Bone Remodeling and Mechanobiology Around Implants: Insights From Small Animal Imaging

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ABSTRACT: Anchorage of orthopedic implants depends on the interfacial bonding between the implant and the host bone as well as on the mass and microstructure of peri-implant bone, with all these factors being continuously regulated by the biological process of bone (re)modeling. In osteoporotic bone, implant integration may be jeopardized not only by lower peri-implant bone quality but also by reduced intrinsic regeneration ability. The first aim of this review is to provide a critical overview of the influence of osteoporosis on bone regeneration post-implantation. Mechanical stimulation can trigger bone formation and inhibit bone resorption; thus, judicious administration of mechanical loading can be used as an effective non-pharmacological treatment to enhance implant anchorage. Our second aim is to report recent achievements on the application of external mechanical stimulation to improve the quantity of peri-implant bone. The review focuses on peri-implant bone changes in osteoporotic conditions and following mechanical loading, prevalently using small animals and in vivo monitoring approaches. We intend to demonstrate the necessity to reveal new biological information on peri-implant bone mechanobiology to better target implant anchorage and fracture fixation in osteoporotic conditions. © 2017 Orthopaedic Research Society. Published by Wiley Periodicals, Inc. J Orthop Res

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Orthopedic implants are used in different applications ranging from temporary fixation of fractures to permanent replacement of damaged bones, joints and teeth. Despite high success rates in healthy individuals, the integration and stability of implants is still receiving considerable attention as, among the millions of implantation procedures yearly performed, implant insertion in aged persons or in patients with bone diseases is constantly raising.[1–3] One predominant skeletal disorders is osteoporosis,[4] with typical consequences being a substantial loss of bone mass[5] accompanied by a deterioration of bone architecture and material properties, [6,7] consequently increasing fracture probability.[8] Clear-cut clinical evidence that osteoporosis has a negative impact on implantation is still lacking.[9,10] Nevertheless, biomechanical experiments suggest that implant anchorage may be compromised in osteoporotic bone.[11–14]

Initial implant stability is of paramount importance for the biological events following implantation and leading to osseointegration, defined as direct formation of bone tissue in contact with the implant.[15,16] Once osseointegration is achieved, the long-term stability of the implant is maintained by bone remodeling,[17] traditionally described as bone resorption followed by formation at the same site. Implantation also triggers reconfiguration of the peri-implant bone, which has to adapt to new loading patterns. This requires bone formation and resorption to happen at different locations, a process called bone modeling. It is customary, particularly in the biomechanics community, to refer to all processes involving bone formation and resorption with the term bone (re)modeling. It is well accepted that (re) modeling is mechanically driven, with local bone formation and resorption taking place at sites of high and low tissue strains, respectively.[18–20] Thanks to a finely-tuned mechanosensory system, mechanical loading have a strong anabolic effect, particularly in healthy bone.[21] The response of load-bearing musculoskeletal tissues to external loading has been attracting considerable attention, and the term mechanobiology has been introduced to describe it.

Most of previous knowledge on osseointegration and the effect of loading on this process is based on analysis of joint prostheses[22,23] and dental implants.[24] Those studies have highlighted the potential of mechanical stimulation to promote early implant osteogenesis.[17] However, there are still clinically relevant concerns related to earliest time, magnitude and frequency of the applied stimulation.[25–28] Moreover, implantation is often performed in aged or osteoporotic bones, which seem to have a reduced "mechano-responsiveness,"[18,29] thus suggesting that higher mechanical stimulation may be required to produce a relevant anabolic response. Nevertheless, high loads can cause the formation of weak fibrous tissues rather than bone, at the bone-implant interface.[30]

The main goal of the present review is to summarize current knowledge on tissue-level peri-implant bone (re)modeling and mechanobiology. Among the vast literature, priority is given to studies using small animal models to evaluate the response of osteopenic bone to implant placement, and to investigate the effect of external mechanical stimulation on implant osseointegration and peri-implant bone adaptation. Even if small animals do not exhibit (re)modeling

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patterns similar to humans (e.g., they lack osteons), they allow well controlled mechanobiological experiments which, in combination with in vivo imaging, can improve our understanding of peri-implant bone regeneration.

