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Micro finite element analysis of continuously loaded orthodontic mini-implants – a micro-CT study in the rat tail model

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Zusammenfassung

Das Phänomen der Implantatmigration beschreibt die Verschiebung orthodontischer Mini-Implantate (OMIs) unter Einwirkung konstanter Kräfte und widerspricht den Grundprinzipien des physiologischem Knochenumbaus. Die grundlegende Biomechanik hiervon ist bis jetzt noch nicht verstanden. Ziel dieser Dissertation war es, den Einfluss lokaler Spannungen auf den Knochenumbau und die Implantatmigration kontinuierlich belasteter OMIs zu untersuchen. Zwei Mini-Implantate wurden jeweils in einen Schwanzwirbel von 61 Ratten eingesetzt. Eine kontinuierliche mechanische Belastung wurde durch die Verbindung der Implantate mit einer Nickel-Titan-Kontraktionsfeder unterschiedlicher Kräfte (0,0, 0,5, 1,0, 1,5 N) erreicht. Longitudinale in-vivo Daten wurden mittels mikro-CT von jedem Tier zu bestimmten Zeitpunkten erhoben: sofort und 1, 2 (n = 61), 4, 6 und 8 (n = 31) Wochen nach der Operation. Neun Volumes of interest (VOI) wurden um jedes Implantat definiert. Um die Spannungswerte in der Umgebung des Implantats zu untersuchen, wurden Mikro-Finite-Elemente-Modelle erstellt. Knochenumbau wurde anhand der Veränderung des Knochenvolumens aufeinanderfolgender Scans analysiert. Für die statistische Analyse wurden ein gemischt lineares Modell und Likelihood-Ratio-Tests verwendet, gefolgt von einem Tuckey-Post-hoc-Test im Falle von Signifikanz. Tendenziell stiegen die Spannungen bis zur zweiten Woche an. Danach zeigten sich abnehmende Werte. Die höchsten Spannungswerte wurden in der oberen proximalen Region berechnet. Ein initialer Knochenabbau wurde in den meisten Fällen bis Woche zwei, gefolgt von einem Knochenaufbau bis Woche acht, beobachtet. Dieses Muster wurde insbesondere in der Gruppe mit einer Belastung von 1,5 N festgestellt. Die Studie legt nahe, dass kontinuierliche Belastungen den peri-implantären Knochenumbau beeinflussen. Implantatmigration könnte durch den Einfluss von Insertionstrauma und kontinuierlicher Belastung ermöglicht worden sein und schien durch eine anschließende Konsolidierungsphase mit hohem Knochenaufbau und Anpassung an die Belastungsbedingungen limitiert zu werden.

Abstract

The phenomenon of implant migration describes the displacement of orthodontic mini-implants (OMIs) under constant forces and contradicts the basic principles of physiological bone remodelling. The fundamental biomechanical mechanism of this unexpected behaviour is not yet understood. This dissertation aimed to evaluate the influence of local stresses on bone remodelling and implant migration around static-loaded OMIs. Two mini-implants were inserted into a single caudal vertebra of 61 rats. Static mechanical loading at different forces (0.0, 0.5, 1.0, 1.5 N) was achieved by connecting the implants with a nickel-titanium contraction spring. Longitudinal *in vivo* data was collected by performing micro-CT scans of each specimen at specific time points: immediately after surgery, 1, 2 (n = 61), 4, 6 and 8 (n = 31) weeks post-op. Nine volumes of interest (VOIs) were defined around each implant. Micro-finite element models were calculated to examine peri-implant stress values. Bone remodelling was analysed by calculating changes in bone volume between subsequent scans. Statistical analysis employed a linear mixed model and likelihood-ratio-tests, followed by Tuckey post-hoc-Test in case of significance. Stresses tended to increase towards week two while decreasing values were observed afterwards. The highest stress values were calculated in the proximal top region (the cortical bone median of the implants). The bone remodelling analysis revealed that in most cases bone degraded within the first two weeks, followed by bone gain up to week eight. This pattern was especially apparent in the group of 1.5 N loading. The study suggests that static stresses influence peri-implant bone remodelling. Implant migration could be explained by the influence of both the trauma from implant insertion and static loading and seemed to be reduced by a following consolidation phase with a high amount of bone gain and adaption to the loading conditions.

