Current Orthopaedics (2007) **21**, 258–261

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Current ORTHOPAEDICS

MINI-SYMPOSIUM: FRACTURE HEALING

(ii) Factors contributing to non-union of fractures

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KEYWORDS
Non-union;
Local factors;
Systemic factors

Summary
Non-union of a fracture can be caused by various factors. This review summarizes current concepts of systemic conditions (malnutrition, diabetes, nicotine usage, osteoporosis and non-steroidal anti-inflammatory drugs (NSAIDs) usage) and local factors (infection, vascularity, biomechanical instability, poor bone contact, iatrogenic factors and magnitude of injury) that may be of etiological relevance. Key points for assessing non-unions include checking for malnutrition and peripheral neuropathy, advising smoking cessation, avoiding NSAIDs, and identifying clinical and radiological signs of delayed healing at the earliest possible instance. The prevention of non-union is preferable to the treatment of non-union.

Introduction

There is no universal definition of fracture non-union. The traditionally generally accepted definition is of an interval of at least 9 months from the time of fracture without fracture healing, during which multiple therapeutic measures have been tried. Waiting the traditional 9 months to diagnose a non-union is unrealistic and is associated with prolonged morbidity, inability to return to work, narcotic dependence and emotional impairment. Non-union of fractures is a multifactorial phenomenon. This review summarises current concepts and understanding of factors which contribute to the non-union of fractures. We review systemic conditions (malnutrition, diabetes, nicotine usage, osteoporosis and nonsteroidal anti-inflammatory drug (NSAID) usage) and local factors (infection, vascularity, biomechanical instability, poor bone contact, iatrogenic factors and magnitude of injury) (Table 1).

Systemic medical conditions

Malnutrition and vitamin deficiency

Patients with long bone fractures have increased rates of catabolism and significant urinary protein loss that may lead to negative nitrogen balance. Protein malnutrition affects callus composition rather than size early in the process of fracture healing.[1] Histological and mechanical testing shows that malnutrition negatively affects early callus composition.[1] Guarniero et al.[2] also showed the beneficial effects of protein nutritional support on the healing of long bone fractures. Protein malnutrition affects both membranous and endochondral bone formation. Protein deficiency has

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doi:10.1016/j.cuor.2007.06.004

Table 1 Etiology of non-union.

Local causes	Systemic causes
Infection	Malnutrition and vitamin deficiency
Mechanical instability	Systemic medical conditions
Inadequate vascularity	Smoking
Poor bone contact	Metabolic bone disorders
Iatrogenic	Medications
Magnitude of injury	

a negative effect on early proliferation and differentiation events of those cells required for fracture repair.

Vitamin B6 deficiency causes changes in bone which causes imbalance in the coupling between osteoblasts and osteoclasts, as a result of marked diminution of Glucose-6 phosphate deficiency (G6PD) activity in the periosteal region of the bone formation and in the developing callus, which significantly delays the maturation of the callus and union.[3] This suggests vitamin B6 status may be important in fracture healing deficiency.

Diabetes

Perlman and Thordarson[4] studied 88 patients with ankle fusions and showed a 28% non-union rate in patients who had diabetes. Sensory neuropathy was implicated as a possible cause of non-union. Morgan et al.[5] reported a 95% arthrodesis rate and failed to obtain fusion only in those patients noted preoperatively to have a neuropathy. Frey et al.[6] also concluded that diabetes contributed to non-union of ankle fusions.

Cigarette smoking and nicotine usage

Although some studies show no clear association between smoking and bone mass, there is overwhelming evidence of an increased incidence of osteoporosis and osteoporotic fractures in patients who smoke cigarettes. There is a 5–10% bone density deficit in patients who smoked compared with patients who were non-smokers.

Human studies of the effect of smoking on bone healing focuses on spinal fusion. Brown et al.[7] found a 40% pseudarthrosis rate in patients who smoked and an 8% pseudarthrosis rate in those who did not smoke. The difference was attributed to a mean peripheral oxygen saturation of 78.5% in the individuals who smoked versus a mean peripheral oxygen saturation of 92.9% in those who did not smoke. Schmitz et al.,[8] in their study with a follow-up of 146 patients with closed and grade I open tibial fractures, showed a 69% delay in radiographic union in the group of individuals who smoked. In a double-blind, prospective randomized study using a rabbit model, Wing et al.[9] demonstrated that chronic nicotine exposure was associated with decreased spinal fusion rates. Discontinuing smoking before surgery improved fusion rates. McKee et al.[10] showed a higher rate of non-union in smokers who underwent Ilizarov limb reconstruction. Chen et al.[11] reported that 30% of patients who smoked had delayed union or non-union after ulnar shortening osteotomy. Nicotine inhibits alkaline phosphatase and collagen production and stimulates deoxyribonucleic acid synthesis, possibly secondary to increased cell death and turn over. Cigarette smoking has been shown to decrease collagen deposition by 30–50%. Feitelson et al.[12] showed that 2 weeks of nicotine treatment caused decreased bone blood flow.

Osteoporosis

The relationship between fracture healing and osteoporosis is complex, and the available clinical evidence is inconclusive. Animal research on oophorectomized rats has shown significant reductions in bone mass and delay in fracture healing. Available evidence suggests that altered bone metabolism in osteoporosis seems to delay callus maturation and decelerate fracture healing.[13]

Nonsteroidal anti-inflammatory drugs

NSAIDs inhibit osteogenic activity and fracture healing. Glassman et al.,[14] in a retrospective review of 228 patients who underwent instrumented spinal fusion, reported an odds ratio with a five-fold increased chance of non-union with NSAIDs. The pathogenesis of NSAID-inhibiting osteogenesis is not clearly understood. Animal studies show reversibility of NSAID effects when prostaglandin E2 levels are gradually restored after short-term treatment.[15] Late exposure to NSAIDs, 61–90 days after a humeral shaft fracture, was associated with non-union.[16] There is a correlation between the use of NSAIDs and non-union, especially when NSAIDs are used for more than 4 weeks.[17] In this series, 70% of patients with non-union had taken NSAIDs. Although all NSAIDs inhibit fracture healing, cyclooxygenase-2 (Cox-2 inhibitors) have been shown to inhibit fracture healing more than the less specific NSAIDs.[15] Current evidence suggests that avoidance of NSAIDs in the post-operative and post-injury period may prevent non-unions.

Local factors

Infection

Although bone infection does not cause non-union *per se*, it can contribute to fracture non-union through bone death because of pus, the creation of gaps by osteolytic infectious granulation tissue, and motion from loosening of prosthetic implants. The inflammatory response to bacteria at the site of the fracture disrupts callus, increases gaps between fragments, and increases motion between fragments, which cause fracture union to fail. Infection causes decreased bone quality, which can cause fixation devices to loosen, thereby causing non-union.

Inadequate vascularity

The extent of vascular damage is directly correlated with failure of skeletal repair. However, the exact mechanisms