Acta Biomaterialia 146 (2022) 1–9

Contents lists available at ScienceDirect

Acta Biomaterialia

journal homepage: www.elsevier.com/locate/actbio

Review article

Concepts and clinical aspects of active implants for the treatment of bone fractures

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ARTICLE INFO

Article history:
Received 20 January 2022
Revised 24 April 2022
Accepted 2 May 2022
Available online 7 May 2022

Keywords:
Fracture healing
Surgery
Trauma
Smart implant
Shape memory alloy

ABSTRACT

Nonunion is a complication of long bone fractures that leads to disability, morbidity and high costs. Early detection is difficult and treatment through external stimulation and revision surgery is often a lengthy process. Therefore, alternative diagnostic and therapeutic options are currently being explored, including the use of external and internal sensors. Apart from monitoring fracture stiffness and displacement directly at the fracture site, it would be desirable if an implant could also vary its stiffness and apply an intervention to promote healing, if needed. This could be achieved either by a predetermined protocol, by remote control, or even by processing data and triggering the intervention itself (self-regulated 'intelligent' or 'smart' implant). So-called active or smart materials like shape memory alloys (SMA) have opened up opportunities to build active implants. For example, implants could stimulate fracture healing by active shortening and lengthening via SMA actuator wires; by emitting pulses, waves, or electromagnetic fields. However, it remains undefined which modes of application, forces, frequencies, force directions, time durations and periods, or other stimuli such implants should ideally deliver for the best result. The present paper reviews the literature on active implants and interventions for nonunion, discusses possible mechanisms of active implants and points out where further research and development are needed to build an active implant that applies the most ideal intervention.

Statement of significance

Early detection of delays during fracture healing and timely intervention are difficult due to limitations of the current diagnostic strategies. New diagnostic options are under evaluation, including the use of external and internal sensors. In addition, it would be desirable if an implant could actively facilitate healing ('Intelligent' or 'smart' implant). Implants could stimulate fracture healing via active shortening and lengthening; by emitting pulses, waves, or electromagnetic fields. No such implants exist to date, but new composite materials and alloys have opened up opportunities to build such active implants, and several groups across the globe are currently working on their development. The present paper is the first review on this topic to date.

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https://doi.org/10.1016/j.actbio.2022.05.001

1. Introduction

Fracture healing is a physiological process affected by a number of biomechanical and biological factors [1–3]. In patients, the progress of fracture healing is typically monitored by infrequent x-ray imaging that comes at the cost of radiation exposure combined with a poor correlation between radiographic scores and biomechanical, and histological data [4]. Apart from x-ray-based imaging, in some cases, specific ultrasound devices may help to monitor fracture healing [5–7]. More continuous monitoring, such as direct mechanical sensing at the fracture site via the implant, would be favourable but is not routinely available for daily clinical practice today [8]. Several technical solutions exist for continuous biomechanical fracture monitoring via stiffness or displacement [9]. Some of them have been applied with internal [10] and external devices [11–18]. Continuous mechanical fracture monitoring seems to allow for a timely identification of delays in bone healing, as well as of events with extensive peaks in forces that may be a threat to fracture healing. The future bending stiffness and course of healing can best be predicted by analysing changes in stiffness between the third and the fourth week after fracture [17]. A bending stiffness of 15 Nm/degree at the fracture site was suggested to be a good threshold value to remove fixation and start full weight bearing [12].

Apart from monitoring and giving individual patient feedback (sensor component), it would be desirable if the implant could also adapt to the individual and specific needs of the fracture site by adapting its mechanical properties (stiffness) and ideally even apply a mechanical intervention to optimize healing and prevent nonunion (actor component). This either could be achieved by a pre-determined protocol, remotely controlled settings or potentially even by processing the data and inducing the intervention itself (closed loop system, 'intelligent' or 'smart' implant) [19,20]. Such implants are not yet available for clinical application in human fracture patients to date. Thus, it is of interest to explore and evaluate interventions that would be beneficial if administered via an implant used for fracture fixation. Apart from mechanical stimulation, implants could in theory also apply biological interventions that are, however, less reproducible since the delivery is not linear (Fig. 1). For this reason, in this paper we will focus on of the measurement and simulation of the mechanical properties of the fracture, callus, and implant, as well as on the manipulation of fracture healing by physical methods.

