J Orthop Spine Trauma. 2022 June; 8(2): 44-7. DOI: http://dx.doi.org/10.18502/jost.v8i2.9309

Review Article

The Contributing Factors of Nonunion Bone Fractures: A Brief Review

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Received: 25 January 2022; **Revised:** 12 March 2022; **Accepted:** 04 May 2022

Abstract

The skeletal system has a high healing capacity. A nonunion fracture occurs when the natural course of bone healing is impaired. Numerous local and systemic factors participate in the development of a nonunion fracture. Patients with diabetes mellitus (DM), smoking history, obesity, and malnutrition are at risk for nonunion. Moreover, the major local risk factors for impaired bone healing are malalignment, infection, mechanical stability, and tissue loss. In this brief review, we discuss the definition, epidemiology, and diagnosis of nonunion. We further explain the major contributing factors which must be considered in patient selection for nonunion revision surgeries.

Keywords: Fracture Healing; Bone; Risk Factors

Citation: Zafari H, Moein SA, Razzaghof M, Mortazavi SMJ. **The Contributing Factors of Nonunion Bone Fractures: A Brief Review.** *J Orthop Spine Trauma* 2022; 8(2): 44-7.

Background

Skeletal fractures are considered one of the most common injuries in human body (1, 2). The healing of bone fractures occurs in a stepwise process. In the first few days after injury, a hematoma is formed at the fracture site. Subsequently, soft callus, fibrous tissue, and hard callus are formed in order. Finally, the remodeling phase occurs, which lasts for the next few months (3, 4). Generally, a nonunion happens if the healing process fails at the expected time. Nonunion fractures can cause a considerable economic burden due to morbidity in the patients' quality of life (QOL) (5). Various patient and surgeon-dependent factors participate in the occurrence of nonunion fractures. Systemic biological factors such as drugs, diabetes mellitus (DM), malnutrition, smoking, and chronic diseases interfere with the normal healing process. Moreover, local factors such as malalignment, bone and soft tissue loss, infection, and mechanical instability must be considered in the management of nonunion fractures (6, 7). Management of these complex fractures tends to be demanding for orthopedic surgeons.

This short review intends to shed light on the definition, epidemiology, and diagnosis of nonunion fractures. Furthermore, we discuss the major contributing risk factors of this phenomenon.

Epidemiology and Incidence

Various rates of incidence have been reported for nonunion fractures. Depending on the country and health care system, a range of 1.9-10 percent has been suggested in the studies (8-10). Scaphoid, tibial, femoral, and humeral fractures have the highest risk for nonunion. The incidence of nonunion peaks at the age of 25-34 years in men and 65-74 years in women. High-energy traumas leading to vascular injury and open fractures make the patients susceptible to nonunion fracture (6, 10).

Definition and Diagnosis

Generally speaking, a nonunion fracture is described as a non-healing fracture that requires further intervention for proper healing. Controversy remains regarding the precise timeline of the nonunion fractures. However, most clinicians suggest that a nine-month-old fracture which does not show any sign of new bone formation in three months would be designated as a nonunion (11).

The most prominent clinical manifestation is pain. Reduced motion and function is another debilitating presentation of this phenomenon. On the other hand, in some patients with chronic nonunion who might only have a minimal level of pain, pseudoarthrosis may occur. In such cases, a significant motion is experienced at the nonunion site, appearing as a new joint (6).

In the literature, various grading systems such as Radiographic Union Score in Tibial fracture (RUST), Radiographic Union Scale in Humeral fractures (RUSHU), and Radiographic Union Score in Hip fractures (RUSH) have been developed for the diagnosis of nonunion fractures (12-14). Nevertheless, in clinical practice, the decision is made via a combination of physical examination and biplanar X-ray imaging. Callus formation and bridging, and absence of the fracture line are suggestive for union (15).

