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■ REVIEW ARTICLE

Inhibition of fracture healing

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This paper reviews the current literature concerning the main clinical factors which can impair the healing of fractures and makes recommendations on avoiding or minimising these in order to optimise the outcome for patients. The clinical implications are described.

Fracture healing is a complex, unique physiological process of repair in which bone heals for the purpose of transferring mechanical loads.[1] The majority of fractures unite by secondary bone healing. This progresses in five stages, as originally described by McKibbin,[2] namely haematoma formation, inflammation, formation of soft and then hard callus and finally remodelling. Different agents or pathological processes may affect all of these stages or only one. Primary bone healing occurs when there is rigid internal fixation. This consists of cutting cones (tunnelling osteoclasts followed by osteoblasts forming new bone) which progress across the fracture site directly in a similar way to normal bone remodelling. Both forms of healing are brought about by a series of distinct cellular responses which are under the control of specific paracrine and autocrine intercellular signalling pathways and can be viewed as a well-orchestrated series of biological events.[1] However, many factors can interrupt the normal flow of this biological series of events.

Over one million fractures occur each year in the United Kingdom, of which 5% to 10% are considered to have problems in healing.[3] As the aged population increases, fragility fractures, such as those of the neck of femur, will become more common and a higher percentage of fractures may have difficulties in healing.[4] It is essential that the surgeon is aware of the factors which inhibit bony repair so that they can be minimised. We have reviewed the factors relating to the patient as a host, namely age, co-morbidities and medication, and to the treatment which we provide.

The patient as a host

Gender and age. There is no correlation between gender and nonunion or delayed union of fractures, although problems in healing are more common amongst males since they have a higher incidence of high energy fractures. A faster rate of healing of fractures in children has been ascribed to a larger subperiosteal haematoma and a thicker periosteum which contribute to more rapid formation of callus.[5] The growing process in paediatric bone[6] provides an osteogenic environment in which many of the processes conducive to healing are already in progress at the time of the fracture. In skeletally-mature individuals it has been suggested that advancing age has a significant impact on skeletal repair.[7] Studies of fracture healing in rats have shown that the formation of cartilage and bone, and cartilage resorption, were delayed in elderly animals;[8] there was evidence that accretion of mineral into the callus was reduced in elderly animals.[9,10] A recent investigation in rats reported age-related changes in fracture healing.[11] These included a delay in the onset of the periosteal reaction, a delay in cell differentiation, decreased bone formation, a delayed angiogenic invasion of cartilage, a protracted period of endochondral ossification, and impaired remodelling of bone. It was noted that this decline in healing capacity continued throughout the life span of the animal. In the elderly human, Street et al[12] found that angiogenesis at the fracture site and the response of growth factor to fracture in the elderly was preserved. However, Robinson et al[13] reported an increased risk of clavicular nonunion with advancing age, and Parker[14] considered that age was predictive of whether nonunion would occur after internal fixation of intracapsular fractures of the neck of femur.

Overall, there is some evidence that increasing age is a factor in the inhibition of fracture repair in the human. In addition to the slowing in the process of repair, many problems are

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encountered in the elderly as a result of difficulties in maintaining fixation of weak, osteoporotic bony fragments for sufficient time for union to occur.