Possible interventions could include active mechanical stimulation of the fracture site by the application of mechanical forces, ultrasound, shockwaves, and/or magnetic fields. In addition, a decrease in implant stiffness may accommodate varying biomechanical needs throughout the healing process. In case of excessive loads, the fracture site could be protected from damage by an abrupt increase in implant stiffness. Composite materials and metals, such as shape memory alloys and dielectric elastomers have opened up a whole new world of opportunities to build active implants [21–24]. The ability of shape memory alloys such as nitinol to shorten could be employed to create an implant capable of varying its length, just as in nitinol cardiovascular implants and implants used for arthrodesis in foot surgery [25–28]. Fig. 2 shows an example mechanism of an SMA-driven plate capable of a stiffer and less stiff state, that in addition may be activated to improve fracture healing via cyclic compression [24]. The development of devices and mechanisms that use such materials for active or even smart implants may improve rates of long bone fracture healing and decrease the incidence of bone healing problems. For example, implants could stimulate fracture healing via active shortening and lengthening, or by emitting pulses, waves, or electromagnetic fields. However, it remains undefined which modes of application, forces, frequencies, force directions, time durations and periods, or other stimuli such implants should ideally deliver for the best result possible in order to optimize the bone-healing conditions [20]. The present paper reviews the literature to answer this question, to discuss possible mechanisms for active implants and to point out where further research is needed.

2. Nonunion

Delayed union and nonunion are complications in the treatment of fractures and responsible for extensive costs, disability and morbidity [29,30]. Nonunion is most prevalent in the long bones, and particularly in the tibia/fibula and femur (both in ∼14% of cases) [31–33]. Among factors associated with an increased risk for nonunion are a higher level of injury (open fractures, multiple fractures), a high body mass index, smoking, alcoholism, diabetes and male sex [29,30,33]. Biomechanical factors play a crucial role in fracture healing, and bone healing problems are frequently related to the mechanical properties of the bone-implant composite and the resulting stiffness of the applied fracture fixation system, which can be either too low or too high [34]. Other geometrical factors include an extended fracture gap or certain fracture types [35]. In this review, we do not take into account the important role of concomitant local soft-tissue damage, which shows a high degree of variation among individual cases [36–38]. Local infection is another major and costly risk factor in nonunion [29,30]. Also, the patient's general condition following trauma appears to be relevant, that can be evaluated using blood samples, and as an example, in the blood, a base deficit of $\geq$ 6 mmol/L within 24 h of injury in polytraumatised patients showed a negative effect to uneventful healing [39]. Further risk factors include the use of nonsteroidal anti-inflammatory drugs (NSAIDs) and opioids [30]. In addition, secondary osteoporosis due to steroid treatment is known to cause slowed fracture healing [40].

The individual roles and contributions of these explanatory variables to nonunion are currently not known in detail [35]. It is also not known in what percentage of cases the cause of nonunion is more biomechanical or biological and which of the many determinants contribute to what degree. Biological interventions include the application of growth factors, scaffolds, and mesenchymal stem cells. These interventions are often applied in various ways to improve the outcome, as they have a positive effect on fracture healing [41,42]. However, it has become evident that such biological interventions help only in some cases, and it seems logical to apply biomechanical stimuli to treat more fractures faster by modulating the mechanical properties of the fracture fixation to activate and stimulate mechanotransduction [43]. The application and intensity of biomechanical stimuli can be controlled more precisely than dosages and kinetics of biological interventions, such as growth factor-loaded biomaterials.

There are two types of nonunion: the hypertrophic type forms an abundance of callus, while the atrophic type does not develop a biomechanically stable callus but non-functional fibrous tissue instead [44]. Non-invasive conservative interventions that may be applied to heal nonunion, such as low intensity pulsed ultrasound (LIPUS) [45–47], extracorporeal shockwave therapy (ESWT) [48], and pulsed electromagnetic fields (PEMF) [49,50] are clinically well established and were reported to have a positive effect in around 80–85%, 75–91%, and 77% of cases *in-vivo*, respectively, taking into account the huge interindividual variability of injuries. These interventions are, however, mainly effective in hypertrophic, but less so in atrophic, nonunion [45]. In addition, a high level of patient compliance is needed for successful application. If the bone does not show fusion or at least ongoing healing 6–9 months after injury, the management of the resulting long-bone nonunion cases is currently surgical revision with autologous bone transplantation [29].