List of Abbreviations

OMI	orthodontic mini-implant
N	Newton
Runx2	Runt-related transcription factor 2
LRP5/6	LDL receptor-related protein 5 or 6
SOST	Sclerostin
DKK1	Dickkopf 1
MMPs	matrix metalloproteinases
M-CSF	macrophage colony-stimulating factor
RANKL	receptor Activator of NF-κB Ligand
RANK	receptor Activator of NF-κB
OPG	osteoprotegerin
NO	nitric oxide
ATP	adenosine triphosphate
BcL-2	B-cell lymphoma 2 protein
DAMPs	damage-associated molecular Patterns
Mincle	macrophage-inducible C-type lectin receptor
PRRs	pattern recognition receptors
TNFa	tumor necrosis factor a
il-6	Interleukin 6
il-1	Interleukin 1
CT	computed tomography
micro-CT	micro-computed tomography
HR-pQCT	high-resolution peripheral quantitative CT
BIC	bone-to-implant contact

BV/TV	bone volume per total volume
FE	finite element
micro-FE	micro-finite element
FEA	finite element analysis
micro-FEA	micro-finite element analysis
VEGF	Vascular Endothelial Growth Factor
VOI	volume of interest
RAP	regional acceleratory phenomenon

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1 Introduction

Skeletal anchorage using orthodontic mini-implants (OMIs) gained popularity owing to additional intraoral anchorage, reduced side effects, improved aesthetics, and novel treatment options [1, 2].

In contrast to dental implants, OMIs are loaded with constant forces of low magnitude. Whereas implants including OMIs were assumed to be stationary stable, recent studies have observed that orthodontic forces may induce implant displacement, commonly referred to as implant migration [3-5].

Previous research revealed that local stresses are a decisive factor for bone remodelling. Bone fraction values were found to be higher in pressure zones and decreased in the absence of forces [6, 7]. However, this fundamental understanding of load-dependent bone remodelling appears to be in contraction with the phenomenon of implant migration, where bone must be resorbed at the side where stresses are highest to move in the pulling direction.

1.1 Bone

1870, the German anatomist Julius Wolff discovered an alignment of bone trabeculae along the direction of the mechanical forces. For this reason, he attributed these forces as the cause for the optimised architecture of bone. His findings, outlined in his article “Ueber die innere Architectur der Knochen und ihre Bedeutung für die Frage vom Knochenwachstum” proposed the idea that bone adjusts to its mechanical loads, with each trabecula having a specific static role in resisting external forces [8]. Consequently, bone not only produces erythrocytes, thrombocytes and leucocytes [9], or stores calcium as part of the mineral balance [10, 11], for example, but essentially fulfils the task of supporting the soft tissue and protection of vital organs while continuously adapting to the external applied load.

Wolff´s Law and Mechanostat Theory

Since the initial ideas of Wolff, the study of the relationship between bone architecture and loading has become a key issue in orthopaedics and other related sciences [12]. Roux postulated in 1881 that bone growth and maintenance are controlled by mechanical stimuli [13]. This theory was later taken up again by Wolff in his idea on bone remodelling [14], which is known today as “Wolff's Law” [15].

According to Wolff's Law, bone builds up and gains density when subjected to loading and degrades when it's loaded less or not at all. There is a balance between sufficient mechanical stability and optimization of the weight [15]. Frost further extended the ideas and proposed the Mechanostat Theory as a model for bone remodelling [16]. It states that local bone growth and loss depend on mechanical, elastic deformation. Bone mass therefore reduces below a certain value of elastic deformation and builds up above a certain value. The plateau in between these values is called the “lazy zone”. Here, the bone does not change due to an equilibrium between bone formation and resorption [17]. This theory can already be recognized in “everyday” situations. In paraplegics, the amount of bone in the unused legs is reduced, while bone in the arm, which is used even more than usual, is built up [18, 19]. Weightlifters often show an increase in bone density as a response to physical training [20], whereas astronauts lose bone mass in weightlessness [21].

To further investigate the Mechanostat Theory, both animal and human studies have since been conducted. While these studies generally agree with Frost´s findings a major aspect was challenged: a linear relationship between local tissue loading and bone remodelling was found, with no “lazy zone” [6, 7, 22]. These studies also indicate that the response of bone to mechanical loading is quite comparable between animals and humans [6].