Co-morbidities

Diabetes mellitus. The effect of diabetes mellitus on fracture repair has been examined in experimental models in the rat. Diabetes may be produced in rats by chemical induction using streptozotocin to poison the pancreatic islets eliminating insulin production[15] and in the spontaneously-diabetic BioBreeding/Ottawa Karlsburg rats which have the autoimmune induced diabetes.[16] A well-conducted study using streptozotocin-induced diabetes showed that after two weeks of healing, fracture callus from the diabetic animals had a 29% decrease in tensile strength and a 50% decrease in stiffness compared with the controls.[17] A further cohort of the diabetic animals was treated with insulin and in this group the tensile strength and stiffness of the callus at two weeks was restored to the same level as the controls. It was also shown that between the fourth and 11th days of healing, there was a 50% to 55% decrease in the collagen content of the callus and a 40% decrease in the DNA content, which is an indicator of the cellularity of the callus in the untreated diabetic animals compared with the controls. These findings have been supported by other animal studies which have shown reduced cellular proliferation, reduced osteoblast activity and reduced collagen synthesis and content in diabetic compared with control animals.[18-20] These reduced tissue properties have also been shown to be associated with decreased strength and stiffness of bone in healing fractures in diabetic animals in biomechanical studies.[21] Tight glycaemic control was critical for returning the process of fracture healing back to that seen in the control animal. Some of the influences of diabetes on fracture repair are related to the inhibition of growth factors, although the underlying mechanism is largely unknown. It has been postulated that in diabetes there is reduced cell proliferation in the early phase of fracture healing as a result of decreased expression of platelet-derived growth factor.[22] The levels of other growth factors (insulin-like growth factor-1 (IGF-1), vascular endothelial growth factor (VEGF), transforming growth factor-beta (TEGF-β)) have also been shown to be significantly reduced in diabetic animals;[23] these studies also showed that the local delivery of platelet-rich plasma restored normal cell proliferation and chondrogenesis in the early stages, and partially improved mechanical strength in the later stages of repair. It was also shown that direct delivery of insulin to the fracture site in diabetic animals returned fracture healing to normal, suggesting a direct effect of circulating insulin on repair.[24]

Clinical studies have demonstrated a significantly higher incidence of delayed union, nonunion, and a doubling of the time to healing of the fracture in diabetic compared with non-diabetic patients.[25-27]

The key to treatment of fractures in patients with diabetes is proper control of the blood sugar level, which will minimise the complications of delayed fracture healing.[28]

Anaemia. Studies in iron-deficient anaemic rats have demonstrated significant deficiencies in bone healing, with a decrease in the rate of union and loss of strength. There is poor mineralisation of the callus. The changes have been attributed to a decrease in oxygen tension and a deficiency of iron, which is required for function of the electron transport system within the cell and for hydroxylation of proline in collagen formation.[29,30] Impairment of wound healing in soft tissue has been observed secondary to anaemia because of acute blood loss without maintenance of blood volume. This was shown in soft tissue to be a result of impaired delivery of oxygen to the wound.[31] Further work in a rabbit model showed an inhibition of fracture healing in hypovolaemia which was attributed to impaired delivery of oxygen to the fracture site. These investigators found that a decrease in blood volume associated with anaemia delayed healing, but normovolaemic anaemia had no adverse effect, suggesting that attention to fluid rehydration following trauma was sufficient and that blood transfusion was not required to maintain normal fracture healing.[32] It appears that fluid resuscitation is important in the acute phase to allow fracture repair to progress normally, while attention to correction of chronic iron deficiency is necessary to decrease the rate of nonunion.

Malnutrition. Nutritional and metabolic requirements increase during fracture repair.[33] In an animal study, vitamin B6-deficiency caused a significant delay in the maturation of callus in rats.[34] Vitamin C has also been shown to be essential for the maintenance of differentiated functions of osteoblasts, including that in fracture repair,[35] and other investigators have shown that supplementary vitamin C in an animal model accelerates fracture healing.[36] Einhorn, Bonnarens and Burstein[37] showed the importance of dietary protein and calcium, phosphorous, and vitamin D in fracture healing, again in an animal model. Deficiencies of any of these dietary constituents resulted in attenuation of healing, as measured both biomechanically and histologically in the rat femur.[37] An animal study which subjected rats to protein malnutrition prior to tibial fracture showed the beneficial effects of adequate protein nutrition on the healing after the fracture had occurred.[38] A more recent study showed that an increase in the vitamin C content in the diet improved mechanical and histological parameters of fracture repair in the rat.[39]

In humans, it has been reported that an albumin level of < 3.5 gs/100 ml was predictive of increased length of stay and in-hospital mortality following a fracture. Patients with a low albumin level were 4.6 times less likely to recover to their prefracture level of independence in the basic activities of daily living.[40] An epidemiological study showed that postmenopausal women presenting with a hip fracture had occult vitamin D deficiency, which was easily treated with supplementation.[41]

While the majority of patients being treated for fractures are unlikely to have a nutritional deficiency, a significant minority, particularly in the elderly with fragility fractures may have. These patients should have their nutritional status carefully assessed with the early involvement of dieticians as it is clear that nutritional parameters, especially calcium, phosphorous, vitamins C and D and protein levels, should be optimised for fracture repair to proceed satisfactorily.