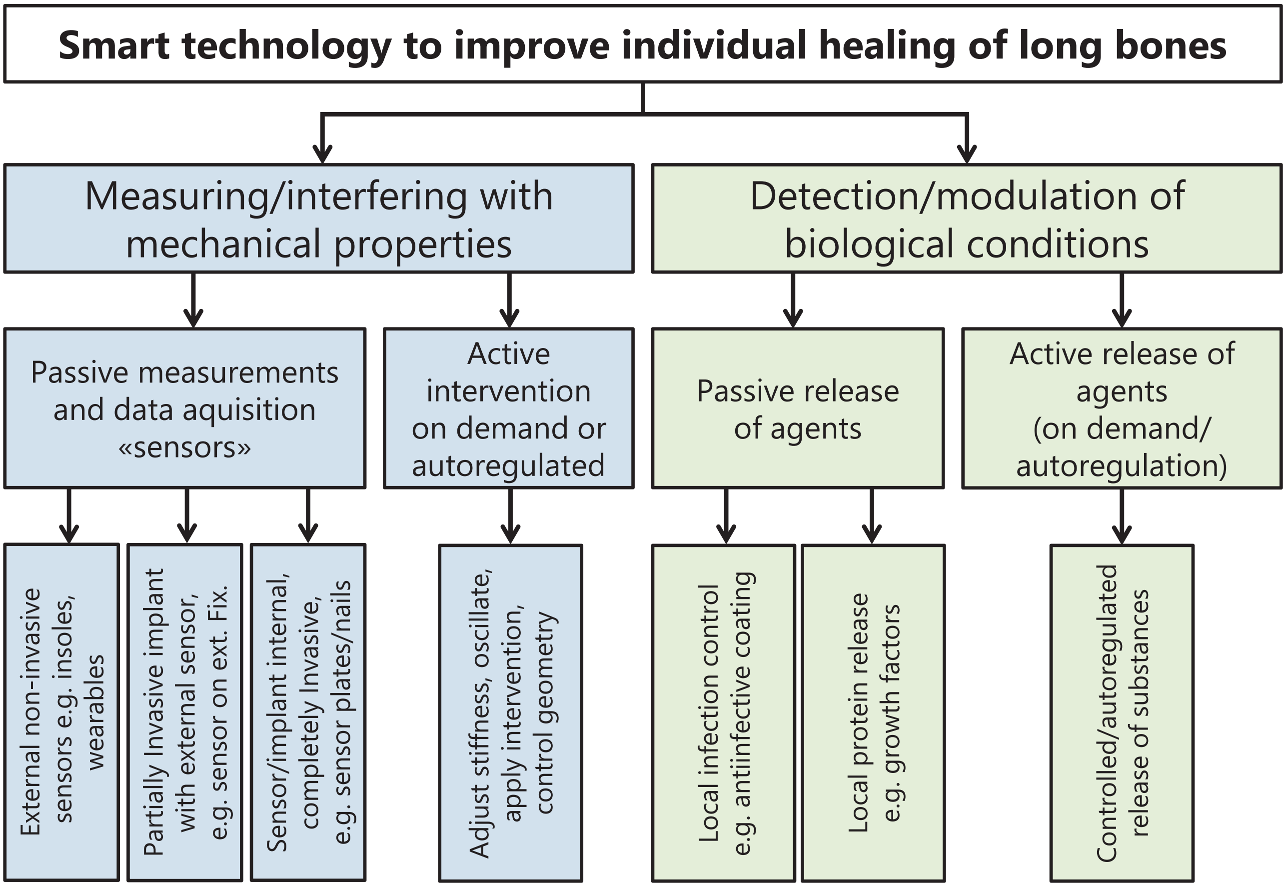

Fig. 1. Systematic overview of 'smart options', which could be implemented in an existing or new active implant (platform options).

3. Pulsed ultrasound, shockwaves and electromagnetic fields in active implants

Stimulation of the fracture site is presently solely applied by external, non-invasive devices. To overcome tissue barriers and potentially increase the efficiency of the stimulus, an integration of the emitter into an implant could provide major benefits. An active implant could have the stimulation device on board that applies stimuli such as LIPUS, ESWT, or magnetic fields to improve fracture healing. In addition to the efficacy of the interventions as such, another benefit is that treatment success would to some extent become independent of patient compliance if the implant provided the application by itself. This approach promises even higher success rates [45–50]. Therefore, LIPUS, ESWT and PEMF seem to be interesting candidates for active implants.

LIPUS uses acoustic waves with recommended pulse clusters of 200 μsec with a frequency of around 1.5 MHz at an intensity of around 30 mW/cm^2 and a repetition rate of the clusters at 1 kHz to stimulate bone cell activity [51]. On the transducer surface, the ultrasound waves are generated by applying an electric current to an array of piezoelectric crystals [51]. The application of LIPUS in clinical practice is usually recommended for 20 min/day in one session [52]. It does not cause pain but can sometimes be felt by the patient. The mechanisms of action include the activation of biological signaling via mechanoreceptors, called integrins [53]. Growth factors, i.e., bone morphogenetic proteins (BMPs), transforming growth factor – beta (TGF-b) and vascular endothelial growth factor (VEGF) are expressed and promote healing. Furthermore, LIPUS upregulates COX-2 in the bone, and enhances mineralization in pre-osteoblast cells [54–56]. LIPUS was shown to cause the formation of focal adhesions between cells via the GTPase, Rac-1 also in the absence of syndecan-4, that is usually responsible for the formation of focal adhesions in wound and fracture healing [53].

As LIPUS increases microcirculation in the surrounding soft tissue, it helps to create homeostasis and promotes healing [57,58]. An ultrasound wearable system that monitors fracture healing, transfers data to a central unit and applies LIPUS interventions when indicated was suggested and demonstrated in animals in 2005 [7]. As the hardware is currently too large to be embedded in a fracture plate or nail, the development of a miniaturized internal device is an important next step and a major technological and regulatory challenge.