BONE REGENERATION AT THE TISSUE LEVEL

Bone regeneration around implants is a highly complex and dynamic biological event. Here, we briefly summarize the main features of this process, focusing on tissue-level modifications in peri-implant bone (re) modeling. A detailed description of the biology of bone regeneration can be found elsewhere.[15,17,31–33] The first event after implantation is the absorption of proteins on the implant surface,[34] followed by the migration of inflammatory cells. A pivotal step of osseointegration occurs when osteoprogenitor cells deposit a layer of non-collagenous proteins on the implant surface.[17] Such a layer is believed to favor bonding between bone and implant and to govern the properties of the bone-implant interface.[34] When osteoprogenitor cells differentiate into osteoblasts, bone formation starts. The final amount of bone around an implant strongly depends on implant location and bone compartment. Usually cortical bone shows higher level of osseointegration[35] but trabecular bone has faster healing kinetics.[36]

Measurements of Bone Response to Implantation

The most common approaches to characterize tissue-level response to implantation are histology, backscattered scanning electron (BSE) imaging and micro-computed tomography (micro-CT). Histology is a two-dimensional (2D) method requiring fairly thin (i.e., $<50\,\mu m$) sections, which can be challenging in the presence of a metallic implant.[37] It allows the quantification of both static and dynamic parameters. It also provides direct information about different tissues around the implant.[30] BSE is a 2D technique based on electron microscopy, which is widely used to measure osseointegration in terms of bone-implant contact (BIC). Sample preparation for BSE is somewhat easier than for histology as thin sections are not required.[37] Previous studies using BSE contributed to understand the mechanisms of bone ingrowth into porous coated implants,[23,38,39] and BSE is now considered the gold standard to quantify osseointegration in vitro. To overcome the 2D and destructive nature of histology and BSE, micro-CT has been used as alternative, also applicable in vivo.[40] This X-ray based technique offers three-dimensional (3D) and non-destructive characterization of peri-implant bone microstructure and requires minimal sample preparation. However, it can be problematic to investigate the interface between bone and a metallic implant. This stems both from beam hardening and increased X-ray scattering caused by the high absorption of the metallic implant. As a result, voxels located in the proximity of the implant have artificially high grey values, leading to a systematic overestimation of BIC.[41,42] Although metal artifacts can be minimized by image processing,[13] there is a zone around a metallic implant which should not be analyzed. Depending on scanning parameters and implant properties, exclusion zones ranging from 50 to 1,500 μm have been reported.[42,43]

When assessing bone response to implantation, it is convenient to distinguish three regions: The bone-implant interface, the peri-implant bone and the host bone.[38] Typically, the bone-implant interface has a thickness of less than $1\,\mu m$[34,44] and is the location where multiple biological events, leading to osseointegration, take place. Implantation causes bone microdamage up to several hundreds of micrometers away from the implant[45,46] and one definition of peri-implant bone could be the region which is damaged by implant insertion.[45,46] Host bone is the intact bone not directly affected by implantation. Generally, micro-CT cannot analyze osseointegration at the interface between bone and (metal) implants but can be used to obtain valuable information on peri-implant as well as on host bone, as explained in the next section.

Time-Lapsed Imaging of Bone Response to Implantation

During and after osseointegration, the bone around an implant undergoes continue (re)modeling, triggered by the need to remove microdamage and to accommodate the implant. The introduction of time-lapsed in vivo micro-CT has provided a new option to analyze dynamic processes in living bone, including (re)modeling and mineralization.[21,47,48] In vivo micro-CT has also been used to monitor the time course of peri-implant bone (re)modeling and microstructure. Li and colleagues[43] analyzed the caudal vertebra of mice weekly for 6 weeks after implant placement (Fig. 1).[43] Large differences in (re)modeling rates were observed when comparing locations close (i.e., $<0.5\,mm$) and far from the implant, with the highest bone formation rate measured close to the implant in the first 2 weeks after implantation. A transient increase in peri-implant bone formation has been observed also by Irish and coworkers[49] in a dynamic histomorphometry study on rats receiving intramedullary femoral implants. The elevated formation rates following implantation reflect the well-established "regional acceleratory phenomenon" reported by Frost to describe the response of tissues to surgical insult.[50] In vivo micro-CT also allows characterizing the rate of bone resorption, which is not accessible with histomorphometry. Elevated resorption rates have been observed in the implanted caudal vertebrae, with the tendency to be less localized around the implant and being sustained for a longer time interval than formation rates.[43] A possible explanation for high bone resorption is the need to remove microdamage produced by implantation.[45]

(Re)modeling in heathy bone triggers microstructural changes which favor implant anchorage.[43,51] Whether such ability is still present in osteoporotic bone will be discussed in the next section.