Peripheral vascular disease. Peripheral vascular disease adversely affects the blood flow to the tissues, including the bone and the surrounding soft-tissue envelope. This will impair delivery of oxygen, inflammatory cells and nutrients to the fracture site. There will be a build up of carbon dioxide (CO_2) and other metabolites rendering the local environment acidic. This combination of factors is likely to be detrimental to fracture repair. Although the correlation between peripheral vascular disease and nonunion has not been directly addressed, investigation of tibial fractures has shown that those with an associated injury to the posterior tibial artery have a significantly higher rate of nonunion and take longer to achieve union than fractures without this vascular injury.[42] The outcomes of tibial fractures with an associated vascular injury are poorest in older patients who are at increased risk of amputation. An injury to one or two of the three major vessels in the leg is associated with a 46% incidence of delayed union, as opposed to 16% if the vessels are not injured.[43]

In patients with reduced or absent peripheral pulses or symptoms of claudication in a fractured limb, a circulatory assessment is necessary and the advice of a vascular surgeon should be taken.

Hypothyroidism. The effect of thyroxine deficiency has been examined in a rat model of fracture healing in which methimazole was used to obliterate thyroid function.[44] This demonstrated that hypothyroidism inhibited endochondral ossification, resulting in an impairment of repair. Treatment with L-thyroxine returned the repair process to normal. This study suggested that hypothyroidism will inhibit secondary bone healing, although primary bone healing appears to be unaffected. This is important clinically as it is known that there is a high rate of undiagnosed hypothyroidism, with a prevalence of over 50/1000 total population.[45]

Clinicians treating fractures should be aware of potential hypothyroidism in their patients as they may have an increased risk of nonunion associated with this, particularly in postmenopausal, elderly females.

Prescribed medications

Non-steroidal anti-inflammatory drugs. Non-steroidal anti-inflammatory drugs (NSAIDs) inhibit cyclooxygenase (COX) activity and are widely used in the management of arthritis as post-surgical analgesia and for the relief of acute musculoskeletal pain. Their mode of action is to inhibit the synthesis of prostaglandins. There is conflicting evidence in the literature as to their effect on fracture repair. A recent review has shown that some animal studies have shown inhibition of repair by NSAIDs, while some have not.[46] Simon, Manigrasso and O'Connor[47] demonstrated a dramatic decrease in the repair of long-bone fractures in a murine model in which mice had the COX-2 gene removed, and in rats treated with the COX-2-selective NSAIDs celecoxib and rofecoxib. Their histological observations suggested that COX-2 was required for normal endochondral ossification during fracture healing but it did not seem to be needed for embryonic skeletal development, as genetically COX-2 deficient animals had normal skeletons. Another study in the rat has not shown a deleterious effect of COX inhibitors, but this may be related to the doses and rapid first-pass metabolisation in the livers of male rats.[48] Studies examining the molecular pathways for the action of prostaglandins have shown that prostaglandin E(2) can control expression of both bone morphogenetic protein (BMP)-2 and BMP-7.[49,50] A large study in mice looking at the specific COX-2 inhibitor rofecoxib, demonstrated that this had an inhibiting effect on fracture repair but also a significant negative effect on the blood flow across the fracture gap, suggesting that the effect on fracture repair may be due to inhibition of angiogenesis.[51]

In clinical terms, there is good evidence for the use of NSAIDs in preventing heterotopic bone formation following a total hip replacement (THR).[52] In a well constructed randomised controlled trial looking at the role of indometacin in preventing heterotopic ossification following the surgical treatment of acetabular fractures, the authors subsequently evaluated the incidence of nonunion in long-bone fractures which had occurred in the same injury. There was a significant increase in the rate of nonunion in the patients receiving indometacin compared with those who received a single dose of prophylactic radiotherapy to the hip or had no treatment.[53] A retrospective study in patients with femoral fractures found a marked association between nonunion and delayed union with the use of NSAIDs after injury.[54] Both specific COX-2 inhibitors and non-specific NSAIDs appear to exhibit inhibitory effects on bone formation in humans. The balance of information suggests that it is prudent to avoid exposure to these drugs during fracture repair.