Bone remodelling

From studies of the past decades, we know that the fundamental mechanism of bone remodelling involves a coordinated interplay between osteoclastic bone resorption and osteoblastic bone formation enabled due to communication among osteoclasts, osteoblasts, and osteocytes [23-25].

Major cell types and pathways

Osteoblasts form bone by producing a type I collagen-rich bone matrix. This extracellular matrix is initially called osteoid and later mineralized by calcium phosphate accumulation in the form of hydroxyapatite, controlled by osteoblasts [26]. For craniofacial bone, osteochondral progenitor cells, derived from neural crest cells, differentiate into bone-forming osteoblasts [27]. This process of differentiation is regulated by several transcription factors such as SOX9 [26, 28, 29]. Further, the runt-related transcription factor 2 (Runx2) initiates differentiation into osteoblasts, showing upregulation in preosteoblasts and reaching its maximum level in immature osteoblasts [30]. Among the signalling pathways controlling bone formation and osteoblastogenesis, the canonical Wnt signalling pathway is one of the most relevant [23]. Wnt, modulated by osteocytes, binds its receptor Frizzled as well as co-receptors such as LDL receptor-related protein 5 or 6 (LRP5/6). This way, the destruction complex of ß-catenin is inhibited and cytoplasmic ß-catenin, important for the specification of mesenchymal progenitor cells into osteoblasts, is increased [31]. ß-catenin then activates target gene expression within the nucleus to upregulate osteoblast proliferation [31]. Sclerostin (SOST), as well as dickkopf 1 (DKK1), both expressed in osteocytes [32] and osteoclasts, act as antagonists of the Wnt signalling way by inhibiting the LRP5/6 [33-36]. Mechanical loading is associated with lower levels of sclerostin, leading to bone formation [37], whereas unloading increases sclerostin levels, leading to bone resorption [38].

Multinucleated osteoclasts develop from the fusion of precursor cells derived from the monocyte/macrophage lineage [39]. Osteoclasts dissolve bone minerals through the secretion of hydrochloric acid, whereas the organic bone matrix is degraded by proteolytic enzymes like Cathepsin K or matrix metalloproteinases (MMPs) [40]. To facilitate this process, these cells have podosomes to enable adhesion to the bone surface and form a sealing zone to ensure an isolated microenvironment [41]. Expressed by Osteoblasts, macrophage colony-stimulating factor (M-CSF) activates osteoclast precursor cells and plays a pivotal role in initiating osteoclast differentiation [42]. Further differentiation of an osteoclast precursor into a mature osteoclast is promoted by the Receptor Activator of NF-κB Ligand (RANKL) binding to Receptor Activator of NF-κB (RANK) [43]. Current understanding suggests that, in addition to osteoblasts, osteocytes in particular express RANKL and thus influence bone resorption [44, 45]. Recent studies indicate that unloading increases RANKL expression in osteocytes, which in turn correlates with bone resorption in the absence of loading [46]. Osteoprotegerin (OPG) acts as an antagonist to this system, inhibiting the activation of RANK by binding RANKL [47]. Until now the major source of OPG is not completely clear [39] but besides osteocytes also osteoblasts and osteoprogenitorcells are considered to secrete OPG [48]. As RANKL and OPG act in the opposite way, the ratio between RANKL and OPG therefore has a major influence on bone remodelling.

Osteocytes, derived from osteoblasts, are located inside the extracellular bone matrix and constitute over 90% of the cellular composition in the bone of an adult human [40]. They form dendritic processes that allow interaction between osteocytes themselves, as well as with bone marrow or bone lining cells [49]. It was found that mice were resistant to underload-induced bone resorption when osteocytes were previously targeted for destruction [50], indicating the core role of osteocytes in Mechanotransduction. Thus, besides the fact that osteoblasts and osteoclasts determine the extent of bone remodelling by adding or removing bone [24], it is now certain that osteocytes have a crucial function in orchestrating bone remodelling by regulating the activity of osteoblasts and osteoclasts [23].

Besides mechanical loading, other factors such as calcium homeostasis [6] or hormones (e.g. parathyroid hormone or glucocorticoids) [51] have a significant influence on bone remodelling.

