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Standardisierte Testung von Knochenplatten-Schrauben-Konstrukten für die Osteosynthese

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Table of contents

List of abbreviations

AO	Arbeitsgemeinschaft für Osteosynthesefragen
ASTM	American Society for Testing and Materials
AWISO	Freie Arbeitsgemeinschaft winkelstabile Osteosynthese
BPS	Bone Plate Screw
DCP	Dynamic Compression Plate
DHS	Dynamic Hip Screw
DIN	Deutsches Institut für Normung
FCL	Far Cortical Locking
ISO	International Standardization Organization
LCP	Locking Compression Plate
LISS	Less Invasive Stabilization System
LTF	Load to Failure
MDD	Medical Device Directive
MDR	Medical Device Regulation
MESH	Medical Subject Heading Search Term
NCB	Non-Contact-Bridging
PC-Fix	Point Contact Fixator
POM	Polyoxymethylene
PMS	Post-Market Surveillance
PSUR	Periodic Safety Update Report
REF	Reference Number
SAL	Sterility Assurance Level
SD	Standard Deviation
SSCP	Summary of Safety and Clinical Performance
VDE	Verband der Elektrotechnik Elektronik Informationstechnik
VDI	Verein Deutscher Ingenieure

1 Introduction

Osteosynthesis is the reduction and internal fixation of a bone fracture using implantable medical devices. It aims to bring the fractured bone ends together and immobilizes the fracture site while healing occurs. In a fracture, that is rigidly fixed, the fracture heals by the process of intramembranous ossification [162]. This medical purpose is accomplished by surgical intervention using surgical implants, such as e.g. metallic bone plates and corresponding screws. Conventional plate osteosynthesis has generally been recommended for the operative fracture treatment since the mid-20th century [162]. Since their initial introduction and subsequent use in daily clinical practice, conventional plating methods have shown to successfully stabilize many types of AO (Arbeitsgemeinschaft für Osteosynthesefragen) fractures and are commonly clinically accepted [137, 184].

In order to preserve the blood supply to the bone by reducing plate contact with the periosteum, fixed-angle, locked-type plate systems were introduced. The pioneer of angular stability is Paul Reinhold, a french surgeon, who had developed a unidirectional, threaded connection between plate and screw in 1931 [234]. These early (locked-type) plating attempts were constantly refined and improved by the AO foundation, represented by a number of innovative surgeons and orthopedics, and were introduced as the PC-Fix and LISS systems. The clinical success of these plates led to the introduction of the LC plates and nowadays many other locked-plate designs by a large number of different legal manufacturers worldwide. Locked plating systems have become a valid alternative to conventional plates. They “provide angular stability with the advantage of improved fixation in osteoporotic bone, and they reduce the risk of primary loss of reduction as final plate-contouring is not required” [234]. Modern conventional and locked-type devices are pre-contoured and adapted to local biomechanics.

However, independent from the type of device used for plate osteosynthesis, whether a conventional or locked-typed device, its primary clinical function remains almost unchanged. All bone plates for osteosynthesis must resist physiological loads to allow fracture union by limiting fracture gap stress. They shall provide sufficient load stability to permit early limb movement and they should not fail before fracture union has occurred. Additionally, disruption of the bone blood supply caused by the construct should be avoided. This medical purpose is synchronized with four major AO principles of fracture fixation, which, although slightly modified over the years, are still valid as of today: “1. Fracture reduction to restore anatomical relationships, 2. Fracture fixation providing absolute or relative stability, 3. Preservation of blood supply, and 4. Early and safe mobilization” [184].

Looking to the history of those devices, it is quite obvious, that plate techniques and designs have changed and improved over the years. In this context, the introduction of a locking

mechanism and the modification of the shape of the bone plate are considered significant changes. However, the requirements and methods for pre-clinical testing within the regulatory clearance process of such devices remain almost unchanged [5]. This is quite remarkable as testing is an important step in the development and safe market entry of medical devices [85, 86, 108].

Bone plates, screws, and constructs thereof are medical products and are marketed in a branch of industry which is highly regulated. Regulation means, that medical devices are placed on the market through special authorization processes, such as e.g. conformity assessment procedures in the European Union. These processes and the applicable regulatory requirements for them may deviate from country to country. The development, pre-clinical testing, manufacturing, distribution and marketing of medical devices is influenced by several stakeholders (Fig. 1). The ultimate goal, the development and availability of safe and effective medical devices for the benefit of the patient, is considered from a different perspective.

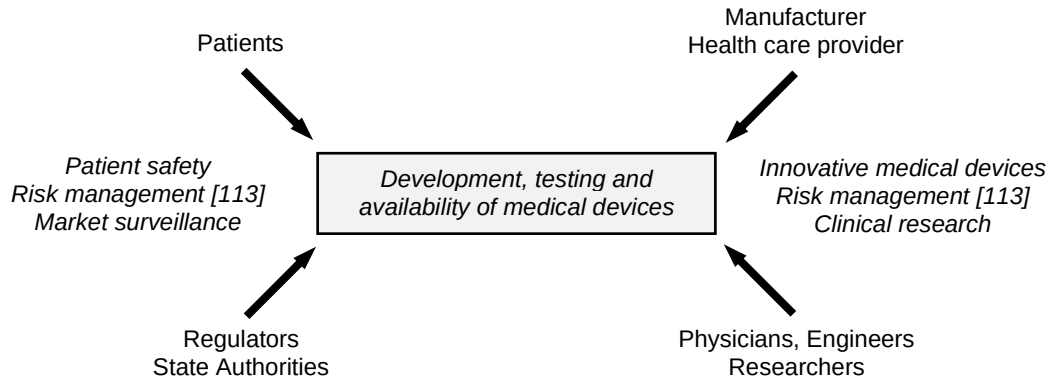


Fig. 1.: Standardized testing of medical devices. Area of conflict in the standardization of requirements due to different perspectives of major stakeholders impacting standardization. Modified acc. to [113].

The patient is the customer [38]. He expects a safe product that fulfills its intended medical purpose. Likewise from the point of view of the state authorities, regulation should primarily serve patient safety by allowing (and maintaining) market clearance only for products, that effectively meet applicable regulatory and statutory requirements. However, “manufacturers shall manage risks so that the residual risk associated with each hazard as well as the overall residual risk is judged acceptable” (Chapter 1, 4. [86]). Risk is defined as “combination of the probability of occurrence of harm and the severity of that harm” [86]. Consequently, there are always “residual risks”, that are accepted by the legal manufacturer [85, 86, 113] or by society [138], provided that the “benefit-risk analysis” and the “evaluation of overall residual risk” is acceptable [113]. For example, 1 out of 10^6 sterile devices is maybe non-sterile and legally on the market (if SAL is set to 10^{-6}). In this context, standardization plays an important role. A standard contains regulatory requirements on a

risk based approach, thus serves patient safety, allowing regulators to effectively (and efficiently [121]) assess product compliance. Applying and meeting requirements of a (product specific) standard often presumes, that residual risks are acceptable, provided that documented acceptance criteria for performance requirements are defined and met [114]. Physicians, engineers and other research groups perform clinical research on medical devices and thus contribute to the development and market availability of those devices. Regulators as well as manufacturers of medical devices have identified the need to set requirements for products and processes, and ideally to harmonize them globally. Where standardized requirements are lacking, registration authorities may set any requirements for devices. As a desired output of standardization, manufacturers expect a quick and reliable, i.e. global market access combined with reduction of cost and liability risks, since standardization facilitates the verification of compliance with requirements [121]. From the regulatory point of view, the verification of compliance to a standard is more efficient than, first, to assess whether the chosen (and validated) test method is applicable and capable to deliver appropriate testing results, and second, to assess whether the results conform to requirements [121].

While the medical device technology, with its emerging efforts to serve patient safety and to standardize products and processes, is highly (and increasingly) regulated, pre-clinical testing of modern bone plate-screw constructs for plate osteosynthesis appears to be quite un-regulated and useful available guidance for standardized testing of such devices is lacking. This dissertation explores the possibilities and constraints when bone-plate screw constructs are pre-clinically tested under standardized testing conditions.

Partial results of this dissertation were published in advance in the following articles*:*

Schorler H, Capanni F, Gaashan M, Wendlandt R, Jürgens C, Schulz AP (2017) Bone plates for osteosynthesis - a systematic review of test methods and parameters for biomechanical testing. Biomed Tech (Berl) 62, 235-243

Schorler H, Wendlandt R, Jürgens C, Schulz AP, Kaddick C, Capanni F (2018) Bone plate-screw constructs for osteosynthesis - recommendations for standardized mechanical torsion and bending tests. Biomed Tech (Berl) 63, 719-727

Halbauer C, Schorler H, Liberto L, Capanni F (2021) Comparison of a standardized four-point bending test to an implant system test of an osteosynthetic system under static and dynamic load condition. Biomed Tech (Berl), doi: 10.1515/bmt-2020-0228

2 Bone plate-screw constructs in a regulatory context

2.1 Definition and biomechanics of bone plate-screw constructs

Bone plates and screws have traditionally been considered as separate items, since screws can be used as standalone devices in surgical procedures. However, a metallic bone plate always depends on its functional combination with corresponding screws. Inevitably, they shall be considered and tested as a functional construct. This is why the term “bone plate-screw construct” (or BPS construct) is introduced.

2.1.1 Definition

A bone plate-screw construct is not yet a defined medical term. A construct is a functional combination of two or more components representing the complete assembly that is used for the treatment of patients, e.g. the complete assembly, that is implanted. This approach can also be found in relevant biomechanical articles [49, 60, 130, 217, 218]. Within the field of trauma care and related products a few constructs are already subject of standardization, such as e.g. “spinal implant constructs” as per ASTM F1717 [11], “external skeletal fixation devices” as per ASTM F1541 [10] or “interconnection mechanisms and subassemblies of spinal arthrodesis implants” as per ASTM F1798 [12]. This aspect applies in particular for angle-stable, anatomic locked-type constructs, but can be applied for conventional plating constructs as well [137]. Fig. 2 shows typical bone-plate screw constructs, selected from different legal manufacturer and for different anatomical regions.

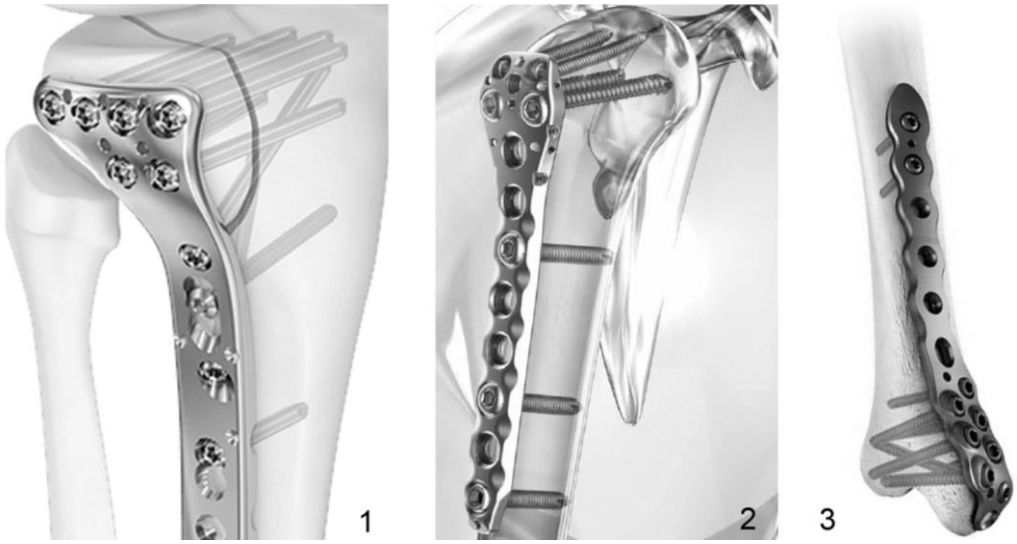


Fig. 2.: Typical bone-plate screw constructs subject to standardized testing. Part 1: 3.5mm VA LCP Plating system for the proximal tibia, company DePuy Synthes [88]. Part 2: NCB Plating system for the proximal humerus, company Zimmer [97]. Part 3: AxSOS 3 Ti plating system for the distal tibia, company Stryker [93]. All pictures depicted in grays.

2.1.2 Conventional and locked-type osteosynthesis

Conventional plate osteosynthesis involves a variety of different plate systems and concepts. Conventional plating is always based on a frictional connection, which requires a high contact pressure between the plate and the bone (Fig. 3, part a). However, this pressure has an impact on the vascularity of the bone, which led to the development of new plating concepts [137]. With the aim to minimize the bone-implant contact area, the development of plate systems such as DCP ("Dynamic Compression Plate"), LC-DCP ("Limited Contact-Dynamic Compression Plate"), PC-FIX ("Point Contact-Fixator"), LISS ("Less Invasive Stabilization System") or NCB ("Non-Contact-Bridging") was the logical consequence [184, 137]. Conventional osteosynthesis, although for many years and still subject of frequent clinical procedures, has certain limitations. Its ability to achieve stability is limited by screw torque [193]. However, decreased bone quality, e.g. due to osteoporosis, may prevent adequate thread fixation in order to create sufficient stability.

Locked-type osteosynthesis, however, is different. It is not designed for a frictional connection between plate and bone but as "internal fixateur" with different biomechanics (section 2.1.3) [193, 233, 234, 235]. There are also mixed systems which can be applied both in conventional mode or as locked-type construct or simultaneously, e.g. LCP plating system (Fig. 2, part 1). Additionally, there are certain devices where the angular stable function is limited to a certain section of the implant, e.g. in the case of a fixation of a DHS ("Dynamic Hip Screw") plate by a screw. "Far Cortical Locking" (FCL) is a special form of an angular-stable fracture fixation. The bone screws are fixed only in the far cortex allowing larger micromovements of the fractured region [193, 234]. "Double plating" can also be considered as a special fixation method. In this case, at least two bone plates are used in the opposite direction in order to prevent a one-sided tilting of the fracture fragments [184].

2.1.3 Biomechanics of bone plate-screw constructs

A locked-type construct is a functional combination of the bone plate with corresponding screws which ensures angular stability. Angular stability means, that the inserted bone screws are rigidly connected to a load carrier, e.g. a bone plate or a nail. This connection is designed to be a mechanically load-bearing construct, which can withstand shear forces and moments that might occur. Bone plates are no longer pressed onto the bone, but can be fixed as an extramedullary attachment, a splint close to the bone [193, 234]. A direct bone contact of the plate is not necessary. The force transmission is not accomplished by means of contact pressure between the plate and the bone but by the complete bone plate-screw construct, consisting of the plate and corresponding screws (Fig. 3, part b). Locked-type constructs claim to deliver primary (exercise) stability, so that mobilization of the affected parts can be carried out early after surgery [193]. The biomechanical principle is

derived from an external fixateur, which stabilizes the fracture fragments via an external mechanical construct. Angular stable implants are therefore also referred to as internal fixators [193, 233, 234, 235]. Locked-type osteosynthesis follows a natural principle ensuring a “biological osteosynthesis” [232]: The fractured region is sufficiently stiff, but is at the same time sufficiently flexible, allowing micromovements in the fracture gap resulting in fracture healing via callus formation [232]. A distinction is made between unidirectional and multidirectional locking constructs. Unidirectional systems have a determined angle between plate and screw. The threaded screw head is anchored into the corresponding thread in the plate. This technique is also used when the plate is not fixed with screws but with angular-stable bolts. Multidirectional systems offer the possibility to insert screws with a variable, conical angle of ± 15° (Fig. 3, part b), depending on the design of the bone plate-screw interface [91]. Fig. 3 explains the biomechanical principle of conventional and locked-type constructs in terms of its characteristic load transmission.