Corticosteroids. For some patients, corticosteroid treatment is essential for making daily life tolerable. Such conditions as rheumatoid arthritis, asthma, chronic obstructive airways disease, inflammatory bowel disease and organ transplantation frequently require prolonged steroid therapy. Corticosteroids are immunosuppressive and anti-inflammatory. Consequently they have diverse side effects, particularly if used at moderate to high doses for more than seven consecutive days. Prolonged systemic administration of corticosteroids causes osteoporosis and increased risk of fracture as a result of the inhibitory effects on the production of IGF-1 and TGF-β.[55] However, despite the well-established effects on bone metabolism, few studies have

been conducted to look specifically at the effect on fracture repair. Waters et al[56] found that prolonged systemic administration in the presence of defects in long bones small enough to heal spontaneously in a rabbit model led to an 85% rate of nonunion compared with 18% in the control group. Another investigation looking at the effects of the short-term administration of prednisolone in rats showed no inhibitory effects,[57] confirming the observations of an earlier study looking at short-term administration of methylprednisolone in rats.[58]

It therefore appears that long-term steroid therapy is detrimental to fracture repair. Often there is no therapeutic alternative for patients on maintenance steroid treatment. The healing of fractures in these circumstances will continue to be a difficult problem unless a local or systemic agent can be found to offset this inhibition. Therefore patients should be given longer estimates of the time for their fracture to heal and surgeons should anticipate the prolonged healing time in selecting the method of stabilisation of the fracture.

Statins. The 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors (statins) are widely used for the treatment of hyperlipidemia and are known to decrease the risk of ischaemic heart disease. It has been shown that statins increase mRNA expression of BMP-2, aggrecan, and type II collagen as well as proteoglycan synthesis by fetal rat chondrocytes early in the period of treatment with statins.[59] The overall outcome is thought to be an anabolic effect on bone. A cell culture study looking at bone marrow-derived mesenchymal stem cells, such as would be recruited into the site of fracture repair, showed that statins did not significantly enhance mineralisation, alkaline phosphatase activity or osteocalcin production.[60] These findings suggest that statins do not increase bone formation in bone marrow-derived mesenchymal stem cells. However, animal studies have demonstrated improved bone formation in rats treated with statins. Skoglund, Forslund and Aspenberg[61] found a dramatic enhancement of fracture healing in a mouse model, with the strength of the fracture 63% greater than that in the control group at 14 days. This was supported by work showing enhanced healing of defects in parietal bone in a rabbit model using statin impregnated carrier collagen.[62] Recent work by Gutierrez et al[63] has shown that transdermal lovastatin enhances callus formation and mechanical strength in femoral fractures in the rat in a similar manner to that found with treatment with BMP-2. However, work in an osteopenic model in ovariectomised rats has found a significant impairment of mechanical properties, particularly at the later stages of fracture healing.[64]

Bauer[65] reviewed the human studies and found that the use of a statin in most observational studies was associated with a reduced risk of fracture, particularly at the hip, even after adjustment for the confounding effects of age, weight and other medication. However, no studies have looked specifically at the effects of statins in fracture repair in the human and it is unclear as to the effect, if any, which these drugs will have on the process.

Non-prescribed drugs

Smoking. Smoking has been shown to adversely affect bone mineral density, lumbar disc disease, the rate of hip fracture,[66] and the dynamics of bone and wound healing.[67] Smoking is a high risk factor for atherosclerosis of the cardiac vessels and the large and medium arteries of the limbs. A review of multiple studies into the adverse effects of tobacco use on fracture repair has been carried out.[67] This revealed that there are several hypotheses as to the mode of action: a reduced blood supply, high levels of reactive oxygen intermediates, low concentrations of antioxidant vitamins and the effects of nicotine on arteriole endothelial receptors have all been postulated. Nicotine in high doses is directly toxic to proliferating osteoblasts although low-dose nicotine may be stimulatory.[68] In one of the few *in vivo* animal studies carried out to look at this, a tobacco extract not containing nicotine significantly reduced the mechanical strength of healing femoral fractures in rats, while nicotine alone did not affect the mechanical properties.[69] Recently the same group reported at the Orthopaedic Research Society that nicotine increased the strength of fracture repair in a dose-dependent manner in the rat femur. It was concluded that this supported the use of nicotine replacement therapy in smokers who should quit after sustaining a fracture, as the other components of cigarette smoke are harmful to bone repair. However, others have shown that nicotine is inhibitory to the strength of repair in distraction osteogenesis in the rabbit[70] and in a fracture model.[71] It has been shown in clinical studies that smokers have a fourfold risk of a closed fracture of the tibial shaft caused by low-energy injury compared with non-smokers, and have a significantly longer time to clinical union, with a higher incidence of delayed union.[72] A prospective, multi-centre trial of 268 compound tibial fractures showed that smokers were 37% more likely to develop nonunion and twice as likely to develop infection. Ex-smokers were also at increased risk of nonunion and osteomyelitis.[73] As well as delayed and nonunion, smokers also had an increased rate of flap failure in open tibial fracture, with rates of failure up to 20%.[74] Smoking is also linked to a higher rate of nonunion and poorer results after fusion of the ankle and spine.[75]