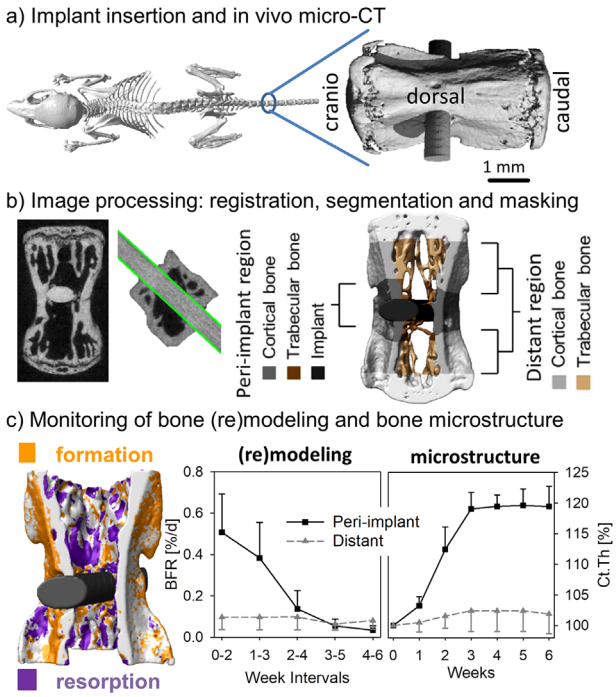

Figure 1. Overview of the different steps necessary to perform in vivo monitoring of peri-implant bone changes with micro-CT. (a) Implantation is performed in mice caudal vertebra. (b) After image acquisition, image processing involved registration of subsequent scans, segmentation of bone/implant system and identifications of different regions to be analyzed. (c) Three-dimensional visualization (left) of local bone formation and resorption events in the implanted bone. Corresponding in vivo quantification (right) of peri-implant (re)modeling (bone formation rate, BFR) and microstructure (cortical thickness, Ct.Th). Figures modified from[43,51] with permission.

INFLUENCE OF OSTEOPOROSIS ON BONE REGENERATION

Here, we summarize recent investigations of bone response after implantation in animal models of osteoporosis (Table 1). The emphasis will be again on microstructural and (re)modeling behavior at the tissue level (Fig. 2), mainly focusing on small animals like mice and rats. These models lend themselves well to study osteoporosis-like bone loss using ovariectomy (OVX) or orchiectomy (ORX) as well as to image their entire bones with longitudinal monitoring approaches. Studies involving larger animals have higher clinical relevance as human implants can be used. Nevertheless, high-resolution in vivo imaging is also similarly challenging as in humans. Being more demanding and involving higher costs, they are less common than small animal models and usually have limited sample size.[52]

Osseointegration at the Bone-Implant Interface

The most used measure of osseointegration is the bone-to-implant contact (BIC), traditionally assessed with histology or BSE. Numerous studies compared BIC between healthy and osteopenic animals from 1 week to several months after implantation. Different skeletal locations have been investigated, the most common being: Proximal tibia,[53,54] distal femur,[55] femoral condyle,[56] jaw bone,[57] and medullary canal.[58,59] Implants which are placed transcortically (i.e., through the cortex into trabecular bone) allow investigating the contribution of both cortical and trabecular bone to osseointegration and are commonly used to characterize the effects of osteopenia on osseointegration.[53,60,61] Insertion into the medullary canal (through the knee joint) is suited to model joint prostheses and has been adopted to assess the outcome of pharmaceutical options.[59,62] Most of those implant models are not weight-bearing and are therefore better suited to describe initial fixation rather than the long term outcome of implantation.[52]

The majority of the literature seems to agree that absolute values of BIC are significantly lower in OVX/ORX than in control animals. Differences in BIC between osteopenic and control animals are particularly marked in trabecular bone (see Fig. 2a and b). Usually, they are higher in the first weeks after implant insertion and diminish in later time points. BIC within the cortical compartment seems to be less affect by OVX or ORX surgery.[60,61]