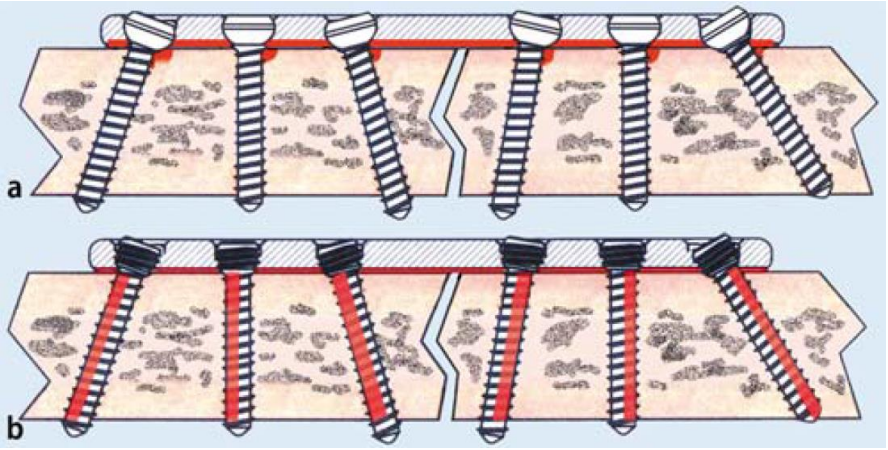


Fig. 3.: Biomechanics of conventional and locked-type constructs. Part a: Area of load transmission (red) with conventional bone plate-screw constructs. Compression of the periosteum and maximum stress at each individual screw neck. Frictional forces between the plate and the bone ensure relative stability of the construct. Part b: Load transmission with locked-type constructs. Load distribution on the entire contact area between the bone and all screws [223, 234].

Many different terms have been used to describe such a mechanical construct while the terms “fixed-angle” [35, 48, 62, 154, 156, 157, 179, 222], “locked plating” [19, 27, 47, 56], or “locked plate/s” [32, 48, 58, 81] seem to be the most common ones used in the literature. Locked plates have shown to be been clinically successful at the proximal tibia, distal tibia, distal femur, as well as for the stabilization of challenging fractures in osteoporotic bone, e.g. for the proximal humerus or distal radius [137]. The design of locked-type constructs is very versatile. There are linear, anatomically shaped as well as irregular asymmetrical devices. They all rely on the same biomechanical principle (Fig. 3, part b), however, the bone plate-screw interface, i.e. the locking mechanism, might be differently designed. The term “angular stability” originates from spondylodesis, the operative internal fixation of

vertebrae [234, 235]. The process of anchoring angular stable screws in the bone plate is described e.g. as the “locking process” for multidirectional systems [233, 235]. For that purpose implant manufacturers have developed various technical solutions. The inter-locking mechanism may rely on form fit, frictional or material connection or a combination of those. A frictional connection results from the radial clamping bracing of the screw head in the pre-formed, undulated lip of the bone plate (e.g. company Medartis [92]). A solid connection can also be realized by a form-fitting connection of two titanium portions of different degrees of hardness” (e.g. company litos [91]). Here, a defined quantity of titanium in the form of a “material lip” is displaced by the thread of the screw head during insertion. The result is a solid material compound [234]. With the aid of “supplemental locking attachments” (“locking caps”), angle-stable implants may also be implemented in a multidirectional manner (e.g. company Zimmer [97]). Even conventional bone plates can be used in angular stable mode, but only in unidirectional function. For this purpose, additional locking inserts are needed, which fix the screw with a corresponding thread (e.g. company Stryker [93], DePuy Synthes [88]). For pre-clinical testing, the method to create such a locking construct is of secondary importance. All implants must comply with the general safety and performance requirements of the Medical Device Regulation, MDR [86], i.e. they must withstand the same (bio-) mechanical loads and/or moments, provided they have the same intended medical purpose. However, the type of anchoring the screws may cause secondary effects, including fretting corrosion (micromotion between screw head and plate hole) [8], bio-incompatibility or design defects (a design, that may inhibit callus formation), which are not subject of this work.

2.2 Regulatory requirements for bone plate-screw constructs

The market entry of medical devices is highly regulated and depends on regional, i.e. country-specific, national, regulatory requirements. The manufacturer of medical devices is responsible for the identification and implementation of relevant regulatory requirements for his products. For the purpose of legally marketing medical devices in the European Union, he typically documents, implements, applies and maintains a “quality management system” “for regulatory purposes” in accordance with ISO 13485 [108], while incorporating and meeting applicable regulatory requirements for all products he signs responsible for.

2.2.1 Requirements for medical devices in the EU

Bone plate-screw constructs are surgical implants and are class IIb medical devices according to the Medical Device Regulation MDR 2017/745 [86]. The regulation was officially published on 5 May 2017 and came into force on 25 May 2017. With the (final)

date of application on 26 May 2021, the MDR will finally supersede (amongst others) the Medical Device Directive MDD 93/42/EEC [85]. Although the regulatory provisions are in a transition phase from MDD to MDR, the MDR is already and will be the most important regulation to market medical devices in the European Union.

Its device classification depends on the intended purpose and associated risk potential of the device. Whoever “manufactures or fully refurbishes a device or has a device designed, manufactured or fully refurbished, and markets that device under its name or trademark” in Europe must meet all applicable requirements of the MDR [86]. One of the “obligations of the manufacturer” is to compile a technical documentation for each medical device that contains proof of compliance to the “General Safety and Performance Requirements” (GSPR), independent from its device classification [86].

Annex 1 of the Regulation includes product related “general safety and performance requirements” which apply to all medical devices and serve as the basis for CE marking, allowing its “placing on the market”, thus enables the free movement of goods in the EU [86]. These requirements are very general and they must be interpreted by the manufacturer whether they (fully) apply or not. Compliance with the “general safety and performance requirements” is an integral part of the “conformity assessment procedure” which each legal manufacturer needs to go through to demonstrate conformity with the Regulation [86]. In this context, the manufacturer shall provide proof of compliance with the GSPR, representing state of the art technology he intends to place on the market [86]. The legal manufacturer usually applies harmonized EN standards, that are published in the official journal of the European Union [87], which, when fully implemented, suppose presumption of conformity. This is why standards play an important role in conformity assessment procedures. This concept remains valid for the MDR, however harmonized standards under the Medical Device Regulation are not yet officially published [86].

2.2.2 General and particular requirements

Based on the “General Safety and Performance Requirements” (GSPR, previously set as the “essential requirements” under the MDD, Annex 1 in [85]) there are three levels of standards (with level 1 being the highest level) for non-active surgical implants and related instruments [111]. Level 1 standards include generic requirements applicable to all surgical implants. Level 2 standards apply to a series or a family of products, e.g. for implants for osteosynthesis and contain product specific particular requirements [111]. Level 3 standards are intended for specific implant types, e.g. metallic bone plates [111]. Tab. 1 describes these relationships for bone plate-screw constructs.

Construct component	*Level 1*	*Level 2*	*Level 3*
Bone plate	ISO 14630 [111]	ISO 14602 [112]	ASTM F382 [5] ISO 9585 [105]
Bone screw			ASTM F543 [7] ISO 6475 [103]

Tab. 1: Applicable standards for bone plate-screw constructs. Level 1-3 standards as defined in ISO 14630 [111] for each component of the construct. EN ISO 14630:2009 and EN ISO 14602:2011 are harmonized under the MDD 93/42/EEC [87], while harmonization under the MDR is not yet clear.

ISO 14630 contains general requirements for non-active implants [111]. In part 7.2 “pre-clinical evaluation” the standard requires that the surgical “implants shall undergo a pre-clinical evaluation based on a) the relevant scientific literature relating to the safety, performance, design characteristics, and intended use of the implant“, … , and “c) analysis of data obtained from testing, including bench-testing and, when available, data from validated techniques for evaluating implant safety and intended performance. Pre-clinical testing of implants should simulate conditions of intended use. Test methods and related limits for specific types of implants shall be defined and justified by the manufacturer“ [111]. Beyond the requirements of ISO 14630, the standard ISO 14602 contains particular, i.e. more specific requirements for implants for osteosynthesis [112]. In section 7.2 “pre-clinical evaluation” it refers e.g. to “static and / or dynamic loading tests”, which shall be conducted based on “accepted test standards, when available” (i.e. Level 3 standards as specified in Tab. 1), or on “customized test models taking into account the characteristics of the implant”. At the same time, it is stated that “because of the wide variance of implants and their features, testing standards might not exist, or may be modified as needed.” This part is just a repetition of what has already been defined in ISO 14630, section 7 [111]. And further down below: “Test methods can be (a) basic technical testing of implants or implant sections for characterization of the device (e.g. tensile, bending, torsion)”. This part is interpreted as mechanical testing for characterization purposes; “(b) testing of mounted components in relation to anticipated loading conditions; (c) testing of assemblies or parts under biomechanical conditions (bone can be replaced by a suitable, artificial material)”. Part (b) and (c) biomechanical testing under physiological loading conditions; “(d) testing under static conditions or dynamic conditions (cycling fatigue), Note 2 in section 7.2 of ISO 14602 [112]. There is no further clarification of how the testing shall be conducted. It is obvious that level 1 and level 2 standards listed in Tab. 1 do not contain specific (bio-) mechanical testing requirements, they deliver at least a framework for testing. While “accepted test standards” for bone plate-screw constructs are those listed as level 3 standards in Tab. 1, biomechanical testing (i.e. for research purposes) represented by a variety of scientific biomechanical articles, remains currently unspecified [33]. Based on the standard requirements stated above, there are generally two approaches to test or evaluate a device for osteosynthesis: biomechanical and mechanical testing.

2.2.3 Characteristics of pre-clinical testing methods

Biomechanical testing for research purposes is characterized by evaluating a bone plate-screw construct under anticipated, almost physiological loading conditions. Related experiments are designed e.g. for laboratory comparison of bone plates, to analyze different fixation techniques or for clinical research on healing capabilities after fracture repair. Test setups for biomechanical testing are very specific and are designed by each research group often for a particular anatomical region. They typically consist of an osteotomized cadaver bone or bone substitute material, modified to simulate biomechanical conditions after reduction and fracture fixation. It often includes a simulation of specific *in vivo* load transmission modalities and a replication of a complex AO fracture. Fig. 4, part 1, 2 and 3, show three typical examples of this category.

Mechanical testing of medical devices for regulatory purposes, however, is different. Principally, it shall be performed based on published internationally recognized testing standards, such as ASTM or ISO standards (although there are maybe regional or national deviations compared to the published ISO version). Fig. 4 shows typical mechanical test setups in this category (Part 4-7) and outlines the differences in comparison to biomechanical testing (Part 1-3). As illustrated in Fig. 4, part 4-7, there is a standardized (but idealized) metallic test setup that shall be used to measure standardized outcome variables. Such a standard testing procedure does not claim to simulate physiological biomechanics for a specific anatomical region but provides a “comprehensive reference” e.g. for bone plates (Scope 1.2 in [5]) to measure “performance related mechanical characteristics determined to be important to the *in vivo* performance of bone plates” (Scope 1.1. in [5]). However, many internationally recognized testing standards do not contain documented acceptance criteria (levels of performance), e.g. specified test limits for the assessment of implant strength “as insufficient knowledge is available to predict the consequences or their use in individual patients for specific activities of daily living” (Scope 1.2 in [5]). There is no specified design input requirement that shall be validated. This is a major disadvantage of many mechanical tests in general. Another important aspect is, that the number of potential variables in the test setup is limited to ensure maximum reproducibility. A comprehensive reference test method can be applied in every (accredited) laboratory and delivers objective evidence for direct implant or predicate device 75comparison. This is the most important advantage of mechanical implant testing, especially for the emerging field of managing regulatory requirements and for the purpose of defining design input requirements as per ISO 13485, section 7.3.3 [108]. Both pre-clinical testing methods are important to ensure a complete pre-clinical assessment of the device. They need to be assessed together, not separately. However, the ultimate goal of a level 3 testing standard is to combine them into one testing procedure. Ideally, a testing

standard shall evoke (all) clinically relevant failure modes prior occurrence, defined as “preventive action”, 8.5.4 in [108]. However, this goal has rarely been achieved [121].

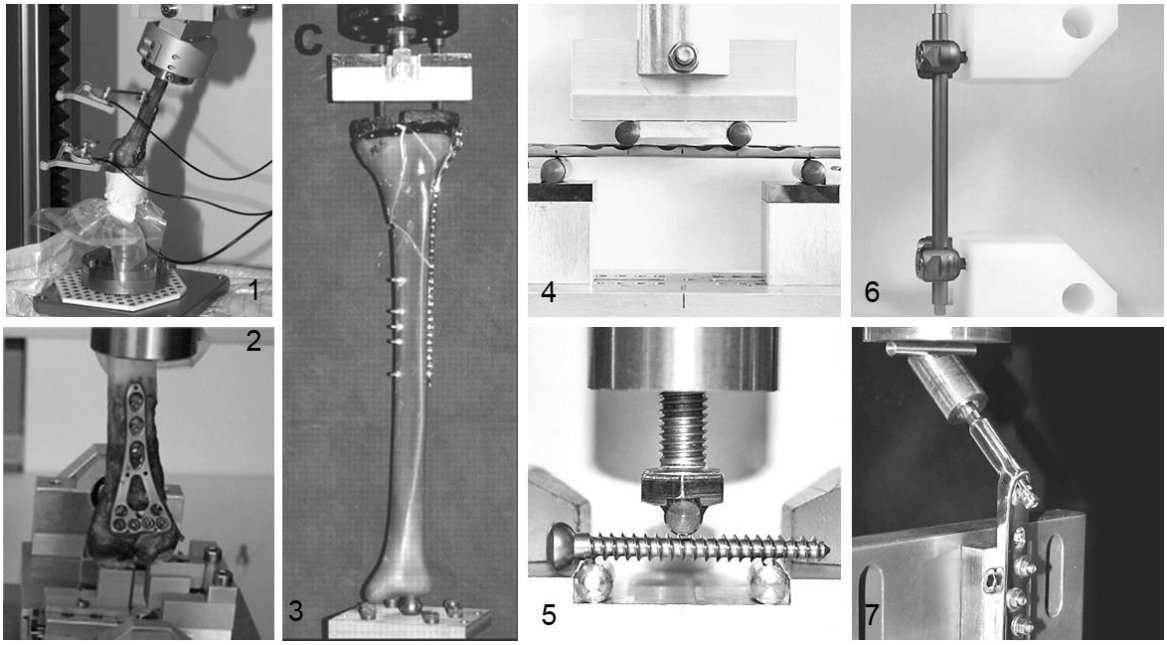


Fig. 4.: Examples of test setups for biomechanical testing for research purposes (part 1–3) and mechanical testing for regulatory purposes (part 4–7). Part 1: Test setup for the “Biomechanical investigation of fixed-angle plate osteosynthesis of the proximal humerus [180]. Part 2: Test setup for the “Evaluation of a polyaxial angle-stable volar plate in a distal radius C-fracture” [174]. Part 3: Test setup for a “comparative biomechanical study for complex tibial plateau fractures: Nailing and compression bolts versus modern and traditional plating” [139]. Part 4: Primary setup for testing of metallic bone plates according to ASTM F382 [5], as shown in [84]. Part 5: Setup for testing of parts of intramedullary fixation devices according to ASTM F1264 [9], as shown in [84]. Part 6: Setup for testing of spinal implant constructs according to ASTM F1717 [11], as shown in [84]. Part 7: Setup for testing of metallic angled orthopedic fracture fixation device according to ASTM F384 [6], as shown in [84]. All pictures were depicted in grays.

2.2.4 Standards related to testing and design evaluation [112]

Recognized level 3 standards related to testing of bone-plate screw constructs are ASTM F382 [5] and ISO 9585 [105] for “metallic bone plates” and ASTM F543 [7] and ISO 6475 [103] for “metallic medical bone screws”. These standards currently provide guidance for mechanical testing. Especially ASTM F382 [5], a standard introduced in 1999 and reapproved in 2003, 2008, 2014 and in 2017 with insignificant changes, is the most important and most recent testing standard applicable for metallic bone plates. ASTM F2502 for “Bioabsorbable Plates and Screws for Internal Fixation“ contains identical test methods [13]. Besides those standards mentioned above there are many level 3 standards which contain product-relevant dimensions or e.g. clinically proven, standardized material for non-active implants. In addition, there are test procedures for specific characteristics of the implant, e.g. for evaluating the coating quality or measuring fretting corrosion of plates and screws [8]. These regulatory requirements may also apply to locked-type devices, but they are of secondary importance for the purpose of this work. Standards of the American

Society for Testing and Materials (ASTM), although widely used and accepted within the regulatory testing community, cannot formally be used for the presumption of conformity, but they may also represent state of the art testing methodologies [50, 86]. ASTM standards for osteosynthesis specify test procedures and measures to be determined from them, but they often do not postulate acceptance criteria that a manufacturer has to fulfill.