ESWT usually applies single pressure waves of around 300 bar to promote biological healing processes through mechanotransduction, that are not painful, but can be felt by the patient [59,60]. The stimulus leads to an inhibition of osteoclasts and an activation of osteogenesis by osteoblast differentiation and proliferation [59]. On molecular level, BMP-2, VEGF, and GF-b1 were shown to be involved, similar to LIPUS, as well as proliferating cell nuclear antigen (PCNA), that indicates activity on DNA level [60]. Apart from delayed bone healing, ESWT is also used to treat conditions such as avascular necrosis, osteochondrosis dissecans, osteonecrosis, bone marrow edema, plantar fasciitis, Achilles tendinopathy, tendinitis calcarea, and calcifying tendinitis [59,61]. The shock waves are currently generated by a number of available biomaterials via electrohydraulic, piezoelectric, or electromagnetic mechanisms [59]. The technical details of ESWT depend on the specific device and are the same as for lithotripsy, as defined in the international standard IEC 61,846 [59,62]. As high energies and high contact pressures can cause damage, ESWT needs to be applied with caution [63,64]. Regarding active implants, the

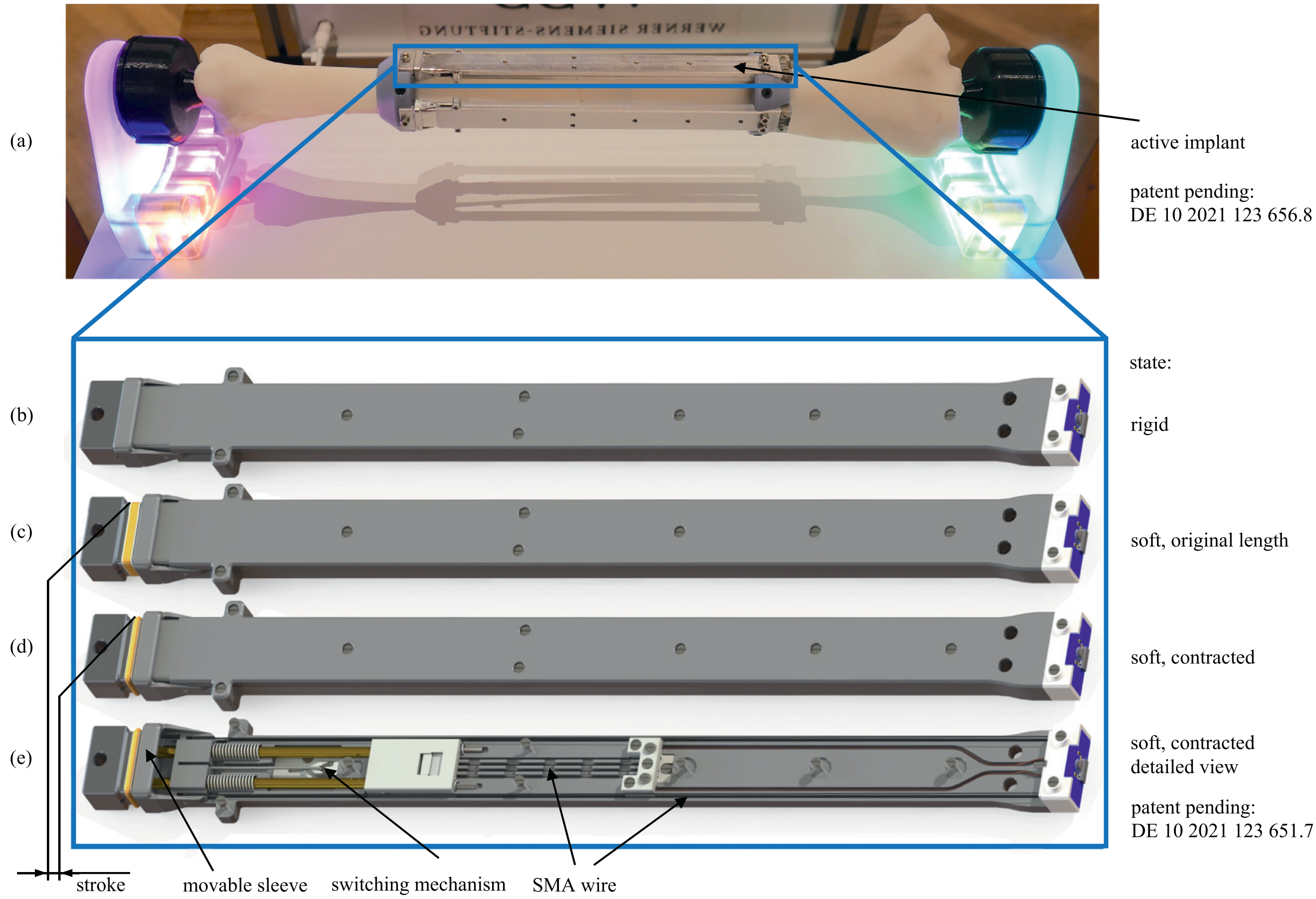

Fig. 2. Example mechanism of an active implant for the treatment of long bone fractures. (a) Early demonstrator of an SMA-wire-based active implant. (b) A movable sleeve can alter the mode of the implant from stiff to soft (two levels of stiffness) by either covering or releasing a soft silicon element. (c and d) When in soft mode, the implant has the capability to actively shorten via SMA wires. Springs will bring it back to its original length. (e) Detailed view of the shortening mechanism.

on-board application regimens and their applicability and efficacy would need to be elucidated, which is another major technological and regulatory challenge.

PEMF are applied in a range of settings to promote bone healing [65]. Patients usually do not feel the application. Common application regimens include an intensity of 0.1–2 mT, a frequency of 15–75 Hz, and a duration of 1–8 h daily [65,66]. While PEMF are usually generated by coils, also electrically active ceramics, such as piezoelectric ceramics and polarized hydroxyapatite have been shown to improve bone formation [66]. Electromagnetic stimulation has been shown to stimulate endothelial cell proliferation and capillary formation, leading to angiogenesis [67]. In addition, via TGF-β1 and BMP-2/4, osteogenesis and calcification, bone matrix formation and bone cell proliferation have been observed [67]. Furthermore, bone resorption is suppressed through activation of the Wnt3a/LRP5/ß-catenin and OPG/RANKL/RANK signaling pathways [66–69]. Small scaled coils would need to be integrated in an implant to generate these electromagnetic fields, but such a technological development has to date not yet been implemented as a solution for fracture plates or nails. Given the known benefits of PEMF for bone healing, clinical applications and possible use with implants for the treatment of nonunion in long bones should be explored.

In the development of internal devices using LIPUS, ESWT or PEMF, the external devices may be used as predicate devices for regulatory translation purposes.