Microstructural Modification of Peri-Implant Bone

The amount of bone in the peri-implant region is commonly measured in three-dimension as bone volume to tissue volume (BV/TV) or in two-dimension as bone area fraction (BF). It is well accepted that osteopenic animals display reduced peri-implant bone volume when compared to control groups (see Fig. 2c).[49,54,58,63–66] Likewise, those animals have deteriorated peri-implant bone microarchitectures. [51,64,67] Clearly, structurally deteriorated bones have a negative biomechanical impact on implant anchorage.[11–13] Conversely, the role of osteopenic conditions on the microstructural changes taking place after implantation is less clear. The time course of peri-implant bone microstructure has been detailed with longitudinal micro-CT: metal-ceramics implants[43] were inserted into the sixth caudal vertebra of OVX and sham-operated (SHM) mice and bone response was measured weekly for 6 weeks. The study demonstrated that not only OVX animals had initially lower BV/TV and cortical thickness (Ct.Th) than SHM, but also that the time courses of osseointegration in these two groups where different, with OVX mice having a reduced ability to augment Ct.Th of peri-implant bone (Fig. 2d).[51]

Peri-Implant Bone (Re)Modeling

Current studies on peri-implant bone (re)modeling in osteoporotic small animal models are sparse and not conclusive. Irish and colleagues[49] compared (re)modeling in OVX and SHM rats. Animals received intramedullary femoral implants and were sacrificed at 4, 8, and 12 weeks post-implantation to evaluate (re)modeling with dynamic histomorphometry. Implant placement increased peri-implant bone formation rates

Table 1. Studies of Peri-Implant Bone Regeneration in Small Animal Models of Osteoporosis

Study	Animal Model	Implantation Site	Method	Bone Architecture	Bone Remodeling	Study Period
Zhang et al.[55]	OVX mice	Distal femur	Static histomorphometry	BIC, BV/TV	–	2 weeks
Li et al.[51]	OVX mice	Caudal vertebra	In vivo micro-CT	BV/TV, Ct.Th	BFR, BRR	0–6 weeks
Giro et al.[57]	OVX rats	Jaw bone	Static histomorphometry	BIC	–	9 weeks
Alghamdi et al.[56]	OVX rats	Femoral condyle	Ex vivo micro-CT, static histomorphometry	BIC, BA	–	12 weeks
Alghamdi et al.[63]	OVX and ORX rats	Femoral condyle	In vivo micro-CT	BV/TV, Tb.Th, Tb.N, Tb.Sp	–	4–6 weeks
Kettenberger et al.[71]	OVX rats	Femoral condyle	In vivo micro-CT	BV/TV, Tb.Th, Tb.N, Tb.Sp	BFR, BRR	0–8 weeks
Virdi et al.[58]	OVX rats	Femoral medullary canal	Ex vivo micro-CT, dynamic histomorphometry	BIC, BV/TV, Ct.Th	BFR, ES	4–12 weeks
Kurth et al.[59]	OVX rats	Femoral medullary canal	Static histomorphometry	BIC	–	4 weeks
Irish et al.[49]	OVX rats	Femoral medullary canal	Ex vivo micro-CT, dynamic histomorphometry	BV/TV, Tb.Th, Tb.N, Tb.Sp, Ct.Ar	BFR, MS, MAR, ES	4–12 weeks
Yamazaki et al.[53]	OVX rats	Proximal tibia	Static histomorphometry	BIC	–	1–24 weeks
Du et al.[54]	OVX rats	Proximal tibia	Static histomorphometry	BIC, BA	–	4–12 weeks
Duarte et al.[61]	OVX rats	Tibia	Static histomorphometry	BIC, BA	–	8 weeks
Vidigal et al.[70]	OVX rabbits	Proximal tibia	Static histomorphometry	BIC	–	12 weeks

OVX, ovariectomized; ORX, orchiectomized; micro-CT, micro-computed tomography; BIC, bone-to-implant contact; BV/TV, trabecular bone volume fraction; BA, peri-implant bone area; Tb.Th, Trabecular thickness; Tb.N, trabecular number; Tb.Sp, Trabecular separation; Ct.Ar, Cortical area; BFR, bone formation rate; BRR, bone resorption rate; ES, eroded surface; MS, mineralizing surface; MAR, mineral appostition rate.

transiently in both SHM and OVX animals; however, no evidence was found that peri-implant (re)modeling was different between normal and osteopenic bone. Others, using molecular analysis combined with static histomorphometry, have indicated the possible influence of ovariectomy on peri-implant (re)modeling to be confined to immediate (2 days)[68] or early (up to 4 weeks)[69] stages of implant osseointegration; at later time points no differences in (re)modeling behavior shall be expected. There is large evidence, however, that peri-implant bone in osteopenic animals is less responsive than healthy bone to treatments for augmenting implant fixation.[53,58,59,70] This calls for an improved understanding of the interaction between (re)modeling and osteopenia in the process of bone regeneration.

