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Epidemiology and management of nonunion fracture

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Abstract:
Non-union is a significant problem in healthcare systems. With limitations to current data collection, we need to devise robust prospective database to accurately estimate the incidence of non-unions. In doing this, we will gain insight into the magnitude of non-unions and allocate resources accordingly through provision of tertiary treatment centres and in research planning. By focusing on early accurate diagnosis, through a standardised pathway we can identify trends and risk factors. The shift towards standardised definitions and data homogeneity will facilitate the generation of predictive models. The models will not only risk stratify patients but highlight a new focus for research. By risk stratifying patients, we can counsel them accordingly and adjust expectations and reduce indirect costs, which may reduce the litigation burden. Management plans can focus on reversible risk factors to enhance outcome of fracture management and patient satisfaction.
Key words: Non-union, fracture and management.

Introduction:

Nonunion is thought to occur in approximately 2% of all fractures [1] but for diaphyseal fractures the incidence can be as high as 20% for certain injuries [2]. The incidence of nonunion in the U.K. is estimated at 20 per 100,000 population with males of the working age being the most common group [3].

The burden of a long bone nonunion is substantial with pain, loss of function and psychological distress commonly encountered [4]. The financial implications can often be extensive for patients due to loss of potential earnings and with an estimated medical expense of up to £79,000 per case being reported [1,5].

Nonunion in clinical practice is most commonly associated with long bone fractures of the forearm, humerus, tibia, clavicle and femur [1,2]. A precise definition of nonunion is difficult. According to the US FDA definition, a fracture ununited 9 months after injury or one in which there is a failure of progression towards union over the previous three months, can be classified as a nonunion [6]. However, 9 months is a long period of time for patients to wait for defining a nonunion. A specific duration of time to define nonunion must be related to the location of the fracture and the severity of the original injury, two factors which will have a profound influence on time to union. In general, lower energy closed fractures can be expected to progress to union in much shorter time than high energy open long bone fractures. Rather than relying on a specific time frame to define a nonunion it has been proposed that a more practical definition of nonunion is a fracture that will not unite without further intervention. Traditional classification and

treatment of nonunion patterns was based on plain radiographs. A hypertrophic nonunion is characterised by abundant callus formation and is usually considered to have excessive motion but good biological potential for healing at the fracture site. An oligotrophic nonunion has poor callus formation and is considered to have viable fracture fragments but has a combination of excess motion but also impaired biological potential for healing at the fracture site. An atrophic nonunion has no callus formation with no biological capacity to heal without some biological stimulus as part of the treatment, most commonly in the form of a bone graft [7]. These categories are no longer considered valid for a variety of reasons. Firstly, many fractures treated non operatively in the past are now treated by internal fixation and the classic radiographic patterns of hypertrophic and atrophic nonunions are less commonly seen. Secondly, histological studies of stiff atrophic and hypertrophic nonunions indicate no difference in the vascularity of the fracture site between the two types [8, 9].

A non-union exists when repair is not complete within the period expected for a specific fracture and when cellular activity at the fracture site ceases and there is no visible progressive signs of healing for 3 months.(10, 11) The healing process prematurely terminates with no further radiological evidence of consolidation. With varying repair times for individual fractures and healing potential of patients, there is no uniform definition for non-union. According to American Food and Drug Administration, a non-union is established when a minimum of 9 months has elapsed since injury and the fracture shows no visible progressive signs of healing for three months.3 It is impractical to apply this to every patient, and clinician's modify according to each individual scenario. Delayed union, non-union and

pseudoarthrosis represent part of the spectrum of bone repair. It is difficult to predict which patient or fracture type will progress to non-union and an even greater challenge is preventing it.