Considering the radiological and morphological appearance of the fracture site, nonunion fractures are categorized into three groups. Hypertrophic nonunion fracture is characterized by significant callus formation without proper bridging. On the other hand, atrophic nonunion fracture is defined as a nonunion fracture with impaired callus formation. Hypertrophic nonunion usually indicates proper local biology, whereas atrophic nonunion implies poor local biology. In situations in which the morphology of the nonunion fracture is on a scale between hypertrophic and atrophic nonunion, the nonunion fracture is called oligotrophic (7, 16).

Contributing Factors

Owing to numerous cells, cytokines, and growth

factors responsible for normal bone regeneration and complex bone healing physiology, various local and systemic factors have been implicated in nonunion bone fracture.

Systemic Factors

Smoking: Smoking is one of the mostly-discussed modifiable risk factors that interfere with normal bone regeneration in the literature. The vascular blood supply of the bone is impaired by smoking (17). Moreover, nicotine is believed to diminish osteoblast activity in a dose-dependent manner in heavy smokers (18). Smoking is also associated with vitamin D deficiency and elevated parathyroid hormone (PTH) levels which, in turn, play a significant role in the bone metabolism (19). The implication of tobacco use in the occurrence of nonunion has been mentioned in foot and ankle surgeries (20, 21), spinal fusion surgery (22, 23), tibial fractures (24), humeral fractures (25), and femoral osteotomies (26) and fractures (27). Overall, smokers were found to have a 2.32 odds ratio (OR) for nonunion fractures (28). Consequently, there is no doubt that candidates for nonunion surgeries should consider smoke cessation for better results. A four-to-six-week gap has been suggested between smoking cessation and the surgery (29, 30).

Diabetes Mellitus (DM): Patients with DM have diminished osteoblastic function and impaired vascular supply, hence increasing chances for infection, malunion, and nonunion (31). In a large cohort of more than 300000 fractures by Zura et al., the OR for nonunion development was 1.4. Despite the unclear mechanism, it was mentioned that non-insulin medications provided protection against nonunion (8). The role of DM in nonunion in foot and ankle surgeries has been well discussed in the literature (32, 33). However, limited studies have evaluated the implication of DM in other sites. In a cohort of 165 patients with DM undergoing foot and ankle surgery, a hemoglobin A1c (HbA1c) of less than 7% before surgery was significantly associated with nonunion (34). Although further studies are required to determine the optimal cut-off point for HbA1c level prior to nonunion surgeries, proper management of DM must be considered in patient selection.

Obesity: Despite the obvious association between obesity and DM, an independent relationship has been suggested between obesity and nonunion. Obesity significantly increases post orthopedic surgery complications such as infection and nonunion (35). Moreover, obese patients tend to have diminished vitamin D levels (36). In the Zura et al. cohort, an OR of 1.19 was suggested for nonunion in obese patients (8). In a meta-analysis by Tian et al. which included over 40000 patients, body mass index (BMI) > 40 kg/m^2 was recognized as a risk factor for tibial fracture nonunion (37). In complicated nonunion fractures, weight reduction must be taken into consideration for more favorable nonunion surgery outcomes.

Malnutrition: Specific amino acid deficiencies could intervene with normal bone regeneration (38, 39). Yet, the major impact of malnutrition on bone healing is made through vitamin D deficiency and osteoporosis. The biologically active form of vitamin D, also known as calcitriol, is essential for maintaining the calcium level in the bone. Furthermore, it is believed that vitamin D and calcium are essential for the constant remodeling of bones and the healing process in the fractured bones (40). In a retrospective study of 62 tibial fractures by Pourfeizi et al., it was demonstrated that vitamin D levels were significantly lower in the nonunion group (41). A modest OR of 1.14 was suggested for nonunion in patients with vitamin D deficiency (8). Vitamin D and calcium supplements could be economically and clinically beneficial in the prevention of nonunion fractures (42).