Mechanotransduction

To enable bone remodelling in response to mechanical loading, the mechanical stimulus is detected by Osteocytes and further converted into a biomechanical signal (Mechanotransduction) [52, 53]. Recent discourse has revolved around the exact way in which stimuli are perceived by osteocytes. Some researchers propose that dendrites of osteocytes not only facilitate cell-to-cell communication but also sense mechanical loading [23, 54, 55]. This capability is attributed to the presence of fluid, located around the dendrites, also referred to as canalicular or bone fluid. When stress is applied, the fluid moves away from the compressed region, enabling osteocytes to detect mechanical loading by registering the flow of canalicular fluid [56]. Other sources suggest a combination of dendrites and the cell body to sense mechanical stimuli [57] while some contend that the primary cilium is most likely to detect the stresses [58, 59]. Evidence exists for each of these theories.

An early response to mechanical loading and fluid flow shear stress is the increase of intracellular calcium levels due to Voltage-dependent calcium channels, present in both osteocytes and osteoblasts [60]. Subsequently, this results in the release of NO, ATP, and prostaglandin, which all exhibit a stress-dependent effect in bone-building [61-63]. For instance, NO, downregulates bone resorption and induces bone formation [23, 64]

In addition, mechanical deformation of osteocytes induces Ca^{2+}-flux dependent release of extracellular vesicles and promotes bone formation [65, 66]. EVs contain mediators such as RANKL, OPG, or sclerostin [66]. This way bone remodelling is orchestrated in part by mechanosensitive osteocytes.

The mechanism of dynamic bone remodelling primarily depends on the fact that the bone is subjected to physiological cyclic loading. In contrast, continuous compression, as seen when using OMIs, could lead to different phenomena since the blood marrow supply could be disrupted. This could result in osteocytic cell death and bone repair, as a response on high static loadings [67-72]. Angiogenesis within the affected area would be feasible as part of the bone repair process [73].

Microcracks and bone repair

Physiological mechanical loading causes micro damage within the bone structure [74]. Therefore, microcracks can be considered a physiological phenomenon, damaging both the dendrites of the osteocytes and the osteocytes themselves. As a result, the damaged osteocytes undergo apoptosis [75]. Since osteocyte apoptosis, either due to fatigue or other factors such as underload or estrogen deficiency [76, 77], is a fundamental process to initiate bone remodelling, it induces the release of ATP via pannexin-1 channels (PANX1) and its coactivation receptor P2X7R [78]. In this context, ATP acts as a localization signal and binds to P2Y2 receptors of the surrounding "bystander" osteocytes [79]. This mechanism causes bystander osteocytes to upregulate the release of RANKL [78] to activate osteoclastogenesis and the resorption of damaged bone. In addition, B-cell lymphoma 2 protein (BcL-2) increases in bystander osteocytes. This anti-apoptotic protein presumably functions to protect against increased osteoclastic activity [80], thus preventing excessive osteocyte degradation.

In addition to these mechanisms, damage-associated molecular patterns (DAMPs) are released when osteocytes die [81]. These either directly activate the differentiation of osteoclasts via macrophage-inducible C-type lectin receptor (Mincle) or reach the junction with the bone marrow through the canalicular network [81]. In the last case they bind to pattern recognition receptors (PRRs) [82] on bone marrow cells, activating them and inducing the release of proinflammatory cytokines such as TNF α, il-6 or il-1 by monocytes and macrophages [83]. These cytokines positively influence the increase of RANKL in osteoblasts, leading to the activation of osteoclast formation again [84].

The insertion process of OMIs induces microcracks in the surrounding bone [85]. Consequently, subsequent post-traumatic bone healing, beginning with an initial phase of bone resorption followed by bone formation, as previously mentioned, could be one factor potentially facilitating implant migration.

1.2 Micro-computed Tomography

High-resolution micro-computed tomography (micro-CT) has been utilized in laboratory settings since the late 1980s [86] for research purposes in both animal and human specimens. Over time its use has grown considerably [87, 88]. Dedicated *in vivo* micro-CT systems such as the vivaCT 80 (Scanco Medical AG, Switzerland) enable longitudinal scans of small animals. The advancement of micro-CT scanners has further enabled high-resolution three-dimensional analysis of the morphology of cortical and trabecular bone [89-92], opening novel prospects in the field of bone research.

Micro-CT in dentistry

In addition to the possibility of studying bone morphology concerning bone diseases and their treatment in preclinical and clinical studies [93, 94], micro-CT is widely employed in the field of dental research (endodontics [95, 96] or oral surgery). Within the latter, studies could focus on augmentation procedures [97, 98], the influence of antiresorptive therapy on bone metabolism [99], or on osseointegration of dental implants [100, 101].