Classification

Weber introduced a classification system based on biological activity at the fracture site which also facilitates treatment decisions.(12) It is widely used and has stood the test of time. Other classifications exist, that are specific to a particular fracture site or injury type.(13,14). According to Weber, fracture non-unions are categorised into Hypervascular (hypertrophic) or Avascular (atrophic) types. (11)

The hypervascular group has adequate vascularity and biological activity to progress to union but limited by bony stability evident on radiographs with excessive callus in response to motion at the fracture site. Callus is a function of both the magnitude and frequency of inter-fragmentary motion.(15)

Inter-fragmentary motion disrupts establish healing, particularly the empty scaffold within the radiographic fracture line.2 Weber further subdivided by radiological appearance (Elephant foot, Horse hoof and oligotrophic). Avascular non-unions lack vascularity and biological healing potential and show no evidence of healing and are associated with factors acting directly on the early phases of fracture healing, while hypertrophic nonunions relate mostly with factors acting on the 're-organisation' phase of bone healing.(16, 17) Avascular non-union can be further sub-grouped by the fracture pattern: torsion wedge, comminuted, defect and atrophic.(12)

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The classification systems to date characterise established non-union cases and are useful in treatment planning. It is important to consider the possibility of infection in all cases, particularly in high-energy open fractures.

Etiology:

The most basic requirements for fracture healing include

(1) Mechanical stability

(2) An adequate blood supply (i.e., bone vascularity),

(3) bone-to-bone contact.

The absence of one or more of these factors predisposes the fracture to the development of a nonunion. The factors may be negatively affected by the severity of the injury, suboptimal surgical fixation resulting from either a poor plan or a good plan carried out poorly, or a combination of injury severity and suboptimal surgical fixation. (18)

Epidemiology:

In the U.S., 100000 fractures go onto nonunion. (18, 19) The rate of all fracture nonunion is between 1.9% to 10%. Variable rates of nonunion exist depending on the anatomic region. Femoral shaft nonunions are estimated to be 8% overall with the use of intramedullary nailing. (20) Tibial shaft nonunions occur at a rate of 4.6% after intramedullary nailing. However, there are several discrepancies, as some studies have shown tibia nonunion to be as high as 10% to 12% overall.(21) Also, soft tissue damage impacts the ability to heal. Studies of open fractures with extensive soft compromise showed nonunions to be much higher at 16%.(22-25) Sex is a predictor of nonunion, showing male gender increases the risk of nonunion, and this was proposed to be because of gender-specific activity types and injury patterns. However, this needs to be taken with caution because l replicated in larger studies could not replicate these findings. Brown and colleagues showed nonunion rates to be similar between males and females (12% vs. 12%). (26-28).

Pathophysiology:

There are several physiologic processes responsible for the nonunion of the bone. One, dysfunctional blood supply decreases the ability for the fracture to heal, which in response decreases osteogenic cells. Second, damage to the osteoconductive scaffold causes reduced new bone formation due to the distance needed to heal bone. Third, (28)pathological biologic processes listed above will not only decrease blood flow but also decrease new bone formation by decrease the biologic growth factors needed to heal bone. Fourth, poor mechanical stability at the fracture site can lower the ability of the fracture to heal.(28,29) If any of these processes are altered negatively, the probability of developing nonunion increases dramatically, and patients should be counseled as such.

Diagnosis:

The diagnosis of a nonunion is sometimes difficult. Both clinical and radiological criteria can be helpful. Typically, patients report inability to bear weight (84%), pain at fracture site (74%), and tenderness on palpation (38%).[18] Radiologically, the lack of callus seems to be more important than persistent fracture lines (75%). Computed tomography (CT) scanning can be supportive;