2.2.5 Applicable standardized mechanical test methods

For bone plates ASTM F382 [5] and ISO 9585 [105] define static and dynamic bending tests using the 4-point bending test setup e.g. as shown in Fig. 5. The bending property is a "critical characteristic of bone plates for orthopedic applications since the bone plate provides the primary means of stabilizing the bone fragments, thus has a direct impact on bone healing (section 7.2 in [5]). The 4-point bending test creates a constant bending moment M_b over the entire loading span, with $M_b = F * h / 2$.

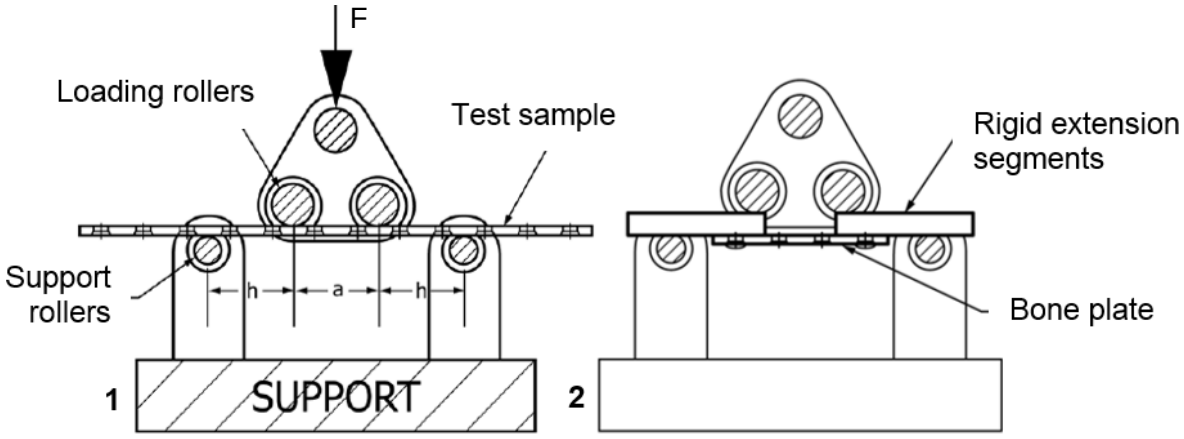


Fig. 5.: Established standardized 4-point bending test setup according to ASTM F382 [5]. Part 1: Preferred method. This is the primary recommended setup for direct bending of straight bone plates (h: loading span distance, a: center span distance [5]). Part 2: Alternative method. This is the proposed setup using rigid extension segments for "bone plates that do not have a sufficiently long section of symmetry or do not have a section of symmetry (as for most "specialty plates") [5]. Those plates "can be attached to rigid extension segments. The rigid extension segments can be used to effectively lengthen the bone plate so that the bone plate can be tested with the four-point bend test method", Annex 1, section A1.6.2.1. in [5].

The test setup as shown in Fig. 5 is suitable for linear or straight bone plates e.g. for diaphyseal femoral or tibial implants, using the primary recommended setup for direct bending of bone plates (Part 1 in Fig. 5). However, this setup cannot be used for all modern plate variants, especially not directly for anatomically shaped plates, locked-type constructs or small plates. And finally, this setup does not constitute a functional test for the bone plate-screw construct. This is why "specialty plates" or devices, that do "not have a section of symmetry", or even small, short bone plates shall be connected to "rigid extension segments" using the "alternative test method" (Part 2 in Fig. 5) [5]. The standard requires, that „if the bone plate is asymmetrical (as in the case with most specialty plates), place it

with two screw holes between the loading rollers so that the position of the fracture, for which it is intended to be used, is located between the loading rollers (A2.8.2.4. in [5]). In addition, the standard states that “when the structurally critical region of the bone plate is shown to be located through a non-uniform region of the bone plate (i.e. a peri-prosthetic, contoured plate), it may be necessary to evaluate the bending strength, bending structural stiffness, or bending stiffness of this region of the bone plate using a different test method. This is because it may not be physically possible to fit the non-uniform region between the loading rollers of a four-point bend test” (A1.1.3 in [5]). Further the standard says, that ”screw holes or other interlocking features or contoured regions may be located at the proximal or distal extremities of a bone plate, and may result in structurally critical regions at these locations” (A1.1.3 in [5]). There is no further specification of what the “different test method” shall be. Consequently, implant manufacturer may test only those (i.e. linear, symmetric) parts of the contoured plate that fit into the test setup or may even manipulate the pre-contoured plate in order to be able to mount it for testing. The standard ASTM F382 [5] contains specified outcome variables in order to mechanically characterize the bone plate. With the help of a “single cycle bend test”, the bending stiffness, shall be determined in the recorded curve X/Y-curve [5]. This technique can be found in several standards [6, 9, 10]. It represents the state of the art in mechanical device testing [86].

The dynamic testing procedure aims to determine the bending fatigue properties of the plate. It is described in two different methods [5], either as “M-N diagram” testing (maximum bending moment levels versus number of loading cycles, characterization of the “general fatigue behavior of the bone plate over a range of applied bending moments”) or as “fatigue strength determination” (“testing a bone plate design at a given number of fatigue cycles”, typically at $n = 10^6$), A2.4.2, A2.8.1.1 and A2.8.1.2 in [5]. In general, 4-point bending tests are widely used in many technical areas and are not only standardized in the medical field, e.g. to determine flexural properties of plastics composites as per ISO 14125 [109]. For bone screws, there are three standardized tests as defined in ASTM F543 [7] (Tab. 1). Since screws are subjected to torsional forces during implantation, limits apply to the minimum torque to be transmitted (1). It is also necessary to determine the twist angle of the screw under torsional loading (2). ASTM F543 [7] also describes the measurement of the axial pull-out force under standardized conditions (3). Pullout is the most clinically relevant failure mode for conventional bone screws [50]. Those test methods may apply to all kinds of bone screws. They do not necessarily simulate the physiological load of the screw, but serve to compare the screws with each other or with products from different manufacturers: "This test method is used to measure the axial tensile force required to fail or remove a bone screw from a defined material. The results obtained in this test method are not intended to predict the force required to remove the subject bone screw from human or animal bone.

This test method is intended only to measure the uniformity of the products tested or to compare the mechanical properties of different, yet similarly sized, products" (A1.1.1 in [7]). “The results obtained in this method bear no direct correlation to the use of the subject bone screw …” (A2.1.1 in [7]). “This test method is used only for purpose of maintaining the uniformity of the product tested" (A2.1.1 in [7]). In sum, ASTM F382 [5] as well as ASTM F543 [7] are valid standards defining independent test methods for plates and screws, but they do not state requirements for the functional construct of those components.

2.2.6 Available non-standardized test methods

Published non-standardized test methods for the design evaluation are rare. The VDE (Verband der Elektrotechnik Elektronik Informationstechnik) has recently published a non-binding guideline VDI 5703, entitled ”systematical development for a model-based testing of medical devices [210]. This guidance document proposes a model-based testing based on the principles of risk management. As an example for applying the methodical approach it covers another fracture fixation device, an intramedullary nail. An excerpt of the risk analysis is shown in Tab. 2. There are two different risk control measures to address the hazard of ”inadequate fracture stabilization” [210]. The first one, ”testing the device on a suitable fracture model” using “reference values from the literature and / or comparison to clinically validated (competitive) products” [210], corresponds to what has previously been categorized as “biomechanical testing for research purposes” in section 2.2.3. Here, a biomechanical setup is used to test the device in order to compare the results to “values from the literature” or with other “products and therapy methods” [210].

Hazard	*Sequence of events Hazardous situation*	*Harm*	*Root cause*	*Risk control measure*
Inadequate fracture stabilization	Stiffness of the Implant-construct low or too high	• Delayed fracture healing • Pseudarthrosis • Re-operation	• Inadequate dimensions • Wrong choice of materials • Incorrect assembly specifications • The construct is not suitable for the selected indication	(1) • Testing the device on a suitable fracture model • Reference values from the literature and / or comparison with (clinically) proven (competitive) products and therapy methods • Outcome variables: e.g. reversible and non-reversible displacement of fractured elements or device components
Inadequate fracture stabilization	Stiffness of the intramedullary nail too low	• Delayed fracture healing • Pseudarthrosis • Re-operation	• Wrong choice of materials • Incorrect assembly specifications	(2) • 4-point bending tests as per ASTM F1264 • Comparison with established devices
	Stiffness of the intramedullary nail too high		• Wrong choice of materials • Incorrect assembly specifications	

Tab. 2.: Testing considered as mitigation measure to reduce risk demonstrated for an intramedullary nail. Excerpt of the risk analysis. Biomechanical testing (1) and mechanical testing (2) considered as separate risk control measures [210]. The risk analysis is incomplete with respect to the requirements of ISO 14971 [113].

The second risk control measure corresponds to “mechanical testing for regulatory purposes” as described in section 2.2.3 and relies on standardized tests and a direct comparison of devices. Both testing methods seem to be equally important and need to be compiled to a complete pre-clinical assessment of a bone-plate-screw constructs. The risk control measure itself is not covered nor further specified therein. The actual "modeling of relevant interaction between the medical device and the human body" and "the design of a test model using a methodical approach" is not described as it shall be developed by the user [210]. This document is helpful to determine the need and to derive test methods based on risk management, but it does not give specific testing guidance (for biomechanical testing) due to the variety of different devices that are potentially within the scope of this document. However, the content is in line with the general distinction of pre-clinical testing methods outlined in section 2.2.3.

2.3 Conclusion

Bone plate-screw constructs are medical devices and are therefore subject to pre-clinical testing for regulatory purposes. Existing standards are applicable for those devices, but they do not set specific testing requirements for them, whether in level 1, level 2 nor in level 3 standards. While static and dynamic bending tests are required, it remains unclear why other fundamental loading conditions, such as torsion or compression, are not taken into consideration for testing. Moreover, since the publication of the 4-point bending setup in 1990 [105], the design of bone plates (and subsequent its postoperative protocol) has changed significantly:

1. Modern conventional and locked-type devices are no longer straight, linear devices, but mostly pre-contoured and adapted to local biomechanics. The (systematic) application of available standards for such plates is not adequately considered [50].
2. Modern locked-type constructs represent a functional, rigid combination of the plate with corresponding screws, a connection which is designed to be mechanically load-bearing, ensuring load stability in the early rehabilitation phase. This is a major design change which did not significantly affect latest revisions of available standards.
3. Small bone plate applications cannot be tested using available standards.

In sum, there is a gap between state of the art plating systems and available pre-clinical testing methods.

3 A systematic literature review of test methods and parameters

3.1 Introduction and purpose of the review

Systematic overview papers regarding test methods for bone plates are rare. A review article for distal radius implants was presented by Mehling et al. focusing on clinical relevance of selected published biomechanical studies [155]. One of the key findings of the authors was, that “the biomechanical studies published differ in terms of the study design, the implants tested, the fracture model used and the biomechanical tests performed (axial compression, bending, torsion, static/dynamic testing, loading to failure). Therefore comparability is limited, yet makes comparison between individual studies almost impossible” [155]. Another review of biomechanical testing methods has been published by Maozen et al. for periprosthetic fracture fixation of the femur following total hip arthroplasty [150]. The authors concluded that “there is currently a lack of standardization in the methods used. In the experimental studies, there is a lack of consistency in both the testing procedures and the measurements. This means it is difficult to make conclusive comparisons between the findings, which would be particularly useful since each experimental study can only examine a small subset of the patient variables and fixation methods available” [150]. A third “scoping review of biomechanical testing” has recently been published by Cruickshank et al. for biomechanical tests conducted at the proximal humerus [33]. The authors “suggest a strong need for standardization of testing parameters to ensure results can be compared between studies” [33]. Currently there is no other systematic review available that focuses specifically on test methods applied by the authors.

Consequently, the aim of this review is to investigate the following question: Which test methods and test parameters are used in the literature to test or evaluate metallic, conventional or locked-type bone plates for osteosynthesis in a biomechanical and/or clinical environment, especially for modern anatomically shaped implants for lower and upper extremity?

3.2 Search process

3.2.1 Publication selection process

A typical biomechanical setup subject to this review consists of a bone plate which is fixed by several screws to an osteotomized cadaver bone or any kind of bone substitute and which is loaded by a materials testing machine in a static and/or dynamic compression

(tensile), bending or torsional loading test or a combination of these. A systematic search process based on the guidelines proposed by Kitchenham [127] was initiated to identify suitable biomechanical articles. In order to identify the most appropriate search terms to capture the largest possible number of biomechanical publications, the term “biomechanical” was set as the basic search term followed by ”testing” and “bone plate“ or “plate” using Boolean AND to combine them. All possible abbreviations, alternative spellings, and synonyms usually related to the meaning of “testing” such as “analysis”, “comparison”, “evaluation”, “investigation”, “difference”, “properties” and “characteristics” were considered.

In many cases the authors intend to determine the “stability” or “stiffness” of such a setup. This is why both terms were included into the title search. The anatomical region was specified by applying medical subject heading search terms (MESH) for each bone (“clavicle”, “humerus”, “ulna”, “olecranon”, “radius”, “metacarpal bones”, “femur”, “tibia”, “fibula”, “metatarsal bones”). The specification of the anatomical region was performed for the title and abstract of the publication since it was observed, that the title alone often does capture the bone plate location under load. All other terms were used to search within the title. Finally, the terms “screw” or “screws” were excluded from the title search to avoid selecting studies on screws only (Database: PubMed/MEDLINE; Search date: 2015-05-14). The total number of studies found was reduced by applying pre-defined criteria for inclusion and exclusion. Fig. 6 illustrates the publication selection process and subsequent analysis in detail.

3.2.2 Selection criteria

Pre-defined selection criteria for in- and exclusion of articles were necessary in order to reduce the amount items found. Out of n = 262 items initially found during the search process the study selection criteria were applied. In total n = 159 papers remain after the exclusion process (Fig. 6). These articles were analyzed (a detailed data analysis can be found in annex 12.1).

The following inclusion criteria were applied for that purpose:

1. Biomechanical studies using locking, conventional or double plating systems.
2. Comparative biomechanical studies using different methods for osteosynthesis, as well as peri- or intraprosthetic implants, if at least one plating system was part of the study.
3. Testing of bone plates using cadaver bones, bone substitute material or solid metallic setups.
4. Biomechanical studies using specific bone setups, e.g. animal or pediatric bone models, unstripped intact cadaver bones and/or joints.
5. Papers published from 2000 to 2015.