Regarding bone-to-implant contact (BIC), which is considered a crucial parameter for osseointegration, the comparison between conventional histological examination and three-dimensional micro-CT analysis indicates no significant difference when the analysis is performed by a trained observer [102]. Moreover, approaches have been introduced to further reduce the influence of metal artefacts enabling peri-implant bone segmentation using only a single threshold [103].

Advantages and disadvantages

Compared to conventional two-dimensional imaging techniques such as histology, micro-CT imaging offers the possibility to analyse larger volumes of interest (VOIs), or even the entire microstructure if required. The micro-CT workflow enables full or semi-automatically extraction of parameters, facilitating the analysis of a substantial amount of specimens [104-106]. In addition to bone morphology parameters such as bone volume per total volume (BV/TV), quality parameters of bone like mineral properties can be measured [87, 107].

Due to the non-destructive workflow, longitudinal *in vivo* studies could be conducted [5, 108]. The integration of bone remodelling analysis with micro-finite element analysis (micro-FEA), for instance, has contributed novel insights into the load-dependent behaviour of bone remodelling [6, 7].

Nevertheless, detailed analysis of cells, released transmitters, or proteins is not possible, and other examination methods such as histology or gene-expression analysis are required [109]. Another major limitation of micro-CT is the potential occurrence of (metal-) artefacts. Particularly, when examining specimens containing highly radiopaque objects such as titanium implants, artefacts can influence the grey values of the surrounding area [102, 103].

1.3 Micro-finite element analysis

From finite element to micro-finite element

In 1972 finite element analysis (FEA) emerged in biomechanics as a “new method to analyse the mechanical behaviour of skeletal parts” [110] and has since become increasingly important. The application of the FE method to human bone initially aimed to evaluate structural failure probabilities [111]. It later evolved to study stresses and strains induced by orthopaedic forces to establish relationships between load-carrying functions and tissue morphology, as well as to promote the development of implants to provide better fixation [12]. Within this context, FEA was used due to its powerful ability to simulate loadings on highly irregular structures such as bone. However, simulations using finite element (FE) models have limitation with regard to the representation of the geometry, material properties and loading [111]. In particular, trabecular bone is not continuous at the microscopic level, thus, concerns arose about whether a continuum representation of the bone would impact the results [112]. This consideration gave rise to the idea of examining irregular bony structures at the microscopic level in terms of a micro-FEA.

The first micro-FEA of a bone sample of reasonable size in 1995 [113] demonstrated its fundamental capabilities. Subsequently, the new capability of micro-CT imaging enabled faster, high-resolution *in vivo* scans. With increasing computational power, the model size increased in recent years making it possible to analyse whole bones [114].

Micro-finite element analysis today

It is now believed that micro-FEA provides better information for measurements of bone stiffness, strength and fracture prediction than parameters such as bone density do [114]. Furthermore, owing to its ability to represent the irregular microarchitectural configuration of the trabecular network, micro-FEA can provide more detailed information than FE analyses representing bone as a continuum [115].

When researching diseases [116] and treatments [117], micro-FEA serves as a tool to acquire detailed information about the micromechanical properties of bone [114], considering the microscopic anatomy [118]. In addition, micro-FEA enabled

new findings and insights into the correlation between bone remodelling and tissue loading [6, 7].

1.4 Orthodontic mini-implants

According to the third Newtonian axiom "Actio = Reactio", every force generates an equal and opposite counterforce (reactive force). As forces are a fundamental part of orthodontic treatment, this law is often found in this speciality and thus leads not only to desired but also to undesired tooth movements of the anchorage units [119-121].

In addition to the possibility of using teeth or extraoral devices, skeletal anchorage allows new solutions to minimize undesirable effects [122-126]. In this regard, skeletal anchorage using OMIs has been used frequently in recent years [1, 2]. Due to their ease of use and low invasiveness, they have proven effective in clinical situations, enabling novel treatment options [127, 128].

Skeletal anchorage in the past

Initial efforts to achieve skeletal anchorage using screws inserted into the bone go back to Gainsforth and Higley 1945, who employed vitallium screws [129]. However, as the screws were lost under load due to insufficient osseointegration and subsequent loosening, titanium was discussed as a possible alternative material. In 1969, Brånemark's research on dental titanium implants demonstrated osseointegration and stability over five years, thus establishing titanium as a highly biocompatible material [130]. In the early 1980s, Schroeder et al. described an ankylotic connection between the titanium-sprayed implant surface and the surrounding bone. This study reports on the first experiments conducted with cylindrical titanium implants implanted in monkeys [131].

