healing process. Endochondral ossification is inhibited but intra-membranous ossification is not inhibited by NSAIDs [45].

Bisphosphonate administration leads to increased mineral content, volume and strength of callus [46–49] but some authors suggest that the arrest of bone remodelling may produce osteoporotic and weak bone [50,51].

(3) Alcohol

Alcohol intake in excessive doses in the post-trauma period inhibits new bone formation and the newly formed bone is lacking of mineralization causing decreased mechanical stability [52].

(C) Injury characteristics and related factors

The impact of trauma (high energy or low energy), vascular injury, soft tissue involvement [53], open fracture (contamination? loss of haematoma?), localization of the fracture (diaphysis, metaphysis or intra-articular) and fracture type (simple transverse, oblique, spiral or comminuted) are some of the factors that could influence fracture healing.

If the injury is the result of a high-energy trauma, the bone and the surrounding soft tissues will be affected more obviously. This high energy injury causes more complex, comminuted and displaced fractures, with more serious damage to the soft tissues and vascular system [16,54]. Local vascularity at the fracture site is one of the most significant parameters influencing the healing response [55]. The de-vascularised bony fragments, periosteal stripping and destruction produces necrotic bony fragments and impairs bone healing. Vascular Endothelial Growth Factor (VEGF) has a role in the regulation of bone formation by interacting with various hormones [56] and could have a direct effect on osteo-progenitor cells, mainly by promoting the differentiation of osteoblasts and by increasing the mineralization of the regenerated bone [55]. Fractures with open injuries have a higher risk to delayed healing or nonunion compared with closed fractures [57,58]. Loss of the haematoma which is triggering the inflammatory phase of fracture healing process and contamination causing infection are the reasons for delayed healing or nonunion. Metaphyseal parts of the bones have more blood circulation so that fractures in these parts can heal better than fractures in the diaphyseal parts. Before consolidation of a fracture, broken cortical bone must be reabsorbed and this period takes longer time in the diaphyseal parts compared with the metaphyseal bone [59,60]. If the bone is comminuted, this can be another reason for delayed healing or nonunion [61]. Transvers type fracture can also be another reason for delayed healing or nonunion [61]. Fractures with long butterfly segments can also be associated with impaired healing [62]. Multiple trauma with important damage to internal organs and larger vascular sections, biological damage, high introduction of toxins and free radicals originating from trauma of the solid organs, large vessels, head and spine may affect patients' general condition and overall healing response [16,63,64].

(D) Treatment modality related factors

For a better healing, fractured bone fragments should be in contact with each other and have a good blood circulation. If the soft tissues around the bone fragments have been disrupted during the trauma or during the surgical approach, extensive periosteal stripping or soft tissue damage [65,66] or there is soft tissue interposition between the fractured ends after reducing the fractured bone segments, the fracture healing process will be negatively effected [67,68]. Initial fracture displacement [69], fracture gap [61,70–72] (distracted reduction >2 cm), segment loss after open fractures [57], contamination and infection [69,73], malposition, bone implantation [74] or soft tissue necrosis [75–79] and compartment syndrome and fasciotomies [80,81] are risk factors for impaired fracture healing. Raise in the intra-compartmental pressure (development of compartment syndrome) is associated with a decreased perfusion leading to ischaemia and cell death [82,83]. Neutrophils contribute to micro-vascular dysfunction and blood flow distribution abnormalities [84]. Disruption of the soft tissues, loss of the formed haematoma containing growth factors and cellular elements contribute to a compromised biological activity at the fracture site [85–89]. Open fractures carry a greater risk for deep infection (osteolysis, necrotic soft tissues, hardware loosening and implant failure) leading to nonunion [73,90]. Infection may

contribute to necrotic bone ends (sequestrum) [90]. Finally delayed weight bearing [91], or early excessive load bearing could have an adverse effect on the fracture healing response [92].

The above mentioned factors, in isolation or in combination can all influence the fracture healing process. Our observations however, have indicated that patients with the same injury profile and similar distribution of risk factors progress to healing whereas other do not. How therefore we can differentiate or predict which patient is at greater risk to develop non-union? This remains a challenge for the clinicians and scientists in the years to come. Development of models of predictability which take into account all of the above mentioned parameters are desirable. Defining early and accurately the patient at risk is the challenge that we need to overcome in the next decade.

Conflict of interest statement

All authors declare no conflict of interest.

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