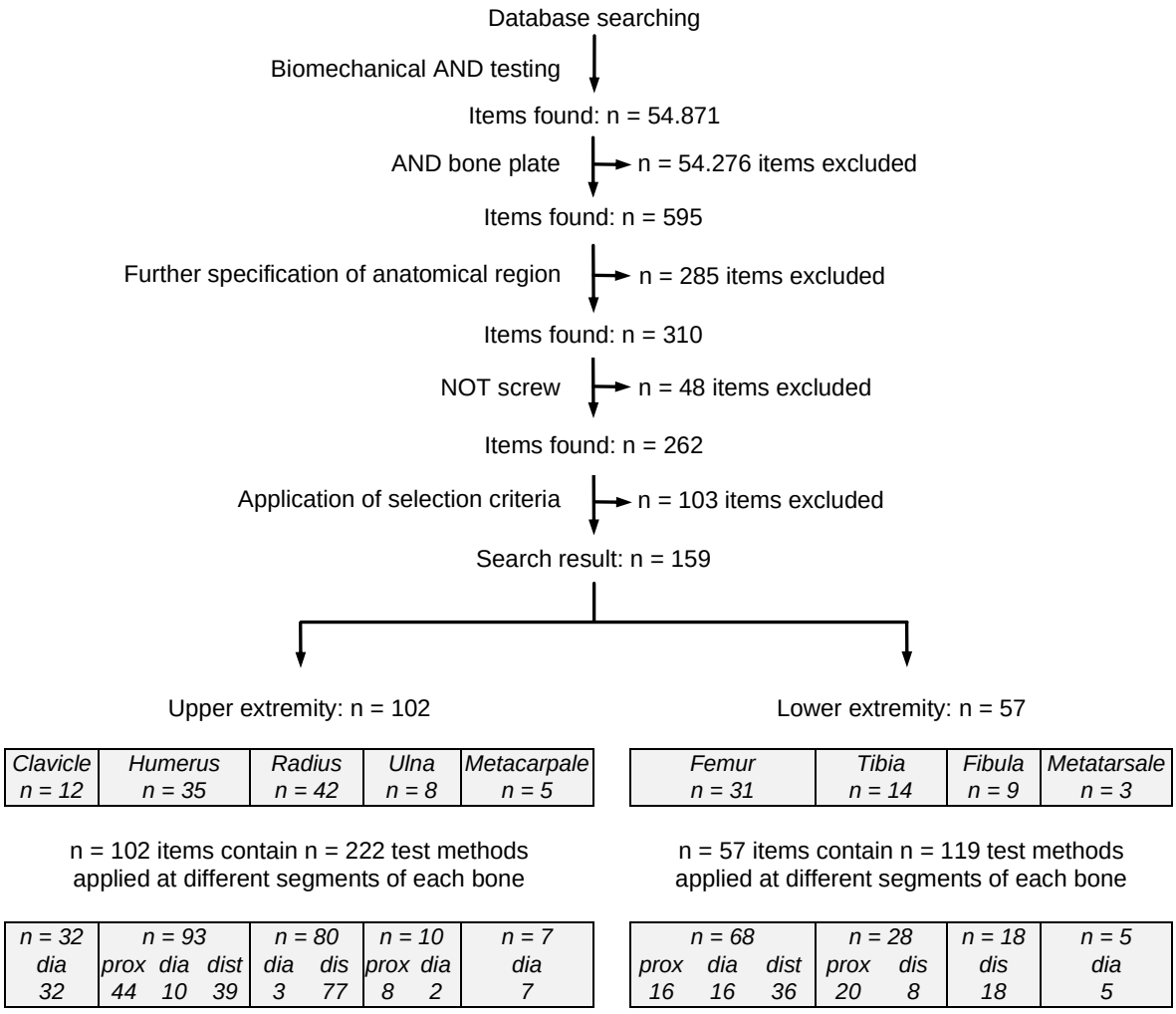


Fig. 6.: Publication selection process and subsequent analysis of data. Determination of the search result, subdivision into relevant groups and analysis of the items found. In each publication the applied test method and relevant test parameters were determined. The last row shows the number and distribution of test methods per bone segment (prox = proximal, dia = diaphyseal, dis = distal).

The following exclusion criteria were applied:

1. Biomechanical studies on implants for other anatomical regions than those listed in section 3.2.1.
2. Biomechanical studies on other implants for osteosynthesis, e.g. external fixators, intramedullary nails, K-wires etc.
3. Any investigation intended to assess the clinical outcome of the treatment, e.g. postoperative treatment analysis, Clinical investigations, Clinical studies, Clinical case reports and others.
4. Digital simulation studies only (without mechanical lab testing).
5. The publication was not available in English or German.
6. Repeated items found during the search process.

3.2.3 Conducting the review

All items found were subdivided per anatomical region under test, resulting in a distribution of test methods per bone segment (Fig. 6). In each publication the test method (either compression, bending, torsion, tensile or a combination of those), the type of test (static or dynamic loading test), the fractured bone segment under load (proximal, diaphyseal or distal element), the specified test parameters applied (e.g. maximum force or moment, loading range, number of dynamic cycles) as well as further test specifics were determined. The chosen bone model (cadaveric or bone substitute material) and the measured outcome variable were recorded as well. The review data extracted from each publication were summarized for upper and lower extremities. In order to systematically analyze the publications found, the following regulations and explanations were indispensable:

1. As a result of externally acting forces and moments four categories of (idealized) test methods were defined. Each test presented in the literature was classified as compression, bending, torsion or tensile test. This regulation was necessary as not all externally acting loads or moments were of “pure nature”, e.g. a combination of an axial force and a bending moment acts on the distal radius when the compressive load is applied with an offset (as illustrated in Fig. 10).
2. The information was taken directly from the methods and materials section of each publication. The units are cited from the original study. No interpretation or calculation was performed, e.g. no calculation of the bending moment was made (if possible) if the value for the bending moment expressed in Nm was not shown.
3. A dynamic test is intended to assess the behaviour of a subject under repetetive loading. For the purpose of this review it consists of more that one loading cycle and a sinusoidal load pattern, if not mentioned otherwise. The interpretation of a dynamic test is very versatile. Since one loading cycle is used for a static test, all tests using more than one loading cycle were categorized as dynamic tests. However, not all dynamic tests identified are therefore capable to determine the fatigue behaviour of the construct. This is why a dynamic test is not necessarily a dynamic fatigue test.
4. A static or dynamic test using two test methods simultaneously is indicated by the word “combined” in annex 12.1, the extracted data of the review. In this context both test methods contribute to the total amount of test methods shown in Fig. 7, Fig. 8.
5. A tensile load is the opposite of a compressive force, in a stress-strain-diagram typically with a positive sign. In the context of this literature review, not all tests, where a tensile force was applied, were categorized as such, e.g. in a biomechanical setup for the

proximal humerus. In this case a tensile load was applied to simulate the load pattern *in vivo* [124]. This test is classified as a bending and not as a tensile test.

As a result of the literature review n = 159 papers that contain in total n = 330 biomechanical tests in the categories upper extremity (n = 102 publications, n = 217 biomechanical tests) and lower extremity (n = 57 publications, n = 113 biomechanical tests) were analyzed. Since some tests were designed as combination tests, the total number of recorded individual test methods included is slightly higher. It was necessary to distinguish between the number of "test methods" identified" (n = 341 test methods) and the number of "physical tests" performed to avoid false interpretations of the total amount of combination tests found in the literature.

3.3 Results

In general, the biomechanical testing literature on bone plates for osteosynthesis is diverse, inconsistent and heterogeneous. Test parameters are not uniformly displayed in the literature. While axial loads were mainly specified in Newtons, other test parameters are presented in many different ways, especially for bending and torsion tests. Depending on the loading mode (load- or displacement-controlled), the units for a bending test were displayed in N, deg or ° (degrees), Nm, mm. Torsion test parameters were reported in Nm, N, deg or ° (degrees). This demonstrates variability in biomechanical testing but limits inter-comparability between studies. The following results were subdivided for upper and lower extremities.

3.3.1 Upper extremity

In total n = 222 test methods from n = 57 publications were identified in studies at the upper extremity and they were further subdivided per bone and bone segment as previously shown in Fig. 6. The following Fig. 7 shows the distribution of test methods identified for each bone. The main test methods observed were compression, bending and torsion. Those test methods were equally distributed for the clavicle and the humerus (except for torsion tests at the distal humerus). However, that does not mean that four possible tests methods appear in each study. Tensile tests were only applied at the clavicle (9 %, n = 3/32). The majority of the tests conducted at the radius were compression tests (76 %, n = 61/80), followed by bending tests (15 %, n = 12/80). Despite the low number of studies included, bending was the dominant testing method for ulna (80 %, n = 8/10) and metacarpale (86 %, n = 6/7).

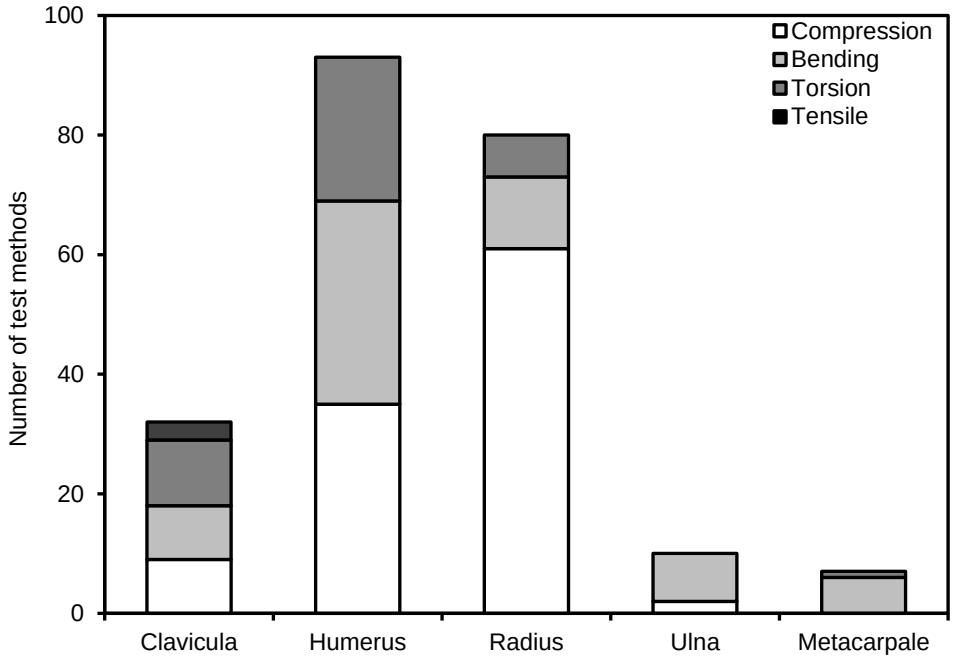


Fig. 7.: Upper extremity. Distribution of test methods applied for each bone (n = 222).

Approximately 60 % of the biomechanical tests were static tests, designed as destructive test or with a predefined maximum test limit. Dynamic test were conducted in 40 %. About half of the publications contain both, static and dynamic tests (56 %). Cadaveric bones and bone substitutes were frequently used across the studies, however, cadaver bones were used more frequently (60 %). The majority of the tests are designed as “single tests” (96 %), meaning a static or dynamic loading test using only one test method. Combination tests were rarely observed in the literature (4 %). The only combination test identified was a combination of compression and torsion (clavicle 1x, prox. humerus 2x, dist. radius 3x, prox. ulna 1x). Furthermore, the maximum testing value per test method for each bone has been determined. Due to the heterogeneity of the data obtained no specified testing value could be determined. However, at least a “guidance value” for static and/or dynamic (stiffness) testing could be derived from the literature, especially for compression testing. Absolute numbers, relative frequencies and related maximum test parameters for all bones and bone segments are comprehensively summarized in Tab. 3, section 3.3.5.

3.3.2 Lower Extremity

In total n = 119 test methods were identified at the lower extremity and they were subdivided as shown in Fig. 6. The following Fig. 8 shows the distribution of test methods identified for each bone.

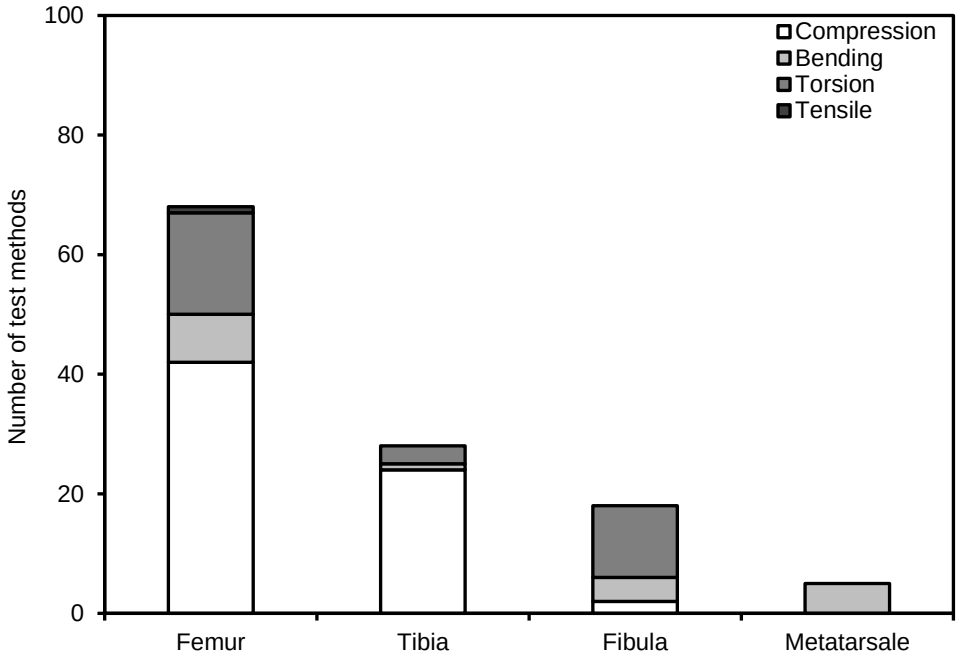


Fig. 8.: Lower extremity. Distribution of test methods applied for each bone (n = 119).

For the femur and the tibia compression tests were conducted in 62 % and 86 % respectively, followed by torsion (femur: 25 %, tibia: 11 %). The majority of the publications selected for the fibula revealed a torsion test (67 %, n = 12/18). All tests conducted at the metacarpale were designed as bending tests (n = 5/5). The majority of the tests are designed as “single tests”. Combination tests represent approximately 10 % of all studies included in the analysis. A combination of compression and torsion was observed for the diaphyseal femur 2x, distal femur 8x, distal tibia 1x and the distal fibula 3x. The data for the relative frequencies for static and dynamic tests as well as for the usage of bone or bone substitute material showed no significant difference compared to the upper extremity. However, compared to the tests of the upper extremity dynamic increasing-amplitude tests were more frequently observed at the lower extremity.

The analysis principally led to the same result as previously summarized for the upper extremity. For the femur and the tibia compression testing has frequently been conducted. Torsion tests were observed much more frequently compared to bending tests, especially for biomechanical testing at the femur or fibula. Due to the heterogeneity of the data no specified testing value could be determined. However, at least a “guidance value” for static and/or dynamic (stiffness) testing could be derived from the literature, especially for compression testing, where a relatively high number of studies were included in the review. Combination tests were rarely found in the literature, mainly in dynamic loading conditions of the lower extremity (distal femur, distal fibula). Absolute numbers, relative frequencies

and related test parameters for all bones and bone segments are comprehensively summarized in Tab. 3, section 3.3.5.

3.3.3 Variability of outcome and test parameters and other testing specifics

Outcome parameters are not commonly applied nor defined. A significant variety of outcome variables was observed, including but not limited to “stiffness” [225], “relative or percentage of stiffness” [37], “strength”, “ultimate strength” [75], “peak load” [129], “failure load” [37], “elastic/plastic deformation” [222], “yield load” [136], “displacement” [45], “interfragmentary motion” [48], “intercyclic fracture motion” [196], “deformation angle” [169], “fracture gap movement” [79], “screw angulation” [148], “cycles to failure” [230], “subsidience” [175], “torque to failure” [54], “range of motion” [174] or “survival rate” [179], and others. This circumstance limits inter-comparability between studies yet makes comparison between individual studies almost impossible.

Stiffness was the main outcome variable identified (74 %), yet four out of twelve papers that contained a stiffness measurement only, concluded an “adequate” or “superior stability” of the construct [56, 117, 142, 160]. However, “stability” is not a defined mechanical term and not attributed to 1 or more outcome variables. There is no “optimal stiffness” defined as a stiffer implant does not necessarily mean that it is “biomechanically superior” [20]. In many articles a “load to failure”-test was observed (64 %), however, the definition of the “failure” is inconsistent as it mainly depends on the type of measurement conducted. A failure of the construct can be a “displacement” [45] or an “interfragmentary motion” [48] greater than x mm, it can be an implant breakage, a drop of x mm in the recorded loading curve, screw loosening, a bone fracture, screw cutout, and others. All load to failure-tests were conducted within the limits of each individual failure criterion, however, as the failure mode is inconsistently applied, the outcome of each study cannot be used for direct comparison.

The test parameters applied vary in particular for bending and torsion tests. Throughout the review axial loads were specified (or recorded) in Newton. Other test parameters are presented or applied in many different ways, especially for bending and torsion tests. Bending test were displayed in N, deg or ° (degrees), Nm or mm. Torsion test parameters were specified or reported in Nm, N, deg or ° (degrees). Consequently, test parameters as well as test results remain valid in each individual scientific study, but are not suitable for comparison of studies and study results. This is caused by the heterogeneity of the test methods applied, e.g. a bending test can be designed as cantilever-, 3-point- or 4-point-bending test, or as bending test induced by tensile forces in a specifically designed test bench [124]. This demonstrates variability in biomechanical testing but limits inter-comparability between studies significantly. Without further (standardized) information about the test setup, comparison between individual studies remains almost impossible.

Static and dynamic tests were equally distributed across all studies selected. The majority of n = 87 papers (55 %) contained static and dynamic tests, while n = 45 publications (28 %) contained a static test only, n = 27 (17 %) a dynamic test only. Although not consistent, this is in line with the standard, which states, that “If static and/or dynamic loading tests are relevant for the evaluation of the implant” … “customized test models” … ”shall be applied” [5], 7.2b). Static and dynamic tests are equally important to assess the clinical performance of a bone plate or a bone plate-screw-construct [5], however, it remains unclear which constructs for which anatomical region shall be subject of static and dynamic loading testing.

