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Review article

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Mechanical stimulation of distraction regenerate. Mini-review of current concepts

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Abstract

Introduction One of the key limitations of distraction osteogenesis (DO) is the absence or delayed formation of a callus in the distraction gap, which can ultimately prolong the duration of treatment. **Purpose** Multiple modalities of distraction regenerate (DR) stimulation are reviewed, with a focus on modulation of the mechanical environment required for DR formation and maturation. **Methods** Preparing the review, the scientific platforms such as PubMed, Scopus, ResearchGate, RSCI were used for information searching. Search words or word combinations were mechanical bone union stimulation; axial dynamization, distraction regenerate. **Results** Recent advances in mechanobiology prove the effectiveness of axial loading and mechanical stimulation during fracture healing. Further investigation is still required to develop the proper protocols and applications for invasive and non-invasive stimulation of the DR. Understanding the role of dynamization as a mechanical stimulation method is impossible without a consensus on the use of the terms and protocols involved. **Discussion** We propose to define Axial Dynamization as the ability to provide axial load at the bone regeneration site with minimal translation and bending strain. Axial Dynamization works and is most likely achieved through multiple mechanisms: direct stimulation of the tissues by axial cyclic strain and elimination of translation forces at the DR site by reducing the effects of the cantilever bending of the pins. **Conclusion** Axial Dynamization, along with other non-invasive methods of mechanical DR stimulation, should become a default component of limb-lengthening protocols.

Keywords: bone regeneration, mechanical stimulation, axial dynamization

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Обзорная статья

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Механические способы стимуляции дистракционного регенерата: мини-обзор современных концепций

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Аннотация

Введение. Серьезным ограничением применения дистракционного остеогенеза является риск отсутствия или задержки формирования дистракционного регенерата, что ведет к значительному увеличению сроков лечения аппаратом внешней фиксации. **Цель**. Рассмотреть различные способы стимуляции дистракционного регенерата (ДР) с акцентом на модуляцию механической среды, необходимой для формирования и созревания ДР. **Материалы и методы**. При подготовке обзора для поиска информации использованы научные платформы PubMed, Scopus, ResearchGate, RSCI. Поисковыми словами и словосочетаниями были: mechanical bone union stimulation, axial dynamization, distraction regenerate. **Результаты**. Последние достижения в области механобиологии доказывают эффективность осевой нагрузки и механической стимуляции образования костной мозоли при сращении переломов. Дальнейшие исследования требуют разработки надлежащих протоколов и способов применения инвазивной и неинвазивной стимуляции ДР. Понимание роли динамизации как метода механической стимуляции невозможно без консенсуса по использованию терминов и протоколов. **Обсуждение**. Мы предлагаем определять осевую динамизацию как возможность обеспечения осевой нагрузки на костный регенерат с минимальным смещением по ширине или изгибающими усилиями. Осевая динамизация может осуществляться через непосредственную стимуляцию регенерата осевыми циклическими нагрузками и исключением изгибающих и смещающих усилий. **Заключение**. Осевая динамизация наряду с другими неинвазивными методами механической стимуляции дистракционного регенерата должна стать стандартным компонентом протоколов удлинения конечностей.

Ключевые слова: костная регенерация, механическая стимуляция, осевая динамизация

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INTRODUCTION

Introduced by G.A. Ilizarov, the principles of distraction osteogenesis (DO) are now used to lengthen and reconstruct limbs to help treat multiple orthopedic conditions, both congenital and acquired [1-3]. However, several challenges remain during its clinical application, including long treatment duration. Extended time in an external fixator exponentially increases the risk of complications [3-8]. Due to long treatment time spent in a frame, “patients may have non-surgical problems, such as social, domestic, educational, and psychological problems, as well as problems that may be cared for by the nursing and physiotherapy staff” [9]. Treatment is often long because the distraction regenerate (DR) must mature enough to withstand weight-bearing. The process is often further prolonged due to delayed consolidation and/or the development of pathologic distraction regenerate [10, 11].

In an effort to decrease fixation time, multiple research efforts are currently focused on stimulating DR maturation utilizing different methods. Proposed solutions include biological stimulation of the regenerate, pharmacological stimulation, physical stimulation, and any combination of the above (Table 1). All these solutions can be performed using invasive (through various surgical interventions) and non-invasive approaches.