Various forms and locations of skeletal anchorage have been explored, including a study initially described by Melsen, in which ligature wires inserted into the maxillary antral wall provided anchorage [132]. Moreover, the influence of orthodontic forces on the osseointegration of endosseous titanium implants (Brånemark, size 10 x 3.75 mm) was studied, demonstrating the suitability of these implants as orthodontic anchorage devices [133]. Endosseous Implants were also placed vertically in the retromolar region for purely orthodontic purposes [134]. Due to poor bone quality and thick mucosa in this area [135] one later switched to horizontal insertion [136].

The aforementioned methods of skeletal anchoring are quite invasive, which is why smaller, more atraumatic implants, also referred to as OMIs were introduced [137]. With these implants placed between or right beside the roots, adjacent teeth in most cases can only be moved 1-1.5mm, before contacting the OMI. Therefore, the idea of placing short implants in the mid-palatal region emerged, which dates back to Triaca 1992 [138]. This region has consistently proven to be a favourable site for OMI insertion, which is why mini-implants are now mostly inserted in the anterior palate, the so-called “T-Zone” [139-142]. In this zone the loss rate on the one hand [143] and the fracture rate on the other hand [144] are low.

Indications

OMIs find numerous applications where a stable anchorage unit is required. As published by Bock et al. [145] examples of clinical indications for OMIs are intrusion [146, 147] or extrusion [148], distalisation [149] or mesialisation [150, 151], (early) class lll treatment using a hybrid hyrax device [126, 152, 153], alignment of ankylosed or displaced teeth [127, 154], pre-prosthetic treatment [155], uprighting of tipped molars [156] or mini-implant-borne rapid maxillary expander [157]. Further indications include en-masse retraction [158] or the possibility of closing gaps by installing temporary pontics [159].

Advantages and risks

As mentioned, the importance and use of OMIs has increased enormously in the past [1, 2]. This is not only due to the versatility of making new treatment options possible [127, 152, 160], but also because of the combination of a high degree of aesthetics [151, 161] with relatively low costs [162, 163]. In addition, OMIs ensure short treatment time with remarkable efficacy [128, 149, 164-168], partly due to minimal reliance on patient compliance[168, 169]. Compared to normal dental implants the insertion and removal procedure is much easier and less invasive [162].

Disadvantages associated with OMIs include the risk of root damage [170] or loosening of the implant. In the literature, studies report an overall success rate of approximately 84 to 88 % [171-173] and a failure risk of 6 % for palatal placed

OMIs [174], and many cases in which OMIs are used unsuccessfully are in the early stages of insertion or loading [175].

In dental implantology, there is general evidence that sufficient primary stability is one of the most important key factors for high success rates [176, 177]. As has been shown in past studies, this point can also be applied to orthodontic mini-implants [178]. For this reason, primary stability is a decisive factor for the successful treatment with OMIs. To achieve this, regions with good bone quality should be preferred [179]. In addition, a thin attached mucosa [180] as well as the correct insertion angle [142] is important to anchor the implants sufficiently in the bone. Accordingly, distinct anatomical regions exhibit different failure rates, such as 1.5-5.5 % for palatal or 9.2-16.4 % for buccally placed implants in the maxilla [181]. Another important factor is the properties of the implant itself.

Properties of OMIs

Many studies have investigated the influence of shape, geometry, and dimensions of the screw to achieve better primary stability [175, 182-184]. In this context the diameter is known to be a dominant factor for the mechanical environment of the screw [182, 185], that's why McNally et al. recommend a screw diameter greater than or equal to 1.8mm [186]. A study by Nienkemper et al. postulates that longer implants of 11mm have higher primary stability than the control group of 9mm [187]. Other studies not only confirm these points [171, 175] but also assign decisive influence to other factors such as material and exposure length [188], screw shape [175, 189, 190] thread shape [188, 191], or thread depth [188]. Longer implants may lead to patient discomfort due to the potential perforation of the nasal mucosa, when placed in the T-zone. This is why today it is customary to employ a 9 mm length implant in the anterior and a 7 mm length implant in the posterior T-zone.