Smoking is associated with other factors including low socioeconomic status, poor nutrition, general ill health and other lifestyle factors making it hard to determine the precise risk analysis of the habit. However, whether it is the nicotine or other components of cigarettes, the balance of evidence indicates a clear inhibition of healing and patients must be advised to stop smoking as soon as they attend with a fracture.

Alcohol. Chakkalakal et al[76] reviewed the effects of alcohol on the skeleton and fracture repair in 2005. He concluded

that chronic consumption of excessive alcohol eventually results in an osteopenic skeleton. Alcoholics experience not only an increased incidence of fractures from falls, but also delays in healing compared with non-alcoholics. Alcohol-induced osteopenia results mainly from decreased bone formation rather than increased bone resorption.[77] Human, animal and cell culture studies of the effects of alcohol on bone strongly suggest that it has a dose-dependent toxic effect on osteoblast activity. In fracture healing, the effect of alcohol is to suppress synthesis of an ossifiable matrix, possibly because of inhibition of cell proliferation and maldifferentiation of mesenchymal cells in the repair tissue. This results in the deficient bone repair observed in animal studies, characterised by tissue of lower stiffness, strength and mineral content.[76]

The inhibition of fracture healing in animal models by alcohol can be reversed by the use of interleukin-1 (IL-1) and tumour necrosis factor α (TNF-α) antagonists[78] and it is possible that these agents may have a therapeutic role in alcoholics with fractures.

Alcoholism is a significant problem in modern trauma practice, with fractures presenting problems in fixation and healing. Rehabilitation programmes for such patients which encourage cessation of drinking are to be supported. Studies are also required to investigate the use of TNF-α inhibitors for enhancing fracture repair in alcoholics.

Treatment and fracture healing

Antibiotics. Antibiotics are frequently prescribed in trauma practice both for the treatment of open fractures and for prophylaxis in procedures for open reduction and internal fixation. Many patients who have a fracture also require antibiotic treatment for an unrelated condition such as a chest infection. There is a paucity of work in the literature looking specifically at the effect of antibiotics on fracture healing. Three fluoroquinolones have been studied in animal models of fracture repair: ciprofloxacin, levofloxacin and trovofloxacin, and showed that therapeutic doses of each of these diminished healing during the early stages of fracture repair in the rat.[79,80] They reported more immature callus in the treatment groups and suggested that the administration of quinolones in the early stage of repair may compromise the healing of fractures in humans. Cell culture studies have shown that the aminoglycoside, tobramycin, is toxic to osteoblasts *in vitro*, an observation which is dose dependent.[81] Isefuku, Joyner and Simpson[82] investigated gentamicin and found that at high concentrations, as achieved following topical application in patients such as with gentamicin beads, the proliferation of osteoblasts was inhibited *in vitro*. They concluded that gentamicin may be detrimental to repair *in vivo*.[82] Other *in vitro* work has shown that rifampicin at doses used in clinical practice can inhibit the proliferation of osteoblast-like cells.[83] A study examining the effects of doxycycline, a tetracycline, found that it reversed the effect of ovariectomy in female rats thereby preventing the worsening of mechanical properties normally seen following ovariectomy. They did not look specifically at fracture repair.[84]

While antibiotics remain an important part of trauma care in preventing infection, the clinician should be aware of these studies which indicate that it is prudent to avoid high doses of ciprofloxacin, rifampicin and topical gentamicin in order to minimise the risk of nonunion. Additional work is required to investigate the whole range of antibiotics used in fracture patients.