Table 1

Various modalities to stimulate distraction regenerate

Distraction Regenerate Stimulation		
Physical	**Biological**	**Pharmacological**
Mechanical (see below)	Grafts [12-14]	Vitamins [15-17]
Ultrasound [18-21]	Bone marrow and PRP [22, 23]	Biometals [24, 25]
Hyperbaric oxygen therapy [26, 27]	BMPs [28, 29]	Supplements [30, 31]
Electromagnetic 21, 32, 33]	Growth factors [34, 35]	Bisphosphonates [36-38]
Laser therapy [39, 40]	Cell therapy [41-43]	

Mechanical stimulation is the foundation of the entire DO process. During the distraction phase of limb lengthening, tension stress affects all tissues inside and surrounding the distraction gap [44]. The mechanobiological phenomena of DR formation during the DO process essentially prolong the body's evolutionary-developed mechanism of fracture healing, where tension stress stimulates connective tissue proliferation, cell differentiation, and angiogenesis. Both angiogenesis and a proper mechanical environment are necessary for successful bone regeneration during DO [45, 46]. As the distraction forces are seized, bone resorption and remodeling take place to convert DR into a mature bone structure that is capable of bearing a physical load [47]. Known as the consolidation stage, this is the longest phase in the DO process, where different mechanical DR stimulation techniques are typically applied.

All known mechanical stimuli can be divided into invasive (surgical) and non-invasive techniques (Fig. 1).

Historically, mechanical stimulation techniques were applied following an abnormal formation of DR in an effort to fight the so-called delayed consolidation. However, there has recently been a shift towards a prophylactic application of mechanical stimulation to accelerate the consolidation and avoid delayed consolidation all together.

The goal of this work is to review the current methods of reducing treatment time during limb-lengthening procedures, with a particular interest on the use of mechanical stimulation to promote maturation of the distraction regenerate.

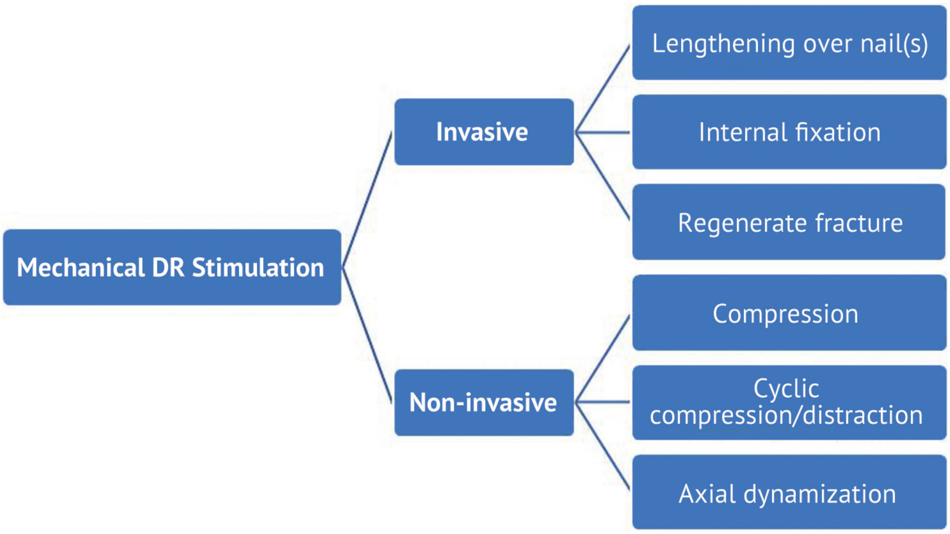

Fig. 1 Various techniques of mechanical stimulation of the distraction regenerate

MATERIAL AND METHODS

We summarize recently (no more than 30 years) published studies about definition, classification, indications and clinical application of methods for mechanical stimulation of bone healing in lengthening procedures. To prepare the review, we searched for information sources at the scientific platforms such as Web of Science, PubMed, Scopus, ResearchGate, RSCI, as well as other published products (Elsevier, Springer) using search words or word constructions: bone lengthening, Ilizarov method, mechanical stimulation of bone healing, dynamization, external frame, clinical translation.

RESULTS AND DISCUSSION

Invasive (surgical) mechanical stimulation

Most surgical methods that involve a change to the mechanical environment are performed at the end of the consolidation stage as a response to delayed consolidation problems. These techniques include plating or intramedullary fixation after lengthening [4]. In most cases, these techniques are considered desperate measures to avoid a regenerate fracture after frame removal. Another desperate technique involving surgical stimulation of the pathologic distraction regenerate relies on performing a fracture through the DR site. The fracture helps re-stimulate fracture healing mechanisms, initiate additional angiogenesis, and re-introduce growth and biological stimuli supplied to the pathologic regenerate. A new development, introduced by Popkov et al. [48], uses a prophylactic placement of intramedullary devices during the initial surgery. This provides extra stability during distraction, as well as creates an environment to recruit additional biological factors for DR maturation. They also illustrated that the use of HA-coated implants increases the effect of DR stimulation [49].