4. Movement and strain in the fracture gap

If active implants were to act on the fracture gap, e.g., by shortening and lengthening, movement and strain in the fracture would need to be optimized. During normal walking, the healthy human tibia experiences extensive physiological deformation in vivo, namely medial bending of 0.38°–0.90°, posterior bending of 0.15°–1.30°, and external torsion of 0.67°–1.66° of the proximal in relation to the distal tibia [70,71]. Despite detailed loading instructions by the surgeon, patients, just as healthy test participants, are usually unable to control the load they put on the fractured leg [72–74]. This inability results in a high variation of ground reaction forces, strain and bone deformation independent of the given instruction. The mechanical environment of the fracture is mainly described by global mechanical factors, such as the gap size or the amount of interfragmentary movement (IFM) [40]. Tibia fractures not only heal in the presence of a relatively large amount of IFM [14,75], but it is also known that healing will not occur in the absence of movement or strain [76]. For example, patients with spinal cord injury have high rates of nonunion [77]. In many cases, depending on the local biomechanical properties, tibia fractures will even heal if treated in a brace, despite 1–4 mm of translation between fragments [78]. Increasing fracture gap sizes are known to lead to a longer duration of the healing process [1]. Comminuted fractures tolerate relatively greater motion, as the strain is applied over a larger distance of fracture fragments. For a given motion, this reduces the local strain [3].

There is clear evidence that in fracture healing, mechanical bone stimulation is superior to rigid fixation [15,76,79,80]. The 'strain window of opportunity' is the strain range that delivers the highest rate of healing [80]. Local interfragmentary strain can only be determined by finite element simulations, which serves to determine the best implant position and configuration, depending on the individual fracture geometry [82–86]. Smaller gap sizes require stiffer fixation and lower IFM [87]. The local strain, however, is currently not accessible to the surgeon. It would therefore be desirable to have finite element simulations based on individual computer tomography scans available to the surgeon to plan the surgery, ideally even directly in the operating theater [88,89]. Such individual simulations should take the temporal development of the bone mechanical properties during healing into account (Fig. 3). Even though theoretical models are available to simulate the healing process [90–93], their outcomes still need to be validated [94,95].

Axial compression seems to be beneficial for fracture healing and is mostly superior to translational shear or distraction [96–99]. A reasonable amount of IFM often comprises around 0.4–0.5 mm, depending on the size of the fracture gap [79,100]. The ideal amount of axial displacement, however, can, only be determined individually. A range of available and programmable IFM options would be desirable for an active implant to be able to adapt the active stimulation protocol to the individual biomechanical needs. Such programs need to consider the varying biomechanical situation throughout the course of healing.