The difference in peri-implant bone (re)modeling between OVX and SHM can be elucidated with longitudinal imaging. As mentioned in the previous section (Microstructural Modification of Peri-Implant Bone), Li et al.[51] monitored peri-implant bone formation and resorption using in vivo micro-CT (Fig. 2f). The authors were able to attribute the lower increase in peri-implant cortical thickness observed in OVX mice in comparison to SHM (Fig. 2d) to impaired peri-implant bone formation. With a similar in vivo approach, Kettenberger et al.[71] investigated the impact of locally delivered bisphosphonates on peri-implant bone remodeling in the femur of OVX rats (Fig. 2e). They demonstrated a dual effect of the medication: A factor of 2 increase in formation and almost a factor of 10 decrease in resorption.

In addition to pharmacological treatments,[52] mechanical loading is unanimously considered an alternative to pharmaceutical interventions to augment bone mass. Its impact on per-implant bone regeneration and implant osseointegration will be discussed in the next section.

EFFECT OF MECHANICAL LOADING ON BONE REGENERATION

At the tissue level, several animal studies demonstrated that mechanical stimuli have a dual effect: Enhance bone formation and inhibit bone resorption, thereby leading to an overall increase of bone mass.[18,20,21] There is evidence that aging and estrogen removal cause dysregulation in the mechanical control of bone (re)modeling, resulting in decreased sensitivity to mechanical stimulation.[18,19] There are also concerns that implantation surgery as well as

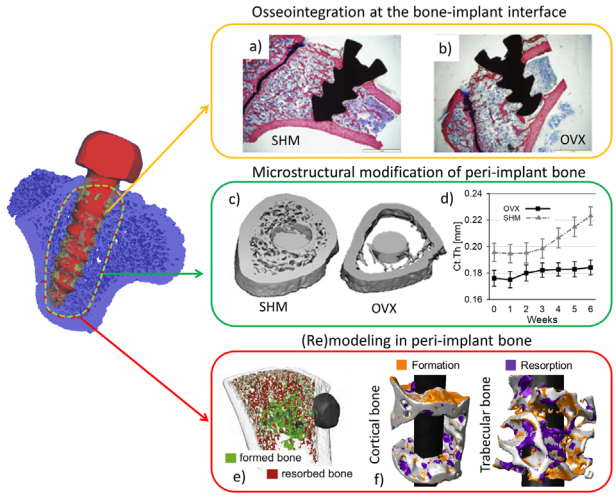

Figure 2. Summary of different tissue-level aspects of peri-implant bone regeneration considered in the present review. Starting from the bone-implant system (left, image courtesy of Y. Gabet and H. van Lenthe, ETH Zurich), the response of bone after implantation is characterized in terms of (i) amount of bone at the bone-implant interface, typically measured with histology or BSE (a and b); (ii) microstructural modifications within peri-implant bone measured with ex vivo (c) or in vivo (d) micro-CT; and (iii) bone (re)modeling (both formation and resorption) around the implant assessed with longitudinal in vivo micro-CT in rats (e) and mice (f). Figures modified from [51,54,58,71] with permission.

the presence of the implant may alter the mechanobiology of peri-implant bone, causing a different response to mechanical loading than bone without an implant.[25]

This section summarizes recent efforts to understand peri-implant bone behavior following in vivo controlled mechanical stimulation in small animal models (Table 2). Three different modalities to administer mechanical loading are considered: (i) loading applied directly to the implant (Fig. 3a); (ii) selective local stimulation of single implanted bone through loads applied via adjacent bones or joints (Fig. 3b); and (iii) generalized whole body loading, commonly in the form of either high or low frequency vibrations (Fig. 3c).