Non-invasive mechanical modulation

Non-invasive mechanical stimulation can be performed in various ways: weight-bearing [46, 50], cyclic compression/distraction (accordion technique) [51-53], destabilization of the frame by releasing nuts on threaded rods, destabilization of the frame by removing fixation elements (wires and pins), and replacing threaded rods with dynamization devices.

Weight-bearing

Since the very first application of the Ilizarov circular fixator, lower limb lengthening has required at least partial weight-bearing as part of the process. Ilizarov listed weight-bearing as a categorically required part of leg lengthening [2]. There are multiple papers emphasizing the positive effect of lower extremity loading during DO treatment for DR maturation and remodeling. It is also the least costly method to mechanically stimulate the regenerate. The only consideration must be patient education and compliance, as a majority of non-invasive DR stimulation techniques rely on patient weight-bearing to be effective [50, 54].

Compression

Compression of the DR is often another desperate measure to solve poor regeneration. It is usually performed during the lengthening stage, when the distraction interzone does not progressively display signs of mineralization on X-rays, or at the consolidation stage, when there are no signs of improvement at the lengthening site [55, 56]. There are two important points to consider. First, patient preparation and education are necessary as the planned amount of lengthening may not be achieved. Second, the shape of the pathologic regenerate must be considered when a fully mineralized cortex on one side of the bone is present [57, 58]. This is commonly known as a regenerate cyst. The cyst prevents any ability to compress the DR and can ultimately cause the development of a deformity, either during compression or later following frame removal. Similar problems can arise from the premature mineralization of the fibula in cases of tibial lengthening. This occurs when the tibial regenerate lags behind, resulting in the fibula acting as a strut that shields the tibia from necessary axial loading. In these cases, early surgical intervention may salvage the lengthening by breaking through the thin mineralized band of regenerate or the prematurely consolidating fibula along with the use of various grafting techniques. An acute compression performed at the end of distraction phase with compression tension of 5.6 N/cm^2 is considered as optimal for bone healing stimulation [59].

Cyclic compression/distraction

Ilizarov was the first to suggest the use of alternating cycles of distraction and compression to improve the quality of bone formation in the distraction gap [2]. Under the optimal frame stability, patient's weight-bearing creates alternating distraction/compression (ADC) forces at the lengthening site as part of the DO process. Therefore, it is logical that the ADC forces created on a fixation device might further improve regeneration. This practice was later named as an accordion maneuver [53] and widely reported as a treatment for poor regenerate [51, 60-63]. Liu et al. [52] performed impressive animal studies to uncover the underlying mechanisms of ADC. The studies showed an improvement of bone formation during DO, suggesting that better outcomes may be achieved by moderately increasing the amplitude and slowing down the rate of the ADC technique [52].

Axial Dynamization

For many years, rigid fixation with internal or external devices was the paradigm of fracture treatment. However, recent advances in our understanding of bone healing and mechanotransduction suggest that systematically altering the construct's stiffness throughout different phases of healing improves regeneration [64-66]. Dynamization has recently become a buzz word in multiple DO publications; however, there are some problems regarding terminology and definitions. Multiple terms that describe DR dynamization are ill-defined and ambiguous at the present. Starting with dynamization itself – multiple publications currently describe different techniques of bone healing stimulation under the same term.

The term dynamization is described as "the transfer of a progressive load to the fracture site at a given point in the healing cycle" [67]. Nowadays, dynamization encompasses many different methods of altering the fixation of fractures as the bone heals [68], such as decreasing the external fixator's stiffness during the healing process by removing stabilizing elements [69]. A new concept of "reverse dynamization" was also recently introduced by Glatt et al., where frame destabilization is performed during the early stages of fracture healing (during the first week after the initial fixation) to produce a larger volume of newly formed callus. The frame instability is reversed to a more rigid fixation after 3-4 weeks to, in theory, encourage blood vessel growth within the callus. Reverse dynamization somewhat contradicts the original Ilizarov idea that frame stability plays an important role in bone healing [1, 2]. In contrast to the intramembranous ossification described by Ilizarov, reverse dynamization generates a large volume of bone callus, possibly through endochondral and trans-chondral types of ossification.