Some authors have tried to define ideal forces in the fracture gap and came to the conclusion that 200 N of axial compression are better than 1000 N without further stratification [79]. Studies have also shown that loading forces between 300 N [11], 360 N [97] or 374–434 N [14] can be measured in the fracture gap during healthy healing. These values, however, need to be viewed with a lot of caution, as the local biomechanical milieu differs for each individual location in the fracture gap. In addition, the axial IFM near the cortex of the fracture decreases with the angle of obliquity, while shear IFM significantly increases with the angle of obliquity [101]. Because of such complexities, it seems to be desirable to run finite element simulations to compute the optimal individual forces. The forces should be applied by the active implant depending on the individual local situation, implant position, and the fracture geometry, rather than in a standardized stimulation program. Just as with IFM, the implant would thus ideally be able to provide a range of force options and should be programmed and configured based on computer simulations and according to the individual needs.

5. Timing and frequencies of stimulation via movement of an implant

Fracture healing occurs in four phases with differing biomechanical demands [102]. Rigid immobilization is best during the initial stages of healing, followed by the benefits of more dynamic fixation with intermittent compression during the later stages [100,103]. Within 2 weeks after fracture, the healing process is sensitive to small periods of daily strain applied axially [79]. In fracture treatment, implants such as femur or tibia nails are often dynamised towards the later stages of fracture healing to accommodate for these needs and improve results [44]. In addition, screws and plates have recently been designed in a way that their mechanical properties can change from "rigid" to "dynamic" over time throughout fracture healing [104,81]. The acceptable amount of weight bearing and the right timing depend on the fracture gap size: For relatively large fracture gap sizes, weight bearing is recommended to commence later as compared with smaller fracture gaps [105].

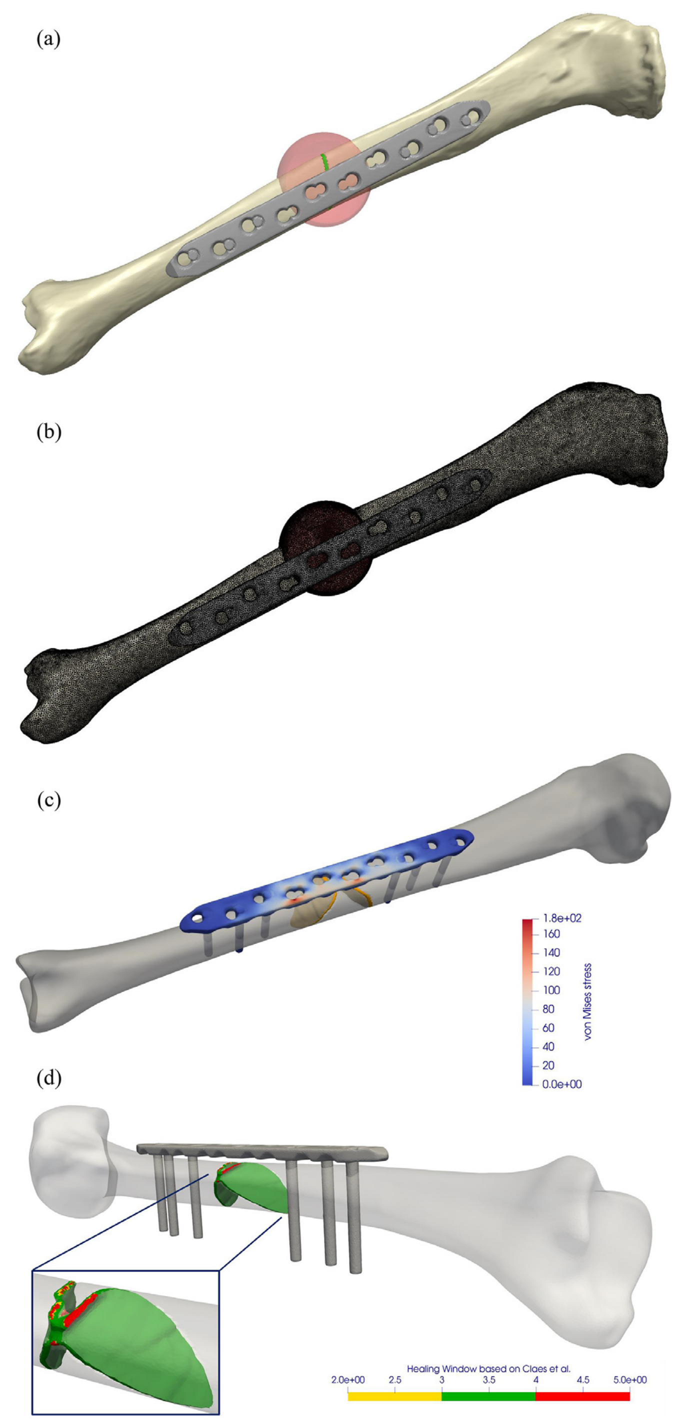

Fig. 3. Computer models (a) integrating a human tibia CT data set with CAD data of the implant (the red ball represents the fracture callus), (b) FEM mesh of the same bone with appropriate material parameters applied, (c) von Mises stress of the implant (fracture shown in orange) at 20 kg axial partial weight bearing, and (d) Claes strain window [1] color-coded in the fracture gap. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