Mechanical Loading Applied Directly to the Implant

This loading option has been extensively investigated in the context of orthodontic implant fixation,[72–74] with the final aim to increase bonding strength at the bone-implant interface. One of the biggest concerns when loading implants is the effect of micromotion on the process of osseointegration, and several pioneering studies investigated this critical aspect.[75–78] The work of Søballe et al.,[75] for instance, analyzed the impact of micromotion on trabecular bone ingrowth into porous coated implants placed into the femoral condyle of dogs. The authors designed special implants that could be loaded during gait cycle allowing for 500 μm of axial displacement and compared bone response against mechanically stable implants. The latter showed the strongest anchorage and the greatest amount of ingrowth, thus suggesting that a micromotion of 500 μm is too high to allow osseointegration. The authors also noticed that unstable hydroxyapatite-coated implants were surrounded by fibrocartilage whereas unstable titanium-coated implants were not. In a subsequent work, the same group demonstrated that hindering micromotion allowed the replacement of fibrocartilage (formed during unstable growth) into bone.[76] Another system which is particularly suited to investigate the effect of micromotion is the so-called bone chamber, characterized by the absence of an initial contact between implant and host bone.[79] Leucht et al.[30] used an in vivo bone chamber model to assess the role of mechanical stimuli on de novo bone formation around small cylindrical implants inserted in the proximal tibia of mice, as a model for implant integration into cortical bone. The authors applied daily controlled axial displacement of 150 μm (at 1 Hz and for 60 s), starting immediately after implant placement. Enhanced osteoblastic differentiation and bone matrix deposition were observed in the loaded group already after 7 days of loading. One drawback of the bone chamber is the difficulty to investigate the response of pre-existing peri-implant and host bone to mechanical loading. To overcome this, others have designed a miniaturized loading device[80,81] to administer well controlled in situ local loading directly to peri-implant bone[82] or to implants during the osseointegration phase.[83,84] Willie et al.,[83] for example, used such a device to characterize the effect of loading on trabecular bone ingrowth into a porous titanium foam implanted into the femur of rabbits. The authors applied compressive loads (1 MPa, 1 Hz, 50 cycles/day, 4 weeks) and evaluated the response of bone with BSE. They reported a positive effect of loading only on trabecular bone ingrowth, whereas the amount of peri-implant trabecular bone was not different between loaded and control animals. A similar approach was followed by Grosso et al.[84] to analyze the combined effect of intermittent parathyroid hormon (iPTH) and loading on peri-implant trabecular bone. They found that peri-implant BV/TV increased significantly (about 50%) with respect to control animals both with loading and iPTH, but the combination of the two treatments had only a modest additive effect, that is, +13% increase in BV/TV compared to iPTH alone. The authors interpreted the poor additive effect in terms of molecular changes of individual genes which showed little evidence for synergy.

Different types of vibrational loading were investigated in the extensive study of Zhang et al.,[85] using a titanium screw inserted into the medio-proximal site of the tibia of rats, where mainly cortical bone is present (Fig. 3a). The authors considered different loading scenarios designed to assess the effect of loading frequency and magnitude. Loading was applied five times a week for 10 min for either 1 or 4 weeks and bone changes were analyzed with histology. The main result is that high frequency and low

Table 2. Studies of the Influence of Mechanical Loading on Peri-Implant Bone Regeneration

Study	Animal model	Implantation Site	Type of Load	Loading Regime	Bone Architecture	Bone Remodeling
Leucht et al.[30]	Mice	Proximal tibia	Micromotion to implant	Immediate, daily, 3–25 d	Bone matrix deposition	–
Jariwala et al.[27]	Rats	Proximal tibia	Cyclic loading to implant	Immediate, bi-daily, 2 wk	BV/TV	BFR, BRR
Ogawa et al.[89]	Rats	Proximal tibia	LMHF loading via WBV	Immediate, 5 d/wk, 3–25 d	BIC, BF	–
Chen et al.[64]	OVX rats	Proximal tibia	LMHF loading via WBV	Delay 1 wk, 5 d/wk, 8 wk	BIC, BF	–
Liang et al.[91]	OVX rats	Proximal tibia	LMHF loading via WBV	Delay 1 wk, daily, 4 wk	BIC, BF	BFR, MAR, MS
Zhang et al.[85]	Rats	Proximal tibia	LMHF loading to implant	Immediate, 5 d/wk, 4 wk	BIC, BF	–
Zhang et al.[86]	Rats	Proximal tibia	LMHF compressive load through tibia	Immediate, 5 d/wk, 1–4 wk	BIC, BF	–
Grosso et al.[84]	Rabbits	Distal femur	Compressive loads to implant	Delay 1 day, 5 d/wk, 4 wk	BV/TV	–
Willie et al.[83]	Rabbits	Femoral condyle	Compressive loads to implant	Immediate, daily, 4 wk	Bone ingrowth	MAR
Soballe et al.[76]	Dogs	Femoral condyle	Micromotion to implant	Immediate, continuously, 4–12 wk	Bone ingrowth	–