3.3.4 Number of dynamic loading cycles

The number of cycles for dynamic testing varies significantly from three cycles for an “increasing-amplitude test” to fatigue testing with n = 10^6 cycles [220]. “Constant-amplitude-tests” were observed in approximately 76 % across all dynamic tests conducted [220]. The determination of the number of cycles for dynamic testing is currently based on assumptions, mainly because there are no measured values available for the amount of limb or body movements after the surgical treatment has been accomplished. In this study only two dynamic loading tests (upper extremity: 1x distal humerus, lower extremity: 1x metatarsale) were based on the assumption that one million dynamic cycles represent the annual cyclic exposure for bone plates (ASTM F382 specifies n = 150 - 250.000 loading cycles for a postoperative period of two to three month, Annex A2, X3.3 in [5]). The majority of the dynamic loading tests (77 %) were designed by specifying the number of dynamic loading cycles anticipated for the postoperative rehabilitation phase (“constant-amplitude-test”) [220]. Such specification is often an individual scientific assumption. The remaining dynamic tests were designed as “increasing-amplitude tests”, a stepwise approach with an increasing load after a specified time period or after completing a set amount of cycles [220]. In order to get an overview of how many loading cycles were specified (but not necessarily applied or accomplished) for dynamic testing, the data for the categories upper and lower extremity were analyzed. All dynamic tests (n = 102) with a constant amplitude were included since increasing-amplitude tests intend to shorten the test period while applying higher loads. Increasing-amplitude tests are not subject of any mechanical testing standard so far. Fig. 9 summarizes the result.

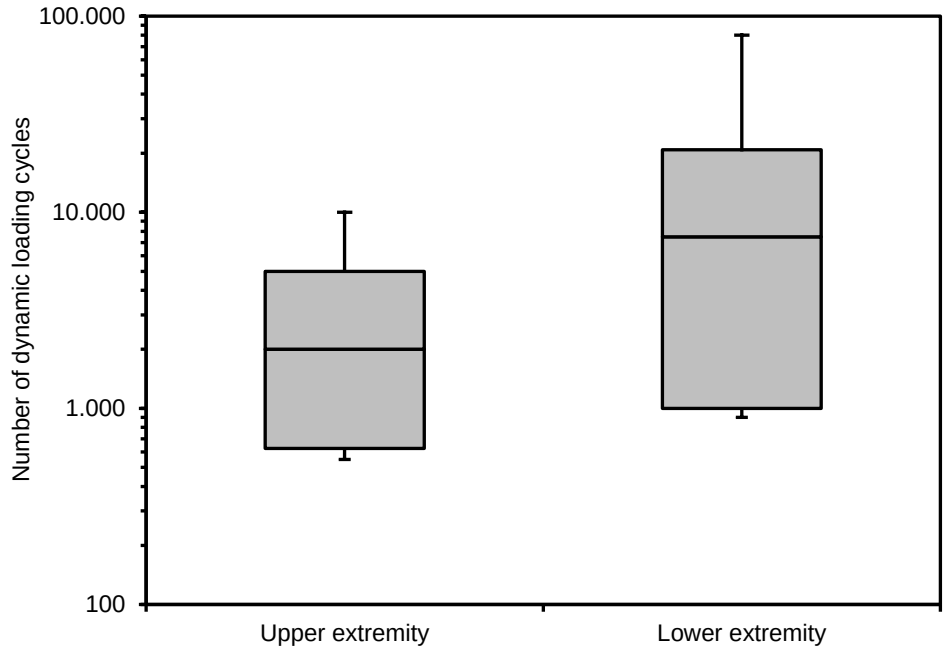


Fig. 9.: Pre-clinical testing under dynamic conditions. Number of specified dynamic loading cycles with a constant amplitude for bones of the upper (n = 78) and lower extremity (n = 24) shown as box-plot (10 %- and 90 %-Percentiles, Quartiles, Median) using a logarithmic y-axis. (Median for upper extremity = 2.000 cycles; Median for lower extremity = 7.500 cycles).

The box-plots indicate, that the number of cycles anticipated for lower extremities is expected to be higher than for upper extremities. The data extracted from the studies show that 90 % of all dynamic cycling tests conducted at the upper extremities were specified with 10.000 dynamic loading cycles or below (upper quartile: n = 5.000 cycles), tests conducted at the lower extremity with n = 80.000 dynamic loading cycles or below (upper quartile: n = 20.833 cycles). That means, that the number of dynamic cycles for lower extremities is expected to be three to four times higher than for upper extremities (multiplication factor based on median). But the data also revealed that the numbers presented in the literature are much lower than those required by the standard [5]. However, looking closer in the informative annex X3.2 of the standard, it is stated, that ”since the time frame, number of loading cycles and loading conditions are uncontrollable and unpredictable, there is no acceptable limit which can be set for the bending moment or number of cycles of load which the bone plate should withstand in any given case [5]. And further down below: ”Even though the test method’s recommendation of one million cycles for estimating the fatigue strength has been arbitrarily chosen, it still can be considered conservative since no bone plate in clinical service would normally be expected to withstand $n = 10^6$ high stress loading cycles” (Annex A2, X3.3 in [5]). Obviously, the standard presents a “reference test method for comparative purposes”, but does not necessarily claim clinical relevance [5].

3.3.5 Summary of the data obtained for upper and lower extremity

Tab. 3 shows a comprehensive summary of the data extracted from the literature review separated for upper (Part A) and lower extremity (Part B). The complete analysis of each literature source is documented in Annex 12.1. Tab. 3 contains relative frequencies for each test method per bone and per bone segment as well as the maximum loading value found in the literature for each test method. These values are specified values taken from the materials and methods section of the publication. They do not represent a performance level, a threshold value which indicates a test failure. Furthermore, no assessment was made whether the planned test parameter had been reached or at which load level / moment the test terminated. The values printed in *italics* in Tab. 3 must not represent the maximum value found due to a lack of consistency of methods applied and units displayed. In that case more than one value appears per bone segment, e.g. for the values shown for static testing at the proximal humerus ("7.5 Nm, 100 N and 4 mm"). While a bending moment specified correctly with 7,5 Nm is unambiguous, bending tests using "100 N" or "4 mm" are not. Consequently, it remains unclear which value would represent the maximum. A complete list of the analysis including a list of all articles reviewed and specific values for each publication is attached in annex 12.1 of this work.

	A	***Clavicle***		***Humerus***				***Radius***			***Ulna***			***Metacarpale***	
		dia.	*%*	*prox.*	*dia.*	*dist.*	*%*	*dia.*	*dist.*	*%*	*prox.*	*dia.*	*%*	*dia.*	*%*
1	***Compression***	9	28	15	3	17	37	1	60	76	2	--	20	--	--
	Static test	500 N	--	500 N	100 N	250 N	--	--	300 N	--	30 N	--	--	--	--
	Dynamic test	500 N	--	450 N	250 N	150 N	--	200 N	800 N	--	100 N	--	--	--	--
	Bending	9	28	14	1	19	37	1	11	15	6	2	80	6	86
	Static test	--	--	*7.5 Nm* *100 N* *4 mm*	200 N	*6 Nm* *120 N*	--	--	*±1.5 Nm* *80 N*	--	--	--	--	--	--
	Dynamic test	*143 N* --	-- --	*7.5 Nm* *5 mm*	-- --	*200 N* *4.5 Nm*	-- --	*75 N* --	1.5 Nm --	-- --	*300 N* --	-- --	-- --	-- --	-- --
	Torsion	11	34	15	6	3	26	1	6	9	--	--	--	1	14
	Static test	-- --	-- --	*8.3 Nm* *4°*	4.5 Nm --	9 Nm --	-- --	-- --	2.0 Nm --	-- --	-- --	-- --	-- --	-- --	-- --
	Dynamic test	*4.97 Nm* *±10°*	-- --	*7.5 Nm* *8°*	*4.5 Nm* *5 N*	-- --	-- --	±2 Nm --	1.5 Nm --	-- --	-- --	-- --	-- --	-- --	-- --
	Tensile	3	9	--	--	--	--	--	--	--	--	--	--	--	--
	Static test	--	--	--	--	--	--	--	--	--	--	--	--	--	--
	Dynamic test	300 N	--	--	--	--	--	--	--	--	--	--	--	--	--
2	*Single test*	29	97	40	10	39	98	3	73	96	7	2	90	7	100
	Combination test	1	3	2	--	--	2	--	3	4	1	--	10	--	--
3	*Static test*	13	43	22	6	25	58	--	46	58	4	2	60	6	86
	Dynamic test	17	57	20	4	14	42	3	30	42	4	--	40	1	14
	Dyn. constant	12	71	17	4	11	84	3	26	88	3	--	75	1	100
	Dyn. stepwise	5	29	3	--	3	16	--	4	12	1	--	25	--	--
4	*Cadaver bone*	17	57	38	4	30	79	--	51	65	6	1	70	4	57
	Bone substitute	13	43	4	6	9	21	3	25	35	2	1	30	3	43
5	*Stiffness*	11	92	11	2	11	69	1	35	86	2	1	38	3	60
	Load to failure	10	83	14	2	5	60	1	25	62	4	2	75	5	100

	B	Femur				Tibia			Fibula		Metatarsale	
		prox.	*dia.*	*dist.*	*%*	*prox.*	*dis.*	*%*	*dis.*	*%*	*dia.*	*%*
1	***Compression***	10	7	25	62	20	4	86	2	11	--	--
	Static test	1.868 N	500 N	1.790 N	--	1.112 N	400 N	--	720 N	--	--	--
	Dynamic test	1.000 N	1.000 N	2.640 N	--	1.000 N	750 N	--	--	--	--	--
	Bending	3	4	1	12	--	1	3	4	22	5	100
	Static test	*50 N*	36 Nm	*300 N*	--	--	15 Nm	--	*3.9 Nm*	--	--	--
		--	--	--	--	--	--	--	*±4 N*	--	--	--
	Dynamic test	--	--	--	--	--	--	--	--	--	*90 N*	--
	Torsion	3	5	9	25	--	3	11	12	67	--	--
	Static test	20 Nm	11 Nm	*20 Nm*	--	--	12.5 Nm	--	*2 Nm*	--	--	--
		--	--	*±10°*	--	--	--	--	*100 N*	--	--	--
	Dynamic test	--	±20 Nm	*±8 Nm*	--	--	--	--	*2 Nm*	--	--	--
		--	--	*±5°*	--	--	--	--	*422 N*	--	--	--
	Tensile	--	--	1	1	--	--	--	--	--	--	--
	Static test	--	--	--	--	--	--	--	--	--	--	--
	Dynamic test	--	--	-20 N	--	--	--	--	--	--	--	--
2	*Single test*	16	14	24	85	19	7	96	14	81	5	100
	Combination test	--	2	8	15	--	1	4	3	19	--	--
3	*Static test*	12	8	17	57	10	7	61	12	72	2	40
	Dynamic test	4	8	15	43	9	1	39	5	28	3	60
	Dyn. constant	2	4	8	57	3	1	40	4	80	3	100
	Dyn. stepwise	2	4	7	43	6	--	60	1	20	--	--
4	*Cadaver bone*	8	5	14	42	7	4	41	12	71	3	60
	Bone substitute	8	11	18	58	12	4	59	5	29	2	40
5	*Stiffness*	5	6	11	71	4	3	50	8	89	3	100
	Load to failure	5	4	7	52	8	0	57	7	78	2	67

Tab. 3.: Summary of the data obtained for the categories upper (Part A) and lower extremity (Part B). Section 1: Absolute numbers, relative frequencies and maximum test parameters for test methods applied per bone segment" (n = 341 test methods applied at the proximal (prox.), diaphyseal (dia.) or distal (dis.) bone element). "If no value is displayed no upper test limit could be obtained. The values printed in italics must not represent the maximum values. Section 2-4: Absolute numbers and relative frequencies for various test criteria: Single or combination test, static or dynamic test including subcategories for dynamic testing as well as chosen bone model (n = 330 biomechanical tests). Section 5: Absolute numbers and relative frequencies for measured outcome variables: stiffness and load to failure (including strength).

3.4 Limitations of the literature review

This systematic review includes several limitations. For the purpose of identifying frequently used tests methods four major test methods were defined to categorize each test presented in the literature. This idealized approach facilitates the classification, but neglects the fact, that external forces and moments create internal stresses, that are often not uniformly distributed. A compression test, for example, includes aspects of bending, if the load is eccentrically applied. Even though the test method is equally classified, it does not mean, that the resulting stress is equal or that the test results are directly comparable.

This review focused on test methods and on essential testing parameters that are relevant for the practical application in the biomechanical lab. However, this is just a subset of relevant test parameters, that may have an impact on the biomechanical assessment. Several important variables were not recorded. Among those are the fracture model chosen, the number of bone plates tested, the number of screws applied including screw configuration, the sequence of tests performed. The analysis does also not include

information about data collection, the results of each study as well as an interpretation of the test result. It is also acknowledged, that not all studies are designed to actually “test” a bone plate for osteosynthesis, but to explore a specific research question. However, the studies included have in common that bone plates are subject to biomechanical experiments under clinically relevant conditions.

3.5 Conclusion

Generally, the biomechanical literature for bone plates for osteosynthesis is diverse, inconsistent and heterogeneous. In this context, the following conclusive statements were drawn:

1. Test methods and test parameters are not uniformly applied per bone plate location: The heterogeneity of the data obtained led to the conclusion that, when designing a procedure for a single anatomical region, test methods and test parameters shall be selected individually. There are no performance criteria defined, which can be applied for pre-clinical testing of constructs. Some test methods were frequently used at the radius, femur, tibia (compression), ulna, metacarpale (bending) and fibula (torsion) justifying a plausible choice of these test methods for biomechanical testing. Test parameters vary significantly, in particular for bending and torsion tests. The variety of test parameters is caused by a) different test methods applied, and consequently b) different units used to specify the applied load or to record the outcome variable.
2. Outcome parameters are not commonly applied nor defined: A significant variety of outcome variables was observed, which makes comparison between individual studies almost impossible. The maximum testing parameters found in the literature can only be interpreted as “guidance values” for static and/or dynamic testing, e.g. for stiffness testing. The values shall not be considered as mandatory clinical “performance levels” for lab testing or as a threshold for claiming compliance to valid requirements of the MDR [86].
3. Dynamic testing is not consistently applied: The number of cycles for dynamic testing varies significantly, from n = 3 cycles (for increasing-amplitude tests) to fatigue testing with n = 10^6 cycles. The number of cycles are often assumptions made by each study designer e.g. to simulate the amount of body movements in the rehabilitation phase. The number of dynamic cycles for lower extremities is expected to be three - four times higher than for upper extremities (for constant-amplitude tests, calculated based on median).

4 Goal of the thesis

Bone plate-screw constructs are medical devices and are therefore subject to pre-clinical testing for regulatory purposes. International standards applicable for those devices are mainly designed for straight bone plates, but not necessarily for all device variants available and not for the functional combination with corresponding (locking) screws. There is a gap between currently available, anatomical plating systems and existing recognized mechanical testing methods. Pre-clinical testing of bone plate-screw constructs is insufficiently regulated and inconsistently applied in the biomechanical literature. Taking into account recent bone plate design changes, i.e. changes in shape and biomechanics, there is a need to improve available testing methods to enhance confidence of testing.

Consequently, the main goal of this dissertation is the development and application of standardized pre-clinical testing methods for straight and pre-contoured, conventional or locked-type bone plate-screw constructs and to assess the results in a clinical context.

5 Development of standardized tests for bone plate-screw constructs

5.1 General approaches for standardization

There are different approaches to standardize in the field of medical technology. The main difference between standards is the level of detail subject to standardization and the scope for which they are intended to be applied. A standard may contain a drawing or device specifications e.g. as in ISO 5853-3 for “Kirschner skeletal wires” [102], it may specify “metallic materials found acceptable through proven clinical use” [112], e.g. as in ISO 5832-1 for “wrought stainless steel” [100], or it may contain more general product-related requirements, e.g. as in ISO 14630 [111] for “non-active implants”. Many standards are applicable for a wide variety of medical products or are not directly product related. In this case, they follow a process-oriented approach, e.g. for “medical device software - software life-cycle processes” as per IEC 62304 [115], or for the “application of usability engineering to medical devices” as per IEC 62366-1 [116]. Therefore the term “standardization” includes different standardization approaches. The following chapters outline possible standardized testing concepts for bone plate-screw constructs.