Due to the requirements for OMIs to provide sufficient retention and yet be easily removed after treatment, grade V titanium alloy (Ti-6Al-4V) [192] with a machined surface is often used [193]. The machined surface of the implants ensures less osseointegration compared to conventional dental implants exhibiting a micro-rough surface. Therefore, the retentive force of the implant is based more on mechanical retention than on osseointegration [194] and the implant can be

removed easily by unscrewing. In this context, until now, it remains unclear to what extent the OMI surface influences implant migration.

Implant migration

Although OMIs [195] can be assumed to be stationary stable when orthodontic forces are applied, migration within bone has been observed [3-5]. This phenomenon, also referred to as implant migration, seems to contradict the Mechanostat Theory since it cannot solely be attributed to the previously described bone remodelling processes: one would expect bone formation in regions of elevated stress due to loading. Consequently, additional factors, such as bone healing following insertion trauma and the effects of continuous loading, must be considered.

A significant correlation between velocity of movement and applied force was recently postulated [5]. The mechanism behind this phenomenon is still unclear and has become an increasing challenge for orthodontic scientists.

1.5 Aims

The overall goal of this study was to achieve further explanations of these unexpected biological patterns enabling implant migration. Specific aims were to assess the local stresses through a micro-FEA at constantly loaded OMIs, to evaluate the impact of stresses, and to correlate these findings with the bone remodelling processes. The following null hypotheses were formulated:

1. H0: According to Mechanostat Theory there is no local tissue loading above which implant migration occurs. With higher tissue loading chances for bone formation increase, limiting implant migration.
   A: There is a local tissue loading above which implant migration occurs (local bone loss instead of bone formation due to high stresses).
2. H0: There is no association between bone formation and implant migration, so that the migration rate does not decrease over time.
   A: With increased bone formation, implant migration decreases over time.
3. H0: Post-traumatic bone healing does not enable implant migration.
   A: Post-traumatic bone healing does enable implant migration.

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3 Discussion

Both preclinical and clinical studies suggest that orthodontic mini-implants subjected to static loading can exhibit movement within the bone while maintaining stability [3-5]. The mechanisms behind this phenomenon, commonly known as implant migration, appear to contradict the fundamental principles of bone remodelling [6, 16, 25, 196] and remain to be understood.

In the present study, 2 implants were inserted into the tail vertebra of n=61 rats and subjected to different static forces (0N, 0.5N, 1N, or 1.5N). *In vivo* micro-CT scans were taken immediately and 1, 2 (n=61), 4, 6, and 8 (n=31) weeks after surgery [5]. To describe the results depending on the peri-implant bone region, nine volumes of interest (VOIs) were defined for each implant. Within each VOI, local stresses around mini-implants were calculated by using micro-finite element analysis (FEA) and further correlated with peri-implant bone remodelling [108].

In brief, stress values tended to peak after two weeks in most VOIs, and bone remodelling analysis indicated initial bone loss within the first two weeks followed by subsequent bone gain, particularly prominent in the 1.5 N loading group. Bone gain trended downwards towards week 8 [108], implying a potential association between movement velocity, peri-implant stresses, and bone remodelling [5, 109, 197]. Correspondingly, stress distribution aligned with the direction of implant movement, reaching peak values in proximal top VOIs (the cortical bone region median of the implants). Elevated stresses were also evident in the lateral middle and distal bottom regions. The findings vary across species, age, and bone regions, necessitating caution when transferring the results to clinical scenarios [198, 199].

It should be noted that this study deviated from assessing strain or strain energy density and opted for stress analysis, since post-traumatic bone healing due to microcracks rather than dynamic bone remodelling was thought to be associated with implant migration [6, 7].

Early healing phases did not involve a functional connection between implants and surrounding bone. When simulation stresses using FEA, bone was disconnected from the implant where tensile forces could be expected, for this reason. In this context, limitations with regard to the FEA exist due to ongoing bone remodelling and the absence of longitudinal *in vivo* histological information

regarding functional bone to implant contact at especially the last time points [109].

Limitations stemming from metal and motion artefacts were addressed to be minimized to less influence the results [103, 108].