Concerning stimulation frequencies for direct mechanical stimulation by movement of the implant, a large range seems to be beneficial for healing. Independent of the frequency, stimulation with any frequency delivers better results compared to no stimulation and rigid fixation [16]. Low-magnitude mechanical signals at 15–90 Hz have been shown to increase cancellous bone volume and trabecular number and thickness, as well as to enhance bone stiffness and strength [106]. However, the ideal frequency for fracture stimulation has not yet been identified. In many studies, 0.5–1 Hz were applied, as this range resembles the frequency of normal walking [15,79,80,97,100,107]. In merino sheep, Augat et al. [108] compared 1.5–10 Hz of external stimulation with nonuniform cyclic tensile strains and found that the frequency had no influence on the healing process. Even extremely low-magnitude (25 µm), high frequency (30 Hz) interfragmentary displacements were shown to lead to stiffer, stronger and larger callus compared to rigid fixation [16]. Stopping cyclic stimulation after 3 weeks into healing delivered worse results compared to continuous stimulation at 1 Hz over 6 weeks [107]. Apart from these direct modes of mechanical stimulation, also the very thigh frequency of LIPUS at 1.5 MHz has been shown to be beneficial for fracture healing when applied externally, while in ESWT, very low-frequency sets of individual shock waves are successfully applied, underlining the large spectrum of appropriate frequencies [51,59,60].

In addition to these considerations regarding the frequency, there is a lack of studies that compare patterns of the stimulation signal (e.g., triangular, sinusoidal, square, ramp, or other), and it is currently not known what is ideal and whether this pattern makes a relevant difference at all.

Based on these findings, we suggest further research that compares different frequencies to identify the optimum for fracture stimulation. As a general statement, however, it seems to be the case that a stimulation of any frequency seems to be superior to no stimulation at all. Just as with the optimal strain, there might be correlations with the properties of the fracture, such as the size of the fracture gap and its configuration. The ideal frequency could even vary throughout the phases of the healing process and differ between bones. The same could be true for the daily time span of stimulation.

6. Discussion

Nonunion of the long bones occurs in up to 14% of cases and is associated with a high socioeconomic burden. Active or even smart implants that stimulate the fracture site might be able to improve the healing rate of long bone fractures, reduce the incidence of bone healing problems, and facilitate recovery.

As outlined, among possible interventions to be implemented in active implants are active shortening and lengthening of the implant itself (e.g., plate or nail), as well as the delivery of pressure pulses, ultrasound waves, or electromagnetic fields via the implant. Biomaterials that have previously been used to apply these mechanisms externally include metals, piezoelectric crystals, and electrically active ceramics, such as piezoelectric ceramics and polarized hydroxyapatite. In case biomaterials are not biocompatible, they may be coated with biocompatible materials to make them implantable to the human body. Active intramedullary nails have been developed and tested but are not yet used in clinical practice. Prototypes include a micromotion-enabled intramedullary nail [109] and an active nail generating axial and shear forces [110]. Nitinol cardiovascular implants and nitinol implants for foot surgery have been developed, but are still rarely used clinically [25–28].

While accurate fracture stimulation via active shortening of the implant requires computer simulations of the individual fracture geometry based on CT data to obtain favourable effects [82-86,111], ultrasound, magnetic field and pulse wave stimulation could be applied without previous individual planning. It is, however, a technical challenge to embed the hardware in the implant, such as ultrasound or pulse wave emitters or coils to generate electromagnetic fields. These could possibly either be located in the implant itself or next to it, which is likely more feasible. Smart materials, such as shape memory alloys and dielectric elastomers, could help to design and minimize the size of devices [21-23,112-114]. In addition to providing innovative methods for biocompatible, highly integrated actuation mechanisms, these materials also feature inherent sensing properties, which will enable continuous monitoring in the future. In addition to these sensing and actuation mechanisms, composite materials with mechanical properties similar to those of bone are increasingly being used in implants and help to create more adaptive devices, including polymer blends and nanoscale particulate systems [115–117].

Voluntary and involuntary muscle contractions lead to a deformation of bone and thereby deliver stimuli for bone formation [70,118]. An active implant could in theory make use of this mechanism by using neuromuscular electrical stimulation (NMES) to stimulate fracture healing via muscle contractions. To do so, electrodes would need to be placed in the correct locations depending on the muscle and fracture locations and geometries, similar to when using NMES to counteract muscle atrophy [119]. NMES has been shown to enhance fracture healing in mice [120], but studies in humans are lacking. Before applying NMES to an active implant, however, it will be necessary to study the applicability and efficacy of NMES for fracture healing further. As initial findings seem promising, the authors consider NMES a future possible candidate for active implants.