Local Factors

Malalignment: Unsatisfactory fracture reduction has been associated with nonunion and malunion (43). For instance, the risk of subtrochanteric femoral fracture nonunion significantly increases with varus malalignment of more than five degrees (44). Diagnosis of the malalignment can be challenging in nonunion preoperative evaluations. Although the diagnosis is usually made with proper biplanar X-ray films, in certain cases, computed tomography (CT) images could be useful (45). Operative osteotomies and osteoclasis are essential to achieve proper alignment. During surgeries, the Arbeitsgemeinschaft für Osteosynthesefragen (AO) distractor can be a valuable tool to avoid malalignment. Overall, surgical revisions are required to correct malalignment in nonunion management (46).

Hardware and Infection: In patients with nonunion fracture, infection must be considered even without frank clinical presentation. The infection rates increase, especially in patients with open fractures and those who have undergone open surgery. Failed hardware should be removed out of the nonunion fracture site. In these situations, infection must be considered as a possible contributing factor (47). High serum white blood cell (WBC) count, erythrocyte sedimentation rate (ESR), and C-reactive protein (CRP) level could predict infection in preoperative evaluations. However, it was shown that 19.6% of nonunion cases could have normal WBC count, ESR, and CRP despite underlying infection. Tissue sampling and culture from surgery site remains as the gold standard diagnostic method for infection in nonunion fractures (48). This calls for a two-step surgery for the management of the nonunion. The failed hardware must be removed in the primary surgery, and tissue samples for infection must be obtained. After proper antibiotic therapy, the second surgery should be performed for the fixation of the nonunion.

Mechanics: Interfragmentary movement (IFM) plays a crucial role in the development of the nonunion. In a case with high IFM, bone regeneration is impaired due to high tissue strain. This would lead to the development of fibrous tissue in the fracture site, which is also known as a hypertrophic nonunion. A hypertrophic nonunion indicates poor mechanical stability with healthy local biology. Furthermore, in cases in which the fracture site is fixed in a very rigid manner, the callus tissue will not be produced, which will, in turn, become an atrophic nonunion. The fracture ends of an atrophic nonunion lack significant healing properties. Overall, high IFM, large fragmentary gap, high tissue strain, and transverse shearing movements impair routine bone healing. In contrast, a moderate compressive movement promotes bone healing (6, 49, 50). Achieving proper mechanical stability with acceptable tissue strain is essential in the prevention and management of nonunion fractures.

Bone and Soft Tissue Loss: Subsequent to either inevitable debridement for infection or high-energy and complex injuries, bone and soft tissue loss remains of utmost importance in managing nonunion fractures. Using bone autograft can compensate for bone loss, and soft tissue loss should be reconstructed through plastic surgery. For segmental bone loss, in a two-step surgery, a cement spacer is inserted into bone defect site which is later covered with a biological membrane as the result of the healing process. In the second surgery, the spacer is removed, and the bone graft is inserted in the biological

membrane which is also known as the Masquelet technique (51, 52). The bone grafting technique could also be further augmented with the use of a reamer-irrigator-aspirator (RIA) device (53).

Conclusion

Various factors intervene in normal fracture healing, which should be considered during patient selection. Especially, correcting the modifiable risk factors is of utmost importance. Hence, correction of the vitamin D level, smoking cessation, proper management of DM with acceptable HbA1c level, and decreased BMI in obese patients are highly recommended in candidates for nonunion surgery. Nonunions should be meticulously evaluated for malalignment. Generally, biplanar X-rays could disclose malalignment, but CT scans could be more helpful in some fractures.

In certain cases, a two-step surgery should be considered for failed hardware removal and nonunion fracture fixation due to possible infection. Although high WBC count, ESR, and CRP level could be used as possible predictors for infection, normal laboratory findings do not rule out underlying infection. Good teamwork is required with the plastic surgery team for the management of soft tissue loss. The Masquelet technique, with the help of the RIA device, could be beneficial in segmental bone loss.

Conflict of Interest

The authors declare no conflict of interest in this study.

Acknowledgements

None.

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