5.1.1 Standardized biomechanical testing of bone plate-screw constructs

Generally, test setups for biomechanical testing are very specific. They often intend to simulate complex biomechanical conditions after reduction and fracture fixation (as outlined in section 2.2.3). There are many potential variations in the test setup (and testing procedure) so that a direct comparison between studies is fairly impossible. The values obtained using those setups deliver at least objective evidence for direct implant comparison within each experimental study. Standardization of biomechanical testing in terms of specific standardized test setups and corresponding procedures for regulatory purposes seems almost impossible. However, it seems possible by applying a “process approach” (e.g. as published in VDE 5703 [210]): For each biomechanical experiment a specific testing setup representing local anatomy and a corresponding testing procedure must be developed (to address the risk of an “inadequate fracture stabilization”, section 2.2.6.) Likewise for every study, there are typical questions (and thus requirements with potential impact on the testing result) that may arise during the development of the testing procedure. The following Tab. 4 contains a summary of characteristics, that shall be considered when developing such a specific biomechanical testing procedure for a single anatomical area. It is divided into three major categories.

Biomechanical modelling. The biomechanical model sums up the current anatomical and biomechanical knowledge that shall be transferred to the test setup with the aid of selected bone replacement materials and which shall be coupled to the testing machine as physiologically as possible while simulating a fracture, which, taking into account the intended purpose of the implant, represents a biomechanically unfavorable fracture type for the implant (worst-case approach [89]). The selection of bone substitute material may depend on the intended patient population and the implantation time. This section also includes the determination of local forces and moments acting at the skeletal system which results in the definition of the test methods further down below.

Sample preparation. This section includes requirements for the selection of construct samples, including screw type and screw distribution. The selection of samples needs to be justified. The assembly of the construct shall follow clinical application routine.

Biomechanical modelling
Intended Use / Intended Purpose 1. Intended patient population 2. Implantation time **Local forces and moments at the skeletal system** 1. Stress analysis: Basic loading and combination loading types 2. Anticipated loading types in the rehabilitation phase **Anatomy and Biomechanics** 1. Local anatomy 2. Functional anatomy (Range of motion) 3. Specifics of biomechanical load transmission and its simulation *in vitro* **Fracture modelling** 1. Bone condition, Bone substitute material (proximal, distal, diaphyseal) 2. Fracture type, AO-classification 3. Biomechanical simulation of the chosen fracture type 4. Limitation of the affected bone in the setup 5. Coupling to the testing machine (proximal, distal, diaphyseal)
Sample preparation
Selection of samples 1. Number of test samples (for static and dynamic tests) 2. Choice of bone plate sample under test 3. Screw type (proximal, distal, diaphyseal) 4. Number of applied screws (proximal, distal, diaphyseal) 5. Screw distribution and working length (proximal, distal, diaphyseal) **Assembly and embedding of the construct** 1. Inclination of screws (locked-type constructs only) 2. Fixation type (unicortical, bicortical a.o.) 3. Plate elevation (locked-type constructs only) 4. Applied screw torque 5. (Standardized) osteotomy, assembly and embedding process

Testing methodology and performance assessment
Measurement technology 1. Control mechanism (Load-, Displacement-controlled) 2. Outcome variable(s) and its determination (for static and dynamic tests) 3. Failure criteria (for static and dynamic tests) **Test methods and parameters** 1. Pre-conditioning 2. Test method (Compression, Bending, Torsion, Combination tests a.o.) 3. Number of applied dynamic loading cycles 4. Type of dynamic tests (Constant/increasing amplitude, test velocity, frequency) **Performance Assessment** 1. Performance criteria (for static and dynamic tests)

Tab. 4.: Specifics of pre-clinical, biomechanical testing of implants for osteosynthesis. Compilation of characteristics that shall be considered, interpreted and applied by the legal manufacturer, by research groups or accredited testing labs when developing testing procedures for a specific anatomical region.

Testing methodology and performance assessment. This section contains specifics for the practical testing part, including technical requirements for controlling the load/moment, the measurements taken, failure criteria and the choice of test methods and parameters. One of the most important requirement is defining criteria for a final performance assessment.

The requirements compiled in Tab. 4 seem suitable to define a standardized process for the development and evaluation of bone plate-screw-constructs in a biomechanical environment. This process would guide the user to finally retrieve a testing procedure. When properly applied, the outcome of the process would be a testing procedure for a specific device or a specific anatomical area. However, the result will always remain an individual, scientific solution developed by the manufacturer of the device or by research groups. Typical examples can be found in the literature for the humerus [23, 191] the radius [174], or the ulna [25]. However, applying that process would still mean, that many assumptions or decisions need to be made by the developer of the study using available scientific information to justify each decision. Consequently, it appears to be quite unlikely, that the test results are directly comparable and thus standardization potentially ineffective.

5.1.2 Standardized mechanical testing of bone plate-screw constructs

As outlined in chapter 2.2.3, mechanical testing does not equal biomechanical testing. Mechanical testing shall be performed based on published internationally recognized testing standards using standardized (but idealized) metallic test setups to measure standardized outcome variables, providing a “comprehensive reference” (Scope 1.2 in [5]) to measure “performance related mechanical characteristics determined to be important to

the *in vivo* performance of bone plates" (Scope 1.1. in [5]). Standards "are developed to allow for consistent characterization and measurement of properties, as well as comparisons of the results of different testing agencies" [206]. This aspect applies to all mechanical standards, that are available for devices for osteosynthesis. It has been acknowledged and it is common sense that the requirements set out in ASTM F382 are applicable and commonly accepted for metallic medical bone plates [5]. Consequently, another more promising standardization approach is the development of alternative (i.e. level 3) mechanical tests for straight and pre-contoured conventional and locked-type constructs for osteosynthesis under the condition, that this approach fits into the existing set of regulatory requirements already applicable for those devices. Such a standard shall deliver objective evidence for direct construct comparison.

5.1.3 Conclusion

Biomechanical testing for research purposes and mechanical testing for regulatory purposes are two separate testing approaches, both of them can be found while interpreting the requirements of ISO 14602, part 7.2 [112]. Therefore, standardized testing seems possible in two different ways, either by developing a standardized "process approach" for biomechanical testing with the general disadvantages of process-oriented standardization approaches, or by specifying standardized mechanical tests to be recommended for bone-plate screw constructs.

Based on the analysis of potential standardization approaches, and taking into account the results obtained from the literature review, the development and application of standardized mechanical tests for bone plate-screw constructs is the logical consequence.

5.2 Development of standardized mechanical tests for bone plate-screw constructs

5.2.1 Distinct loading conditions and resulting test setup design

During the process of bone healing every implant is principally loaded by three major loading conditions, which are transmitted through the bones with its muscular and ligamentous support. Axial loading, bending and torsion must be overcome by any method of fracture fixation [137] and those three basic loading modes comprise almost 99 % of all test methods identified in section 3. Consequently each loading mode shall be considered for pre-clinical testing. The development is based on the experimental research methodologies presented by Bottlang et al. [19] and Fitzpatrick et al. [47], and follows the well-established testing philosophy of ASTM F382 [5]. In this context, the test setups and specific testing requirements detailed below shall serve the purpose of a) standardization and/or b) testing under worst-case conditions [89]. Torsion, bending and axial loading tests are to be considered, provided that testing is conducted using the assembled conventional and/or locked-type bone plate-screw construct.

Torsion. Torsion is a basic loading not covered by ASTM F382 [5] but which is required by other standards for comparable devices, including ASTM F543 [7], ASTM 1264 [9] and ASTM F1798 [12]. Torsion tests were frequently observed in biomechanical research, e.g. at the humerus or femur (Fig. 8). Additionally certain fracture patterns classified by the AO are attributed to torsional loads e.g. a “simple fracture, spiral” (e.g. AO-42-A1, AO-12-A1) is a fracture type where torque is considered to be major impact factor [95]. This fracture reveals a characteristic pattern associated with torsional impact. Consequently, torsional loads appear at the skeletal system and shall be considered for pre-clinical testing.

Bending. Bending is a basic loading mode already standardized by ASTM F382 [5] or ASTM 1264 [9] and in other technical areas [109], typically designed as 3-point or 4-point bending test [9]. The recommended bending testing strategy is based on section A1.6.2.1 (“rigid extension segments”). Bone plates that do not directly fit into the test setup or “that do not have a sufficiently long section of symmetry” can be attached to rigid extension segments (i.e. solid bone substitute material). This technique, although only indicated for a small subset of plates, ensures that the complete pre-contoured bone plate-screw construct can be tested with the 4-point bending test method while still applying a well-known and accepted testing methodology. This approach is applied for all loading conditions, since the bone plate fulfills its intended use only in combination with corresponding bone screws (i.e. as a construct assembly). However, the method must be modified and further specified to also cover locked-typed plate-screw constructs.

Axial loading (Compression). Bottlang et al. [19], Fitzpatrick et al. [47] and many other authors in biomechanical research, have (additionally or exclusively) applied axial loading along the “bone axis” for plate evaluation. Axial loading tests are frequently observed in biomechanical research and were found in almost 36 % of all publications analyzed. However, this is not surprising as this is the anticipated and most physiological loading condition for bones of the upper and lower extremities. Under the condition that the construct is fixed to “healthy, strong bone” (or any other rigid material, bone substitute such as sawbones, POM, aluminium a.o.), axial loading (across the “bone axis”, Fig. 10) is not a (pure) compressive load, but a combination of a compressive force and a bending moment. The compressive force is applied to bone with an offset between the “implant axis” and the loading axis determined by the anatomical area (Fig. 10, part 2: “compressive bending”). Therefore biomechanical (clinical) failures that are maybe related to the “quality of bone” as such, e.g. “screw loosening” in osteoporotic bone are excluded. It is anticipated that the simulated fracture gap will be closed under external load and that the plate will be bend until failure occurs.

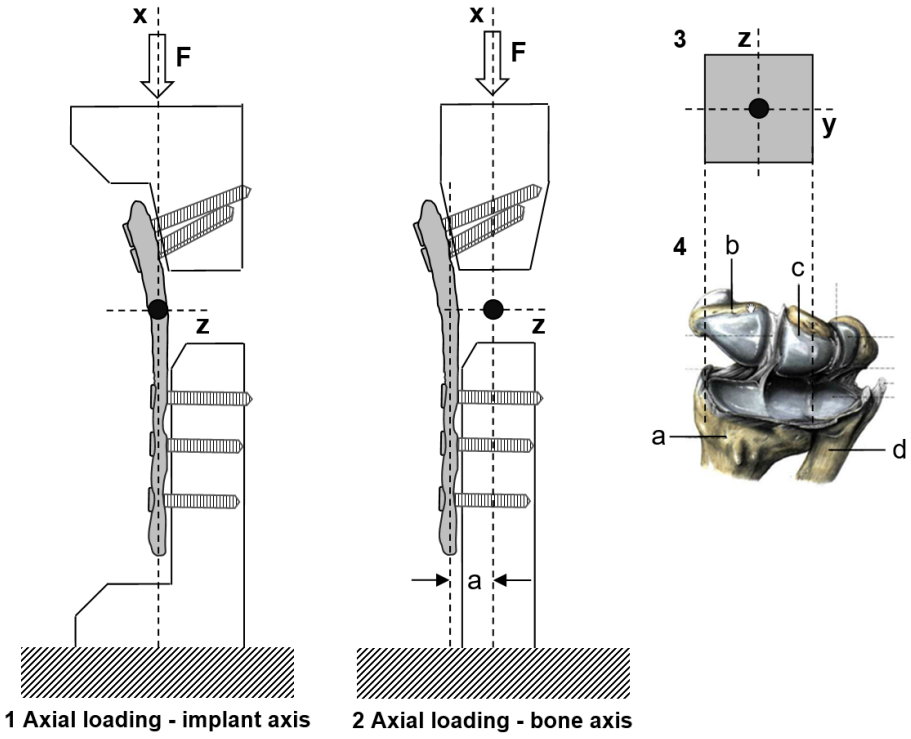


Fig. 10. Axial loading for research purposes demonstrated at the distal radius. Variations in axial loading. Part 1: Axial loading along the implant axis. This testing scenario does not deliver suitable testing results as the strength of the plate is much higher than the strength of bone. Part 2: Axial loading along the (calculated mean) of the physiological bone axis (illustrated in part 3) with an offset to the implant axis (Part 2.a) leading to “compressive bending”. However, this setup would just be a simplification of the physiological mode of axial load transmission as there are three articular surfaces, which contribute to the axial force transmission (Part 4). For the distal radius (4.a) scaphoid (4.b) and fossa scaphoidea and lunatum (4.c) and fossa lunatum are involved, for the ulna (4.d) the distal radioulnar joint. For the in-vitro-modelling the following applies: An axial force F_{total} is divided in two partial forces F_{radius} (80 %) and F_{ulna} (20 %) [224]. About 60 % of F_{radius} is transmitted via the scaphoid and fossa scaphoidea and about 40 % via the lunate and the fossa lunata [70]. However, Rikli et al. concluded, that “more force is transmitted across the ulnar side of the radioulnocarpal joint than previously thought” [177].

Axial loading is suitable and recommendable for biomechanical testing e.g. as it also addresses shear forces to induce mechanical screw failure. However, under the condition that the plate is rigidly fixed to “healthy bone”, which is the case here, axial loading along the “bone axis” represents a “special case” of a bending procedure, e.g. a “compressive bending” test (using a physiologically correct center of rotation). Alternatively, axial loading across the “implant axis” (i.e. along the x-axis in Fig. 10) would not deliver suitable additional testing results as the axial strength of the bone plate is much higher than the strength of bone. This test setup is purely theoretical with no practical relevance. Finally, axial loading is inherently prone to test results with large standard deviations as the test setup shows high sensitivity towards the precision of the axial alignment, a circumstance, that makes it less suitable to deliver reproduceable testing results for regulatory purposes [73]. In sum, under the given test conditions (i.e. testing on “healthy bone”) there is no additional benefit for singular axial loading tests, however axial loading remains recommendable for biomechanical testing. Fig. 10 summarizes possible variations of axial loading at the distal radius and explains a) why testing along the bone axis (using rigid bone replacements) is a variation of a bending procedure and b) why this mechanical loading type still remains a simplification of the physiological loading mode. Consequently, a comprehensive mechanical characterization of the construct seems possible using torsion and bending tests.

5.2.2 Positioning of the construct in the test setup

Torsion and bending tests are recommended test methods for bone plate-screw constructs. The following chapters 5.2.3 to 5.2.8 explain the test setups and the testing procedure in detail, however the starting point is the correct positioning of the plate in the test-setup. Due to the anatomical shape of the plate, it is necessary to align the plate in the setup using common specifications. The positioning of the construct is based on the following approach as demonstrated in Fig. 11 for two randomly selected bone plates for different anatomical areas (clavicle, distal tibia). For each implant a virtual “testpoint” is defined (indicated with a black circle in Fig. 11). The testpoint is centered within the “implant axis” and the “bridge span” (the anticipated fractured region of the bone, section 5.2.5). The implant axis equals the x-axis in Fig. 11. The coordinate system as shown in Fig. 11 is used for positioning the construct. The majority of contoured plates have an “almost linear” (diaphyseal) fixation part. Generally, this section of the bone plate should be aligned to the x-axis (as shown in Fig. 11, part 2-4). Any additional rotation needed for the alignment (e.g. rotation along the z-axis for torsion) shall be conducted in a way as to minimize the sum of the distances of the screw holes to the implant axis (as shown in Fig. 11, part 2 for the clavicle plate). Fig.

11, part 3-4 also shows that, depending on the geometry of the plate, the testpoint must not necessarily lie on the plate (e.g. in part 4).