however, the evaluation of the sometimes complex configuration can be difficult. Calori et al[19] suggested evaluating and quantifying the cross-sectional area, indicating the presence of a nonunion when bone bridging was less than 5% and considering the fracture healed when bridging was more than 25%. The frequently quoted statement that a fracture is radiologically stable when bone healing is present in three out of four cortices is doubtful, because it is based on an animal study with 21 rabbits and is not necessarily transferrable to humans.[19] Scoring systems provide a more systematic approach and were first introduced by Whelan et al,[21] presenting the RUST score evaluating status of consolidation of each cortical side of the bone.
CT scanning can help; however, considering a specificity of only 62% it may be seen critically, because clefts in bone are of uncertain clinical importance, and there is a risk of operating on an already healed fracture.[22] In relation to this, Kleinlugtenbelt et al found in a rather small cohort no additional value for CT scanning compared to X-ray alone.[23] When in doubt how to treat a potential nonunion after evaluation of conventional radiographies then an additional CT scan usually leads to surgery.

Management and treatment:

As is with the entire nonunion disease process, treatment requires a multifaceted approach.
Initial non-operative Treatment [28-31]:

- Use of a fracture brace for an extended period of time postoperatively or immobilization in a cast
- Pulsed low-intensity ultrasound or other external bone stimulation **Operative Treatment (31,32).**

Treatment is tailored via the classification of nonunion. It is important to understand that multiple surgical techniques exist and that it is critical to utilize multiple techniques tailored to the patient's specific needs.

- Hypertrophic nonunion: the goal is to improve mechanical stability with internal fixation

❖ Compression plates
❖ Exchange nailing
❖ Augmented plating with ORIF
❖ Dynamization of nail (should not be used in the humerus because dynamization cannot work in a non-weight bearing limb

 Atrophic nonunion: the goal is to fix the biology and mechanical stability

1. Internal fixation with biologic stimulation (28)

Biologic stimulation with bone graft

❖ Bone morphogenetic protein (BMP):
❖ Use of BMP-7 is FDA approved for tibial nonunions
❖ BMP-2 is FDA approved for 1 level degenerative disk disease in spinal fusion
❖ Autologous iliac crest bone graft
❖ Intramedullary reaming, irrigation, and debris aspiration (RIA)
❖ Demineralized bone matrix (DBM)
❖ Systemic parathyroid hormone (PTH) therapy, teriparatide

2. Oligotrophic nonunion: Use a combination of both internal fixation and biologic stimulation depending on the clinical situation
3. Infected nonunion: Must obtain WBC, ESR, CRP, and nuclear bone scan. Intraoperative cultures are the gold standard for guided antibiotic therapy

 A 2-staged surgical treatment protocol is the gold standard

- 1st stage - removal of loose or chronic infected hardware, debridement, and revision fixation of nonunion, and treatment of infection with culturespecific local and systemic antibiotics.(28)

- Modalities used for initial fixation in case of infection
- Antibiotic beads
- Antibiotic nails
- Antibiotic cement spacers
- Masquelet technique
- External fixation
- Soft tissue coverage with a flap

 2nd stage

- Begins after a period of antibiotic therapy when both serologic and clinical signs of infection are absent
- Definitive fixation proceeds with internal fixation and bone grafting, other biological treatment, bone transport, depending on specific fracture characteristics.(29-33)

Complication:

- Nerve injury - e.g., the radial nerve in the humeral shaft fractures
- Persistence of nonunion
- Eventual need for amputation
- Infection with further damage to surrounding anatomy
- BMP-2 can cause osteolysis, heterotopic bone formation, retrograde ejaculation in spine surgery, and wound complications (34, 35)

Conclusion:

Nonunion remains a challenge to predict and common risk factors need to be evaluated critically for a specific fracture. Risk factors such as smoking, alcohol intake, non-steroidal use and diabetic control are amenable to modification and this may improve the prognosis for treatment. Infection as a contributory cause should be considered particularly after open fracture or in fractures initially treated surgically which fail to heal. When nonunion is encountered there is good evidence available to guide decision making and successful union can usually be achieved with conventional trauma fixation techniques in the majority of cases. Biological augmentation of fracture healing is not necessary in most cases but needs to be considered in higher risk cases with a mobile atrophic pattern.

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