In addition to the direct application of cyclic forces on the fracture via external fixators, ground-based vibration platforms have been used to stimulate fracture healing in experimental settings, however without much success [121]. In clinical practice, whole-body vibration therapy (WBV) via vibration platforms is used to improve balance and motor function for neurorehabilitation [122]. While in sheep trabecular tissue stiffness of the femoral condyle was shown to increase with WBV in the absence of a fracture [123], WBV did not seem to sufficiently increase bone mineral density in older people and patients with osteoporosis [124,125]. These findings seem to indicate that mechanical stimulation should ideally be applied directly at the fracture site to avoid absorption of stimuli in other tissues. Thereby, these findings support the approach of developing active implants that act exactly where the stimulus is needed.

Apart from these design considerations, an open question is whether the fracture site needs to be stimulated only in case of delays in fracture healing, or if a patient is at risk for nonunion, versus fracture stimulation by an active implant to accelerate fracture healing in patients not at risk of nonunion. This question implies that it is currently unknown if it is necessary to have a sensor component that measures the stiffness in the fracture and activates the intervention in case of delays, or if this is even superfluous, as everyone benefits from the intervention anyway. The benefit and harm of the possible interventions for patients not at risk of nonunion therefore urgently need to be studied. In any case, it seems to be best to place an active implant in the first place and not as a revision surgery, as we think that either active implants become so small and prove to have a benefit for all patients that they will be used for everyone, or that they will be used primarily in patients particularly at risk of nonunion.

In line with this question, it is of interest whether the named stimulation mechanisms increase risks in case of local infection. Nonunions are often associated with low-grade bacterial infection, even if this is not clinically obvious [126]. In patients with infected nonunion, external LIPUS application did not worsen results, but it was shown to support the healing, just as without an infection [47]. For shock wave therapy and magnetic field application, we found no such data, but also no evidence for adverse effects in case of infection.

In addition to improving fracture healing, another task for an active implant could be the protection of the fracture site from excessive forces. If the implant stiffness could be actively increased in case a pre-defined threshold in displacement is exceeded, the destruction of the newly formed and still fragile bone tissue could be avoided and healing promoted. To do so, a microprocessor would need to compute the sensor data and initiate the intervention. The requirements for such a mechanism might vary throughout the healing process, as we know that dynamic implants are more favourable than stiff implants toward the end of fracture healing [44,79,100,103].

In addition to these concepts and applications, active implants could also be used for limb lengthening, to correct bone deformities, and ideally even perform complex corrections in multiple directions [127,128]. Such interventions are often necessary in children with genetic bone defects or in reconstructive surgery [129,130]. The concept involves one or several osteotomies of the bone after application of the device and consequent slow correction to the desired configuration over several weeks or even months. The slow correction allows the surrounding tissues to adapt and lengthen accordingly while the bone heals following the correction path. Currently, the gold standard in the correction of bone deformities is the use of hexapod external fixation devices that are applied together with an osteotomy, such as the Taylor Spatial Frame [130]. These are, however, associated with patient discomfort because of the external frame, the necessity to make daily changes to perform the correction according to a pre-calculated plan, and the need to take care of the pins to avoid infection [131]. It would thus be a great improvement if multidirectional corrections could be performed via active implants under the skin on or inside the bone.

Despite the great progress that has been made in the systematic scientific and clinical treatment of fractures, a small but significant number of healing failures and nonunion still have to be accepted with the currently available implants and surgical strategies. The ability to intervene and modulate the local situation throughout the healing process, even after surgery, would take surgical fracture care to a new level. The next steps are the development of miniaturized internal devices for fracture stimulation, and *in-vivo* studies that compare the ability of the named mechanisms and settings to treat nonunion.

Conclusions

To avoid delayed healing and nonunion of long bones, active/smart implants could stimulate the fracture site by cyclic shortening and lengthening of the implant itself, as well as by emitting stimuli such as ultrasound waves, pressure waves, or electric fields, or by activating neuromuscular stimulation. Such smart implants could also protect the fracture site from excessive forces by increasing stiffness and they may be used to correct bone deformities. Further research is needed to compare different modes of stimulation and settings to find the ideal and most efficient intervention for active fracture stimulation by an implant. This particularly applies to the stimulation frequency and the ideal timing throughout the separate phases of fracture healing.

Funding sources

This work was supported by the Werner Siemens Foundation [Smart Implants 2.0].

Declaration of Competing Interest

TP is president elect and board member of the AO Foundation, Switzerland, and extended board member of the German Society of Orthopedic Trauma Surgery (DGU), the German Society of Orthopedic Surgery and Traumatology (DGOU), and the German Society of Surgery (DGCH). TP is also the speaker of the medical advisory board of the German Ministry of Defense. The other authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgements

None

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