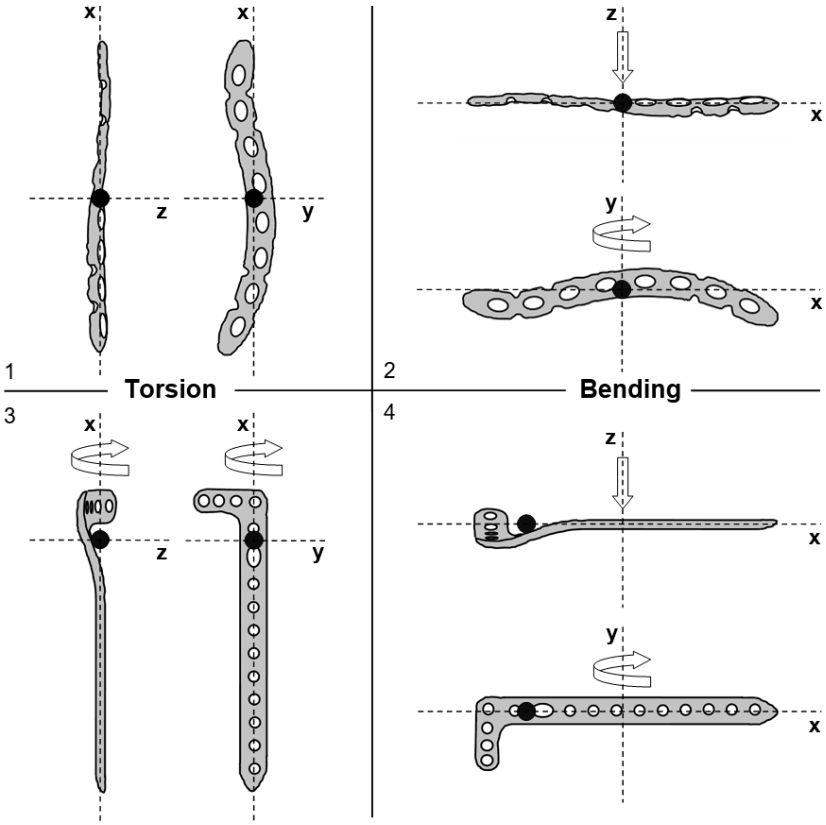


Fig. 11. Coordinate system for positioning the construct and guidance for alignment within the test setup for two randomly selected bone plates per anatomical area. Parts 1 and 2: Torsion and bending alignment for the clavicle, midshaft. The plate is rotated along the z-axis and y-axis in order to align the plate accordingly. Parts 3 and 4: Torsion and bending for the distal tibia, anterolateral. In this case the testpoint does not lie within the z-axis as there is a constant bending moment in the center span distance.

The following sections contain two examples of proposed test setups when applying the testing philosophy described above, using either a straight linear (5.2.3, Example 1) or a contoured bone plate-screw construct (5.2.4, Example 2).

5.2.3 Test setups for a straight bone plate-screw construct, locked type

The following Fig. 12 shows two test setups for torsion and bending tests of a straight bone plate-screw construct, locked-type, e.g. as intended for the ulna shaft. The developed test setups are designed to simulate a worst-case clinical scenario, i.e. a simulation of a large fracture gap with implant hardware subjected to highest mechanical stress. The fracture gap is designed so that the fractured parts do not touch each other during the test, e.g. by a applying a large fracture gap and a phase to the rigid material for the bending test. Fig. 12 shows a straight bone plate-screw construct with a defined distance between the plate and the bone (Fig. 12, No. 3: plate elevation) in order to mechanically stress the locking

mechanism of the bone plate-screw interface in a worst-case approach [89]. In this example, the screws are vertically locked in the plate and screwed bicortically. However, due to the use of the rigid and uniform bone substitute material bicortical screw application is not mandatory. The torsion test setup follows the same principle. The plate is aligned to the x-axis and the rigid material is adapted to the plate. The setup is positioned on an x/y table, a typical method to overcome translational forces during the test. Further specific testing requirements are defined and explained in section 5.2.5. In sum, these setups represent a worst-case load bearing condition between the bone and the construct with a maximum load being bear by the construct.

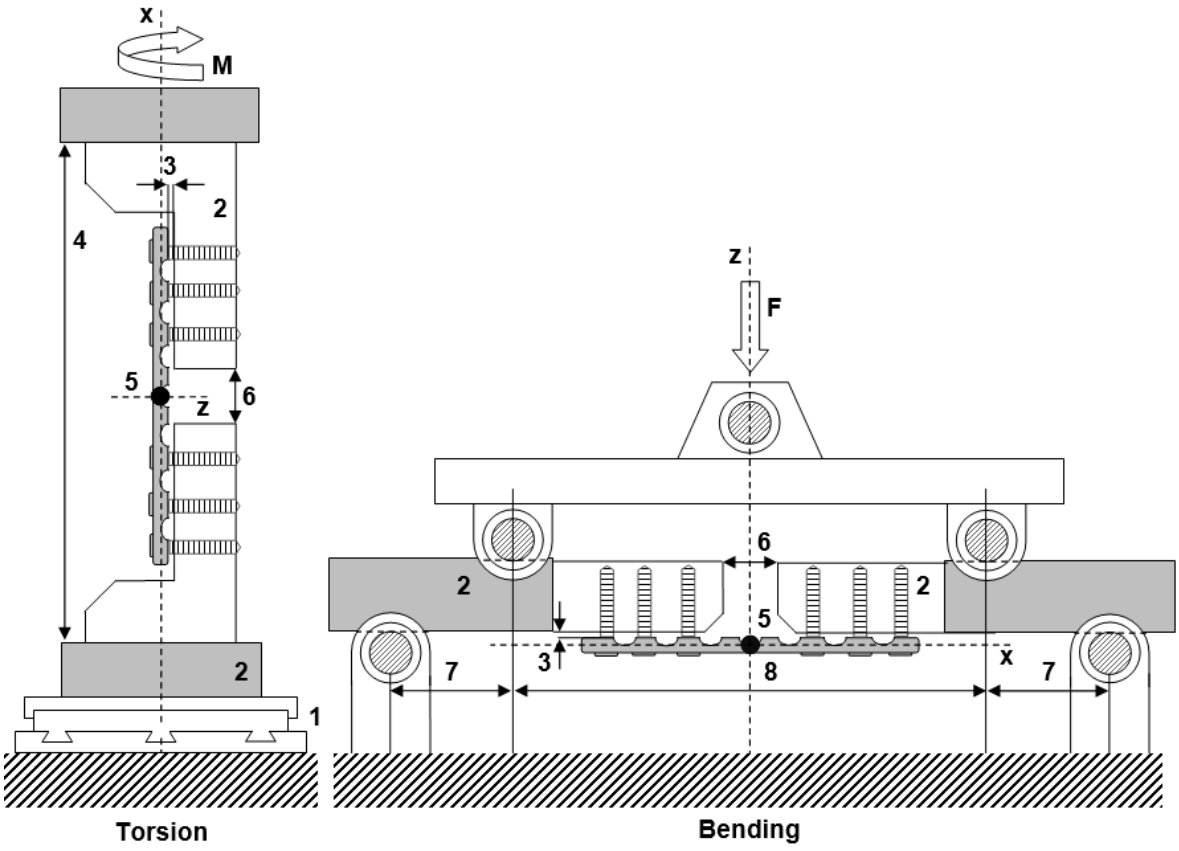


Fig. 12.: Example 1 - Mechanical testing of straight bone plate-screw constructs. Setups for torsion and bending tests. 1. X/Y-table, 2. Rigid bone substitute material or metallic support material, 3. Plate elevation, 4. Setup length, 5. Testpoint, 6. Bridge span, 7. Loading span distance [5], 8. Center span distance [5]. The 4-point bending setup shown is subject to mechanical testing chapter 6 of this work. The layout is schematic and dimensions are not to scale.

5.2.4 Test setups for a contoured bone plate-screw construct, locked type, distal radius

The test setups for contoured BPS constructs rely on the same testing principle (Fig. 13). Due to the bone matching shape of the plate, the geometry of the rigid blocks must be adapted as needed in order to be aligned with the shape of the plate. This adaptation is

demonstrated in Fig. 13 for a medical device intended for the distal radius. Due to the wide variance of implants no further guidance can be given at this time, unless the construct is correctly positioned using the principles outlined in section 5.2.2.

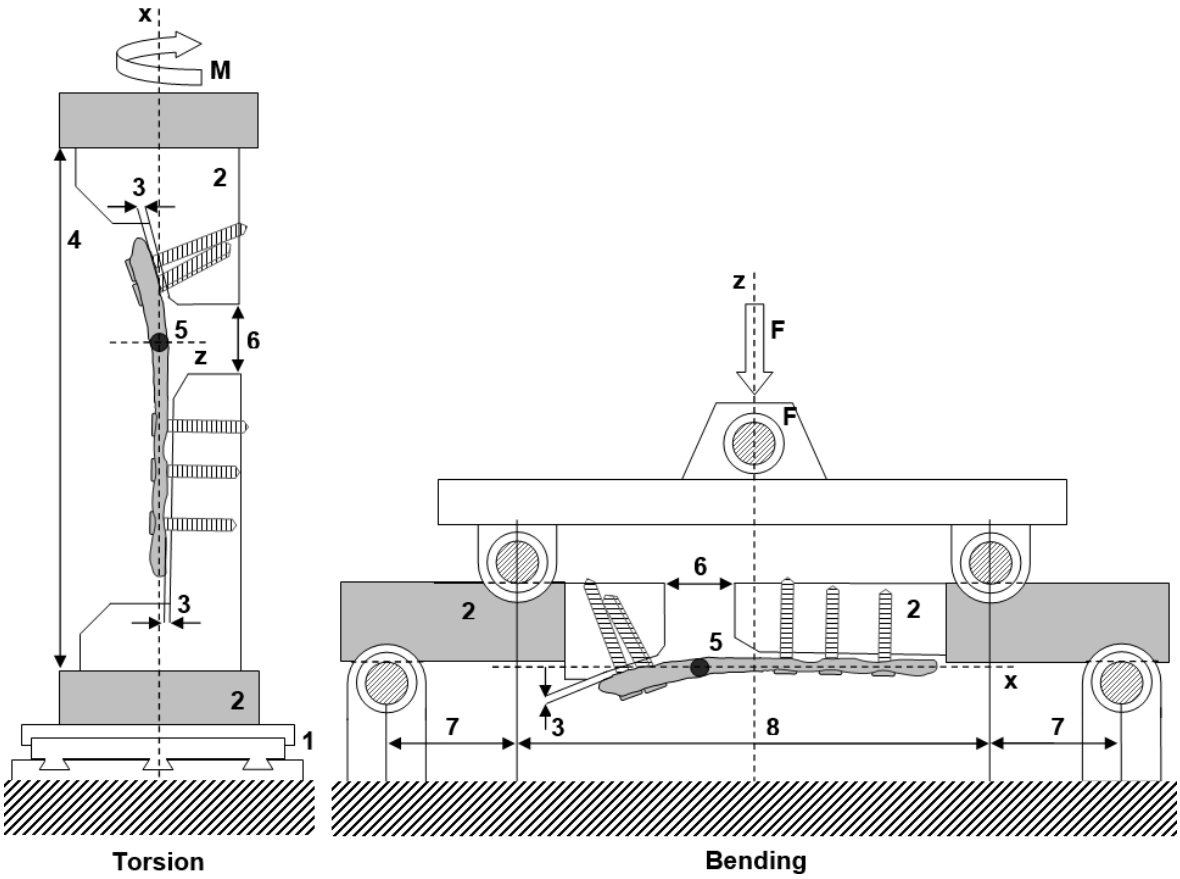


Fig. 13.: Example 2 - Mechanical testing of contoured bone plate-screw constructs at the distal radius. Setups for torsion and bending tests: 1. X/Y table, 2. Rigid bone substitute material or metallic support material, 3. Plate elevation, 4. Setup length, 5. Testpoint, 6. Bridge span, 7. Loading span distance [5], 8. Center span distance [5]. The layout is schematic and dimensions are not to scale.

5.2.5 Specific testing requirements

The following section contains a definition and explanation of specific characteristics of the setup as shown in Fig. 11 and Fig. 12, such as “plate elevation”, “bridge span” or “setup length”. In order to apply the test methods consistently, it is necessary to explain and specify those testing requirements.

Plate elevation. The plate elevation is the physical distance between the implant and the bone cortex [47]. It is necessary to address the plate elevation, since locked-type constructs can be applied with a specified distance to the bone. Testing under this condition would constitute a worst-case testing approach [2, 89, 163]. Consequently, all bone plates shall be fixed directly on the bone cortex, i.e. conventional osteosynthesis implants (refer to 2.1.2). All angular stable devices shall be fixed with (at least) 1 mm plate elevation, unless

otherwise justified. It can be particularly difficult to exactly realize 1 mm plate elevation in the test setup, not only in the recommended setup above, but also in clinical procedures.

Bridge span and **number of applied screws**. The bridge span is the anticipated fractured region of the bone, where the external load/moment is exclusively transferred through the bone plate-screw construct (A2.4.1 in [5]). There is no need to address a value to the bridge span, however it shall be ensured that both fracture segments do not touch each other while testing. The bridge span shall contain structurally critical regions (e.g. screw hole, interlocking feature) whenever such a feature is close to the testpoint. There shall be at least one remaining screw hole within the bridge span not used for fixation, unless there are only three screw holes designed for the diaphyseal fixation, e.g. for smaller plates. Consequently, three screws shall be used for the fixation in the diaphysis and at least three screws in the metaphysis. Large plates shall be fixed with four screws in the diaphysis, making sure that there are at least two remaining screw holes within the bridge span not used for fixation. It is not necessary to arrange the bridge span in the center of the setup, whether for bending nor for torsion.

Rigid bone substitute material. The choice of the bone substitute material (including any embedding and/or support material) is of vital importance. The mechanical properties of the substitute material have direct impact on the test performance and thus on the outcome of the test. As the failure is expected to occur at the implant construct assembly, the substitute material shall be sufficiently rigid (e.g. by using POM, Polyoxymethylene) and shall be designed so that it does not “interfere with the bone plate’s deformation” during the test [5]. The use of rigid test blocks eliminates the effects of bone heterogeneity associated with cadaveric testing. Due to the bone matching shape of the plate, the geometry of the block must match the shape of the bone plate as well. The test configuration is based on the use of adjusted rigid test blocks simulating the fractured bone parts. The process of adjusting is not further specified as it depends on the device under test.

Setup length. The length of the test setup for torsion shall be designed in such a way as to minimize the impact of the chosen bone substitute material on the test result. This can be achieved by reducing the setup length as low as possible. The length of the setup for bending is determined by the location of the loading rollers as defined in ASTM F382 [5].

Center span and **loading span distance**. Both terms are defined in ASTM F382 [5] and ASTM F2502 [13]. The 4-point bending setup creates a constant bending moment over the entire center span distance, however, a loading span distance, that is too small, may route the applied force over the bearings instead of creating a bending moment. Therefore, it must be ensured that the loading span distance is large enough to be effective. Principally, the center span distance should equal the loading span distance [5, 9]. This approach is

commonly applied. Halbauer et al. recommended a loading span distance of at least 75% of the center span distance [66].

5.2.6 Failure criteria for static and dynamic testing

During the literature review it was observed, that many different outcome variables in biomechanical research limit inter-comparability between studies yet makes comparison between individual studies almost impossible. This is why it is important to define uniform failure criteria. The following criteria are suitable to characterize the device and are set to be uniformly applied for static and dynamic testing:

Bone plate and/or screw breakage. Bone plate and screw breakage include any breakage or surface signs of a breakage of a component of the construct. This failure of the device is obvious and typically expected under dynamic testing conditions close to the bending strength of device. For locked-typed constructs screw loosening or any reduction of the locking capability constitutes a failure.

Plastic deformation of the construct. This criterion summarizes all plastic deformations of the construct that may occur during testing, but that are not related to the bone substitute material or the setup itself. It includes bending of the plate and bending of the screw (or both) or any other type of “changes within the construct” such as micromovements within the plate-screw interface. Any characteristic of the setup that may have an impact on the deformation of the construct, should be avoided.

All other criteria, although widely found in the biomechanical literature, may terminate the test, but do not constitute a mechanical failure of the construct, e.g. bone substitute breakage, screw loosening (in bone). Those failure criteria are typically associated with the “quality of bone” and are not suitable for testing under standardized conditions. They are also not expected when constructs are applied to rigid bone replacements.

5.2.7 Outcome parameters for static testing

For static testing the following test records shall be created in a x-y-diagram: For torsion, the torque versus rotation angle curve (X: rotation angle in degrees°; Y: torque in Nm) and for 4-point bending, the load versus displacement curve (in X: displacement in mm, Y: load in N) shall be recorded. Based on the test records the following construct related characteristics shall be determined.