As previously discussed, osteocytes are crucial in orchestrating the extent of bone remodelling [23]. This mechanism allows the bone to respond to mechanical stress and adjust its volume accordingly. Given this understanding, it appears implausible that implants could migrate through bone as demonstrated within this study since high stresses would be expected on the side toward which the OMI moves, further restricting implant migration. Therefore, the observed movement cannot be explained by the Mechanostat Theory. At this point it is important to mention that static implant loading combined with insertion trauma is not a physiological loading process.

Therefore, it could be hypothesized that static loading fractures the peri-implant bone, leading to local bone resorption and facilitating implant migration. However, the Micro-FEA conducted within this study revealed comparatively low peak stress values that would not cause any bone damage. Therefore, bone fracture due to unphysiological overloading is not likely to cause early bone loss [200].

More complex factors such as microcracks due to implant insertion trauma and ischemia caused by continuous compression could be more relevant factors:

The insertion of mini-implants induces microcracks in the surrounding bone. Microdamage stimulates bone remodelling by initiating resorption through osteoclasts and new bone formation by osteoblasts [85]. Consequently, these microcracks lead to an accelerated rate of bone remodelling, a process known as regional acceleratory phenomenon (RAP) [201-203]. Under physiological loading conditions, damaged areas are repaired effectively, [204], whereas the accumulation of microcracks and unphysiological (e.g. static) loading compromise the mechanical properties of the bone [205]. RAP is frequently observed in combined surgical and orthodontic treatment, where perioperative remodelling within the alveolar process accelerates tooth movement. In this context, it is conceivable that the local peri-implant RAP, and the associated microcracks, facilitate implant migration.

Additionally, continuous compression of bone interrupts the blood marrow supply, leading to local ischaemia and bone necrosis following osteocytic cell death [67-72]. Osteocyte apoptosis triggers the release of ATP, acting as a localisation signal for the surrounding Osteocytes [39]. These osteocytes induce the release of RANKL and subsequently activation osteoclastogenesis [39]. Furthermore, during this aseptic inflammation, cytokines such as TNFa promote osteoclast differentiation and enhance the release of VEGF, which upregulates the angiogenesis in this area [73]. High levels of angiogenesis are related to enhanced local bone remodelling, as observed after two weeks of loading within this study trail [197].

In summary, the findings could be explained as follows: Bone resorption was generally observed in most VOIs during the first two weeks, likely due to microcracks caused by implant insertion and RAP. However, bone resorption was more pronounced in regions subjected to high static stresses (e.g. proximal top), where local ischemia may have further contributed to bone resorption due to the constant forces exerted on the OMIs top, it is conceivable that the implant could relocate into the newly resorbed area and therefore migrate through bone. Continuous loading may enable the implant movement due to an initial disbalance between bone resorption and bone formation, especially within the first two weeks after implant loading. After these two weeks, bone was able to adapt and more bone formation was observed, regardless the VOI. However, more bone formation was observed in VOIs of higher Stresses. This process of bone densification resulted in decreasing stress values after two weeks and Implant migration could be limited this way, underlining the high potential of bone adaption to new loading conditions in terms of bone remodelling.

Future studies could aim to research the influence of aseptic inflammation and initial bone resorption on implant migration by analyzing relevant biochemical markers TNFα, as well as the influence of delayed implant loading and surface modifications, which could affect the osseointegration and peri-implant bone remodelling processes. It remains unclear if implant migration would have been possible after successful osseointegration and delayed implant loading.

Conclusion

The highest stresses were calculated in the cortical region near the implant neck, aligning with the loading direction where the high-loading group previously indicated implant migration. All groups exhibited a net bone loss up to week 2, coinciding with the phase of the highest reported migration velocity [5]. This suggests a potential influence of both the trauma from implant placement and continuous loading, facilitating early implant migration. Subsequently, all groups showed a net bone gain, suggesting a consolidation phase limiting further implant migration. These observations imply that after successful osseointegration, implant migration may be improbable. Further *in vivo* studies employing a delayed implant loading protocol are necessary to confirm these findings.

With reference to these inferences, the hypotheses outlined above can be assessed as follows:

1. H0 is rejected. Within the first two weeks, particularly in zones of high stresses, an increased amount of bone loss enabling implant migration was observed. A certain threshold of stresses could not be identified.
2. H0 is rejected. Increased bone formation seemed to reduce implant migration from week two onwards and the course of bone remodelling shown is in line with the reduction of implant migration over time.
3. H0: is rejected. Factors such as post-traumatic bone remodelling seem to enable implant migration.

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