Anticoagulants. Low molecular weight heparins are used routinely in patients with a fracture of the lower limb to reduce the rate of thromboembolism. Many patients admitted to hospital with fractures are treated with warfarin if they have had a previous thromboembolic event. While heparin and warfarin have been shown to reduce the rate of deep-vein thrombosis and pulmonary embolism,[85] several animal studies have demonstrated significant attenuation of the process of fracture healing, both biomechanically and histologically.[86,87] No studies have addressed this in a human population.

Fracture treatment. The majority of fractures heal satisfactorily without surgical intervention and often only require a cast or simple immobilisation. However, certain fractures, such as of the shaft of the tibia, and certain types of fracture such as those of the ankle with talar shift, require reduction and stabilisation. However, elements of surgical intervention can have a detrimental effect on fracture healing. Poor reduction with an associated gap at the fracture site adversely affects healing, and animal studies have shown that a gap of more than 2 mm inhibits bony healing.[88-90] The size of the gap has been shown to directly affect revascularisation and tissue differentiation in callus healing in the ovine metatarsal.[91] Open reduction and fixation of fractures with dynamic compression plates aims to achieve compression and absolute stability in order for primary bone healing to occur. This involves some stripping of the periosteum for placement of the plate. Periosteal stripping caused by surgery as well as that caused by the injury removes the cambial layer, which is the key source of osteoprogenitor cells, and affects the periosteal blood supply. A study in sheep showed a decrease in perfusion of cortical bone immediately after plating a tibial fracture to 60% of prefracture levels.[92] Reaming of the intramedullary canal for internal fixation interferes with endosteal blood supply and destroys the nutrient artery.[93] Despite this, studies have shown that in these cases the direction of cortical blood flow changes from a centrifugal to a centripetal direction with a sixfold increase in the periosteal supply,[94] which was initially suggested by Trueta in 1974.[95] This increase in periosteal blood flow is associated with an increase in blood flow to the cortex and the callus.[96]

For a fracture to heal uneventfully, the mechanical environment must be appropriate. This depends on the mode of fracture repair, either by direct osteonal healing or by secondary healing with callus formation, chosen by the

treating surgeon. In order that direct osteonal healing can proceed, there must be no gap at the fracture site and rigid fixation is required. However, the majority of fractures heal by secondary union in which a degree of micromotion at the fracture site is necessary to stimulate the formation of callus. The type of movement which occurs is important. Axial movement has been shown to be beneficial in the healing of tibial fractures, although there are boundaries in the magnitude of strain and the rate of application of applied movement which, if exceeded, inhibit healing.[97] It is important that movement is applied early because the same movement applied late has also been shown to inhibit healing. Axial movement has also been found to be beneficial in models of distraction osteogenesis using the Ilizarov technique.[98] Similarly, excess interfragmentary shear or rotational movements inhibit repair and can result in a significant delay to healing.[99] Therefore, during secondary fracture healing a degree of motion at the fracture site assists the process. Early weight-bearing is often prescribed to encourage healing in fractures of the lower limb and is advantageous in terms of functional outcome.[100] However, excess motion and instability at the fracture site leads to nonunion.[101] Excessive motion during fracture repair causes hypertrophic nonunion with gross callus formation but no bridging of the bone ends. This may be the result of inappropriate surgical treatment resulting in failure of the fixation device or poor surgical technique.[102]

The mechanical environment provided for secondary healing to progress during fracture repair must be that which allows a degree of movement but not an excess or instability, which will inhibit fracture repair. This represents a fine balancing act which trauma surgeons face as part of their daily routine.

Recently, the use of systemic and topical agents such as BMPs have gained popularity for the treatment of nonunion, peri-prosthetic fracture and osteotomy.[103] However, the high costs involved precludes their use in all patients. The identification of patients at high risk of delayed or nonunion may enable clinicians to identify subgroups of patients in whom this expense is justified. Those identified in this review may benefit from treatment with such agents when first seen in order to redress the balance between inhibition and progression of bone repair. Delayed and nonunion are associated with much morbidity and all measures to prevent inhibition of healing should be taken.

We have examined the current evidence of intrinsic and extrinsic factors that have been reported to inhibit fracture repair. Some of these factors may have an inhibitory action throughout the repair process whereas others may only act during certain stages of fracture healing. This may account for some of the controversy that exists in the literature. For instance, steroids and NSAIDs may have a major effect during the inflammatory phases of repair but little effect during the later stages.

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