OVX, ovariectomized; LMHF, low-megnitude high-frequency; WBV, whole-body vibration; BIC, bone-to-implant contact; BF, peri-implant bone fraction; BV/TV, trabecular bone volume fraction; Tb.Th, Trabecular thickness; Tb.N, trabecular number; BFR, bone formation rate; BRR, bone resorption rate; MAR, mineral apposition rate; MS, mineralizing surface.

magnitude (HF-LM, i.e., 40 Hz and 8 μm) was the only loading regime able to augment BIC in cortical bone after 4 weeks, whereas no effects could be detected within the medullary cavity or in peri-implant bone. This study raises the question whether different locations and different bone compartments would require specific loading protocols.

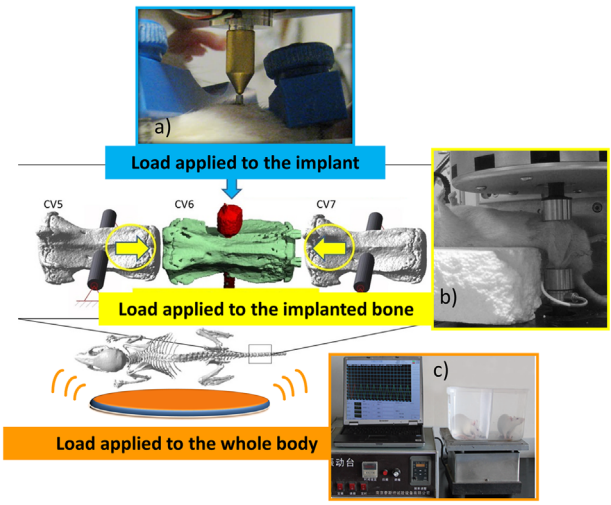

Figure 3. Overview of the main modalities reviewed here to apply controlled mechanical loading to implanted bones. Considering small animal models, mechanical stimulation can be (a) applied directly to the implant through miniaturized devices, (b) administered to the single implanted bone through loads coming from adjacent bones or joints, and (c) delivered through generalized whole body vibrations. Figures modified from[85,86,91] with permission.

Jariwala et al.[27] adopted in vivo micro-CT to characterize the time course of trabecular bone regeneration around loaded and non-loaded implants. The authors inserted titanium-coated high performance plastic implants into proximal tibia of rats. The cyclic loading protocol had two loading magnitudes (60 or 100 μm) applied at 1 Hz for 60 s every other day for 14 days. Changes in peri-implant bone volume fraction (BV/TV) and remodeling rates (BFR and BRR) were characterized with longitudinal micro-CT at 2, 5, 9, and 12 days post-surgery. The authors reported a significant increase in peri-implant BV/TV following implantation as well as different time course for BFR and BRR, but could not detect a significant effect of loading on those parameters. However, a substantial increase in pull-out strength was measured only for the loaded group, indicating that mechanical stimulation applied to the implant has a positive effect but only confined to the bone-implant interface. In conclusion, loading applied directly to the implant, which is a model for load-bearing scenarios, has always a large influence on osseointegration at the bone implant interface. Conversely, the effect on peri-implant bone is more debated and probably only present if the implant is able to efficiently transmit the external stimulation to the peri-implant bed.

Mechanical Loading Applied to the Implanted Bone

A second option is to administer mechanical loading only to the single implanted bone with the goal of increasing peri-implant bone quantity. The bone-implant system

can be selectively loaded in a quasi-physiological way by using well-established tibia-loading models, where external load is applied at the proximal and distal end of the tibia. Zhang et al.[86] implanted titanium screws into the medio-proximal site of the tibia of rats and used a protocol consisting of four loading phases and two loading periods. Histology was used to measure changes in the amount of cortical bone at the bone-implant interface as well as in peri-implant bone. The authors observed a positive effect of local vibrational loading in peri-implant bone, albeit confined to regions adjacent to the implant (i.e., less than 100 μm away from implant surface) and only when using 1 week of low frequency-high magnitude (LF-HM) loading. Conversely, bone-implant contact was enhanced by HF-LM and LF-HM protocols in both loading regimes.