Many other vague terms are often used in conjunction with dynamization to describe the mechanical stimulation of the distraction regenerate, including but not limited to stable fixation, rigid fixation, and micromotion. First, the term micromotion should be avoided in scientific literature. The physiologic load of an external fixator typical configuration can lead to an axial displacement of bone fragments away beyond 3 mm [70]. This amount of fragment displacement cannot be described as micro [71]. Secondly, we propose that rigid fixation be reserved to describe stabilization without any meaningful load on the bone healing site, essentially inhibiting the mechanobiological processes necessary for optimal bone regeneration as fixation is too rigid. In contrast, stable fixation of bone fragments minimizes the amount of shear and bending strains at the fracture or lengthening site, while still allowing for some axial loading to promote bone regeneration.

Dynamization should only describe and be used interchangeably with Axial Dynamization. We propose to define Axial Dynamization as the ability to provide axial load at the bone regeneration site with minimal translation and bending strain. Shear and bending strains are both undesirable forces, whereas axial loading and unloading promote regeneration [2]. However, it remains doubtful that most modern external fixator assemblies will be able to entirely eliminate all instances of bending strain [70]. The original fixator developed by Ilizarov incorporates built-in Axial Dynamization with the use of thin wires only, which act as a fixed beam bending when under a load. As a result, the frame provides some axial displacement of bone fragments during weight-bearing [72]. Extended use of half-pins in modern external fixators has increased frame rigidity and replaced fixed beam bending with cantilever bending, which ultimately creates undesirable bending and translation forces.

There are many other methods of altering fixation stability that should not be considered dynamization, including removing stabilizing elements of the fixation device, destabilizing connecting elements of the fixator, or removing some of the external fixation pins and wires. These methods would be better named as partial fixation removal or fixator destabilization.

When applying dynamization, simply untightening the nuts of the fixator connecting rods, will not provide the proper conditions to eliminate shear and bending strains. Instead, the best way to dynamize is with spring-loaded devices or elastic washers to provide axial loading with a dampening effect. An example of such dynamization would involve mounting the original De Bastiani dynamization washer [67] or a spring-loaded device between the external fixator rings [70]. Use of such spring-loaded dynamization devices not only stimulates bone healing but also improves patient comfort, allowing better weight-bearing and indirectly improving the healing process [70].

Axial Dynamization works [73, 74] and is most likely achieved through multiple mechanisms: direct stimulation of tissues by axial cyclic strain and elimination of translation forces at the DR site by reducing the effects of the cantilever bending of the pins. However, it remains unclear when dynamization should be applied during limb lengthening. Frames are traditionally dynamized at the end of the consolidation period before the external fixator is removed. Nonetheless, we have started dynamizing frames earlier, at around 3-4 weeks after lengthening is complete. There is also an argument to initiate dynamization during the distraction period to mimic the effects of all-wire frames, which include properties of built-in dynamization as previously stated. Introducing dynamization during the early distraction period would likely result in a mechanical environment similar to the traditional all-wire fixator developed by Ilizarov and ultimately help develop better DR. However, it must be noted that dynamization also depends upon the patient putting weight on the treated extremity, which could be a challenge during the early stages of limb lengthening. Whereas late dynamization performed during the consolidation period would actually improve patient comfort by reducing the cantilever bending of the fixator pins and providing a dampening effect. This would allow for more weight-bearing and physiologic walking that will help stimulate DR maturation.

Advancements in automated distraction will possibly allow for a more frequent rhythm of distraction, plus the ability to use passive Axial Dynamization techniques alongside frequent patient-independent cycles of compression/distraction.

CONCLUSION

Mechanical stimulation is the most accessible and usually most affordable way to speed-up the mineralization of the distraction regenerate. Multiple publications prove the effectiveness of mechanical modulation techniques involved in DO for improving the conditions of bone healing. Non-invasive techniques of DR mechanical stimulation should become a default component of the limb-lengthening procedure, rather than reserved to rescue pathologic regeneration and delayed consolidation. Axial Dynamization using spring-loaded or elastic devices proves effective in achieving cyclic axial loading, while minimizing shear and bending forces on the regenerate. There is a need for a consensus on the definitions and protocols that surround Axial Dynamization. Therefore, additional research is needed to develop the protocols and process of Axial Dynamization, which will most likely involve incorporating a combination of early and late dynamization techniques into the treatment of limb lengthening.

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