The minor effect of loading on peri-implant bone contrasts with the large anabolic response on intact bone reported in many studies,[20,87,88] therefore suggesting that in the complex context of peri-implant bone regeneration, the local mechanical control of the (re)modeling process may be disturbed. As literature on this topic is sparse, more investigations would be needed to elucidate further aspects of peri-implant mechanobiology.

Mechanical Loading Applied to the Whole Body

Mechanical loading at the whole body level, referred to as whole body vibration (WBV), is receiving considerable attention, especially as non-pharmacological therapy for osteoporosis. The application of WBV is relatively straightforward but its mechanisms of action at tissue and cellular level are less understood. The effect of mechanical stimulations on bone regeneration in the form of low (~1–10 Hz) or high (~10–100 Hz) frequency vibrations have been investigated in animal models.[64,89–91] Ogawa et al.[89] placed titanium screws in the proximal tibiae of rats and applied daily (5 days a week) WBV starting immediately after implantation. The loading protocol consisted of 15 consecutive steps of increasing frequency (from 12 to 150 Hz), each step comprising 2,000 cycles (at 0.3*g*). Peri-implant trabecular bone was analyzed with histology after 3, 7, 14, and 25 days post-implantation. BIC as well as the amount of bone in a region close to the implant (i.e., less than 0.5 mm away from the surface) were always significantly higher in the loading group and showed a significant increasing trend with time. Only loading but not time related effects could be detected further away from the implant (i.e., from 0.5 to 1 mm), which may reflect that the effect of mechanical stimulation is independent from peri-implant bone regeneration and may give an estimation of the extent of the bone region influenced by implantation.

Another comparison between pharmaceutical (i.e., based on bisphosphonates) and non-pharmaceutical (i.e., based on WBV) options on peri-implant bone quantity and implant fixation in estrogen-depleted rats was carried on by Chen and colleagues.[64] The authors used either alendronate or WBV to augment bone regeneration around implants inserted in the femoral medullary canal of rats. The WBV therapy lasted for 8 weeks and was delivered 5 days per week (20 min per day) with vibration frequency and acceleration being 30–35 Hz and 0.3 g, respectively. Histological examination was used to measure bone response at the implant interface as well as within a circular region extending 100 μm away from the implant. Although WBV significantly increased BIC and peri-implant bone area, its effects were smaller in comparison with alendronate, and also significantly smaller than load-driven augmentation in peri-implant bone mass occurring in sham-operated rats. This last study emphasizes that current physical therapies cannot completely replace pharmacological treatments but may be used in combination with them, possibly to reduce their dosage.

CONCLUSIONS AND OUTLOOKS

The present review has highlighted that (i) osteoporotic conditions may compromise implant osseointegration and anchorage due to a reduced ability of modifications in peri-implant bone (re)modeling, and that (ii) mechanical stimulation is able to augment implant osseointegration and peri-implant bone mass both in healthy and diseased bone. However, the effect of mechanical loading seems to be confined to the vicinity of the implant and the response of implanted bones to mechanical loading is generally inferior to the one of intact bones. Moreover, in estrogen-depleted scenarios, mechanical loading alone is not enough to lead to the same increase of peri-implant bone quantity as observed in healthy conditions.

The combination of in vivo longitudinal micro-CT to measure local bone (re)modeling with in silico finite element analysis to compute local strains has recently allowed to experimentally assess the so-called Wolff's law of bone (re)modeling in animals[18,29] as well as in human subjects.[19] These studies have demonstrated that both bone formation and resorption are mechanoregulated processes and that in ageing or estrogen-depletion, the mechanical signal has a decreased ability to stimulate osteoblasts or inhibit osteoclasts.[18,29] Our review demonstrates the necessity to reveal similar biological information on peri-implant bone mechanobiology, possibly to better combine pharmaceutical strategies regulating bone formation and resorption with mechanical loading for improving early and long term stability of implants in osteoporotic bone.

AUTHORS' CONTRIBUTIONS

The conception and drafting of this review were conducted by Z.L, R.M., and D.R. All authors have read and approved the final manuscript.

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