Construct stiffness. The maximum slope within the elastic portion of the recorded curve. This is the general definition of “stiffness” found in the literature, expressed in N/mm and standardized not only in ASTM F382 [5].

Construct (yield) strength. The torque in Nm applied along the y-axis necessary to produce a plastic deformation of 2° (“torsional yield strength” [7]) or the bending moment in Nm applied to produce a plastic deformation equal to 0,2 % of the center loading span distance (“bending strength” in [5]). The torsional construct yield strength can be determined by applying the „offset method“ within the torque versus angle of rotation curve (as proposed in A1.3 of ASTM F543 [7]): A parallel line with a 2° torsional offset and with the same slope as the test sample line determines the construct yield strength at the y-axis graphically at the intersection of both graphs. The same technique can be used to determine the bending construct proof load P in N. The corresponding construct yield strength in Nm can then be calculated by $M_b = P * b * 0,5$ with P = proof load and b = loading span distance.

Ultimate construct strength. The maximum torque/load recorded in the x-y- diagram. This is the general definition of “strength” as found in the literature, expressed in N. As the expected characteristic of the recorded graph is the result of the test and thus unknown, it is maybe not possible to determine all three characteristics listed above.

5.2.8 Outcome parameters for dynamic testing and statistical analysis

Static and dynamic tests are equally important to evaluate a bone plate-screw construct and, for the majority of available constructs, except e.g. cranium, midface, evaluating a bone plate based on static tests alone is not sufficient. This statement is supported by the literature review where the majority of n = 87 publications (55 %) contained both static and dynamic tests. Dynamic testing can be conducted in several different ways, however not all methods are capable to determine the “fatigue behaviour” of the construct, i.e. fatigue life, fatigue strength or median fatigue limit. The following testing strategies seem suitable and are generally accepted, published methods for regulatory purposes.

Fatigue life or **fatigue strength**. A well-defined loading range determined during static testing shall be selected and applied, and a logarithmic graph of the applied load / torque (y-axis) versus number of cycles to failure (x-axis) shall be created (A2.8.1.1: “M-N diagram” Testing [5]). There is no definition of a “well-defined” loading range, but the wording implies that the range is wide enough to allow estimating the fatigue behaviour and specific enough to capture the main range of interest. Practically, the range is naturally limited by the number of available test samples. This testing strategy can principally be transferred to torsion testing using an alternating, sinusoidal load and an R-ratio = $M_{max} / M_{min} = -1$: Torsional stress is likely to occur in both directions, whereas bending stress with an R-ratio < 0 is clinically unlikely to occur. The resulting curve shall be statistically analyzed, e.g. as defined in ISO 12107 [107]. This standard provides methods for the analysis of fatigue properties at a variety of stress levels. Principally, there are two different approaches to analyze and

determine the “fatigue behaviour” of the specimen, the determination of “a) the fatigue life for a given stress, and b) the fatigue strength for a given fatigue life.” The first option requires the definition of a specified load the construct has to withstand while cyclically stressed. The second option requires the definition of the anticipated fatigue life of the device, e.g. a run-out criterion specified as dynamic loading cycles the construct must withstand in the bone healing phase. For metallic bone plates a run-out criterion of $n = 10^6$ loading cycles is set by ASTM F382 [5]. This limit is set for comparative purposes. It does not necessarily simulate anticipated loading cycles expected to occur in the rehabilitation phase. As there is insufficient and limited knowledge about a) ultimate performance thresholds for static and dynamic testing, and b) measured values for the amount of limb or body movements after the surgical treatment has been accomplished, assumptions need to be made for either options. For consistency reasons the criterion given in ASTM F382 [5] shall be used, especially for constructs at the upper and lower extremities.

Median fatigue limit. The median fatigue limit for torsion and/or bending shall be determined by applying the ramp up-and-down testing strategy defined by Little et al., ASTM STP73 [14]. This method includes an increase or decrease of the applied torque and/or load based on the initial dynamic testing result(s), either a run-out at $n = 10^6$ loading cycles or a failure. “The up-and-down test method strategy concentrates testing near the median fatigue limit” [14]. It “is recommended for small sample applications” provided that sufficient preliminary testing data is available, such as “stress amplitudes at which specimens are and are not likely to fail” [14]. The median fatigue limit is the number of cycles at which 50 % of the constructs under test do not fail under a given load. Fatigue strength and Median fatigue limit are two separate and independent testing strategies, that are described in the literature and are generally well accepted in several standards already existing.

6 Application of standardized tests on bone plate-screw constructs

This section contains the realization and practical application of standardized tests presented in section 5 using established bone plate-screw constructs that are already available on the market for many years. The intention is 1. to evaluate and assess the behaviour of the bone plate screw-construct under standardized testing conditions and 2. to explore the difference between the standardized tests proposed herein and the established methods of ASTM F382 [5] in a constant dynamic loading test of 90 % proof load (bending strength). This test represents a subset of the dynamic “M-N diagram”-Testing approach specified in ASTM F382 [5] and it can be considered as the “initial test” (out of at least five to eight test samples) when applying ASTM STP731 [14] for the determination of the median fatigue limit (section 5.2.8). It is not the intention to fully characterize the bone plate-screw construct for regulatory purposes, as it would be e.g. for new and unknown devices without a proven clinical history, but to evaluate and to compare these test results with the results obtained when applying ASTM F382 [5]. For this purpose well-established, CE-marked straight constructs for the diaphyseal ulna were selected for testing.

6.1 Bone plate-screw construct under test

The bone plate-screw construct consists of a straight, CE marked bone plate intended for the diaphyseal ulna and corresponding CE marked self-tapping, locking screws. Both devices are legally marketed by litos GmbH, D-22926 Ahrensburg, Germany. The bone plate is made of unalloyed titanium, grade 1, as per ISO 5832-2 [101], the screws are made of titanium, grade 4/5, as per ISO 5832-2 [101], torx thread. The solid connection between the plate and the screw is realized by a form-fitting connection. While inserting the screw into the plate a defined quantity of titanium is displaced by the thread of the screw resulting in a solid material compound [91]. Principally, this plate is available in five dimensions, ranging from 61 mm to 121 mm length (adding 15 mm per length step) with an equal plate cross-section, plate thickness of 4,0 mm and width of 12,0 mm. Each plate is equipped with four to eight screw holes, depending on plate length. The plate length of 121 mm has been chosen as this is the longest plate available (REF 3608121T). The longest plate may encounter the greatest bending moment representing worst-case testing conditions. This plate may clinically be used with three screws on each fracture side leaving two screw holes empty and being compliant with the requirements set in section 5.2.5, No. 3. Fig. 14 shows the bone plate and the screw together with a picture of the construct prior to the fixation

process. Screw lengths are available ranging from 12 to 50 mm with a constant core diameter of 2,5 mm and an outer diameter of 4,0 mm each. For testing, a screw length of 30 mm has been chosen. The diameter of the bone substitute material (POM, Polyoxymethylene) was set to 25 mm to ensure sufficient bending stiffness. A total set of 16 bone plates (REF 3608121T) and 80 screws (Mini 1, REF 3505030T) were available for testing together with a torque limiter, medium, specified for 2,5 Nm max, REF HGRDMB25.

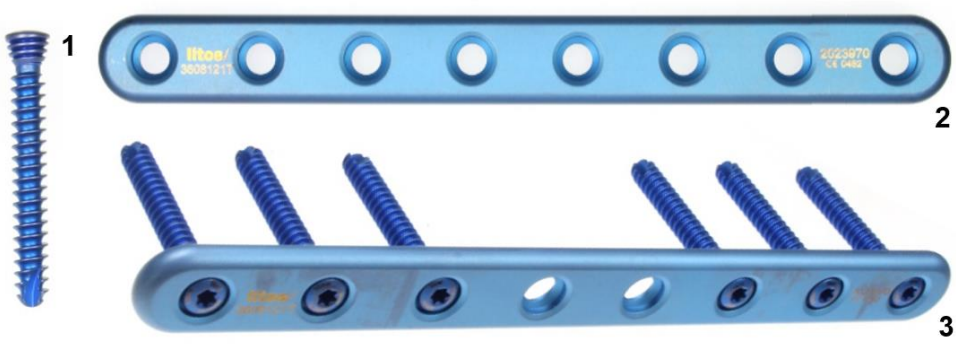


Fig. 14.: Bone plate-screw constructs under test intended for the diaphyseal ulna. Part 1: Self-tapping bone screw, Mini 1, 30 mm, Torx 9, REF 3505030T. Part 2: Single straight bone plate as delivered by the manufacturer, 121 mm, REF 3608121T. Part 3: Complete BPS construct assembly prior fixation procedure. Pictures provided by Endolab GmbH.

6.2 Assembly and fixation

The bone plate-screw construct must be assembled and applied to the bone substitute material in a way to prevent any stress that might occur when drilling the screw into the bone or fixing the screw head into the plate. For that purpose, all six screws were initially fixed to the bone plate using a torque wrench provided by the manufacturer and a specific guiding tool designed and built by Endolab GmbH (Fig. 14, part 1). The POM block shown acts as a guiding tool to manually fix the screw head into the material lip of the plate (German: “Verblockung”) while securing an angle of 90° between plate and screw (Fig. 13, part 3). Although the plate design allows an angle of 75 - 105°, a right angle of 90 % is a common choice by physicians, which is at the same time useful for standardization [94]. The screws were locked at 2,5 Nm as recommended by the manufacturer using a torque limiter. In order to minimize potential stress on the threads of the screws, fixation to the bone substitute material was then accomplished by gluing using UHU Plus Endfest 300, diluted 1:1, a solvent-free two-component adhesive based on epoxy resin [96]. For each of the six screws a canal was pre-drilled into the POM material using the same drill as mentioned above. The construct was then fixed in the final position and the screws holes were filled with resin. The construct was finally ready for testing after 24h of curing at 90°C

as recommend by the glue manufacturer [96]. Fig. 15, part 2 and 3, show the result of the assembly process.

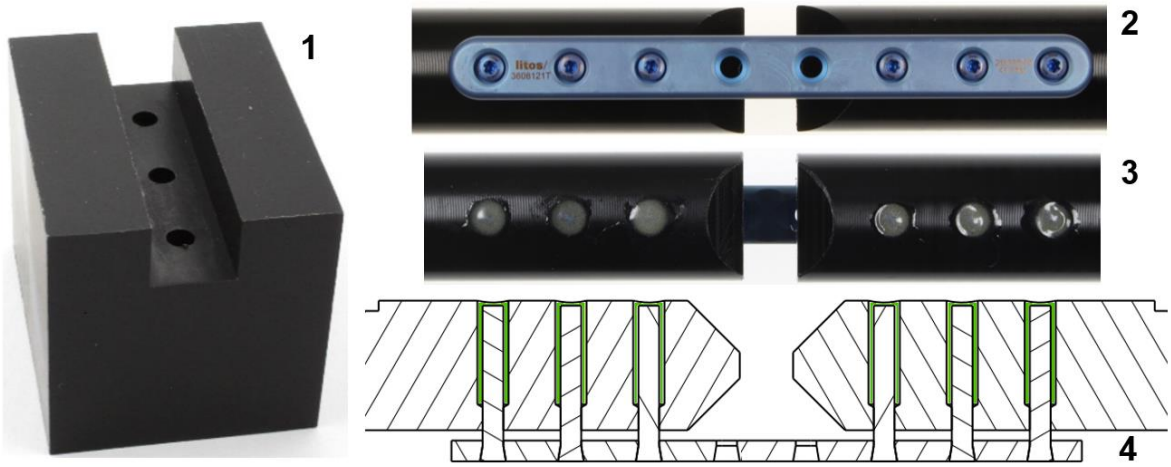


Fig. 15.: Assembly and fixation of the bone plate-screw construct. Part 1: Guidance tool for the fixation and initial construct assembly. Part 2: Final construct assembly. Part 3: Final BPS construct after assembly and fixation with pre-drilled screw holes filled with glue. Part 4: Drawing of the construct. Pictures provided by Endolab GmbH.

6.3 Test equipment and test environment

All tests were prepared, conducted and recorded at Endolab Mechanical Engineering GmbH, Ahornweg 8, 83083 Riedering, Germany. The existing experimental 4-point bending setup of Endolab together with its installed, operationally qualified and calibrated testing equipment has been used for this evaluation. For static tests the materials testing machine type 5569A from Instron with Software Bluehill 2, Version 2.35 has been used. For static tests as per ASTM F382 [5] the machine was equipped with a load cell ±1 kN, Instron, Type 2525-806. The displacement change has been detected by the integrated measurement system with an accuracy of 0,5 % of the measurement range. The same equipment has been used for the construct static tests, but the setup has been expanded by an advanced video extensometer, Instron, Type 2663-821 to measure the plate bending at the center of the setup. For dynamic testing as per ASTM F382 [5] Endolab's hydraulic pulsator device was equipped with Lastrahmen Type SHA-20kN-05, a 20 kN load cell, Burster, Type 8524/6020 and a position measuring system, MTS, Type 39-340-901, measuring range 20 mm. For dynamic testing of the BPS construct the hydraulic testing machine was equipped with two different setups. Lastrahmen, Type SHA-10kN-08, together with a load cell 750 N, Tovey Engineering Inc., Type FR10M-750N-B221 and a position measuring system Trans-Tek, Type GLCC-00288, measuring range 100 mm for the first sample, and Lastrahmen, Type SHA-20kN-05, together with a load cell 20 kN, Burster, Type 8524/6020 and a position measuring system MTS, Type 39-340-901, measurement range 20 mm for all other

samples. A calibrated caliper from Mitutoyo, Type CD-20CPX has been used for any length or distance measurement. All tests were conducted at ambient air and room temperature. No additional physiological testing medium has been applied.

6.4 Selection of test methods

Standardized mechanical torsion and bending tests have been described in section 5.2.3. However, not all basic loading conditions seem equally important for each anatomical area. Bending is the dominant testing method at the ulna observed in the literature (section 3.3.1). Since it is not intended to fully characterize the construct under test, but 1. to evaluate the behaviour of the bone plate screw-construct under standardized testing conditions and 2. to explore the difference between the standardized tests proposed herein and the established methods of ASTM F382 [5], the evaluation was conducted in 4-point bending mode only. Additionally, Torsion testing is not regulated as per ASTM F382 [5] and thus excludes a comparison of test methods.

6.5 Specification of the test setup

6.5.1 Loading specification of bone plate-screw constructs

The existing experimental setup at Endolab's accredited mechanical laboratory has been used for this evaluation, located at Ahornweg 8, 83083 Riedering, Germany. However, a detailed loading specification has been determined for the construct including the fixation of the construct to the bone substitute material. A detailed drawing of the loading conditions is shown in Fig. 16. The diameter of the bone substitute material (POM round bar) was set to 25 mm to ensure sufficient bending stiffness, the length was set to 200 mm. The loading rollers with a diameter of 12 mm were applied in a cut-out-zone of 2 mm depth to avoid a single point contact between the rollers and the bone ensuring a stable position while testing. The center span distance was set to 161 mm adding 20 mm space at each side between the plate and the center span contact point. The fracture gap was set to 10 mm and the plate elevation to 2 mm [2]. An increased distance by +1 mm (plate elevation has been specified as "at least 1 mm" in section 5.2.5) eliminates the risk, that the plate is supported by bone contact under progressive bending conditions, which might impact the test result. The POM block was shortened (in an angle of 45°) in the fractured region in order to avoid contact between the plate and the bone when being bent. According to ASTM F382 [5] the loading span distance shall be set to 161 mm, however, 70 mm were chosen

instead for practical reasons [66]. The specification of 70 mm is based on and supported by a finite element analysis under identical 4-point bending conditions (parameterized half-symmetric FE-model, ANSYS v19.1). Halbauer et al. have evaluated the impact on plate-screw construct stress in MPa (von Mises) under different variations of the loading span distance (from 60 mm to 140 mm, 20 mm steps), and plate elevation (from 0,0 to 1,5 mm, 0,5 mm steps) [66]. It was reported that, “an increased loading span distance leads to a higher resultant moment and therefore decreases the error of the resultant moment in the center of the bone plate”, and also that “a plate elevation greater than zero decreases the overall stiffness of the construct leading to a rising deflection and increased resulting stress in the bone plate center” [66]. Consequently, bone plate-screw constructs “with locked-type screws should be tested with a plate elevation greater than zero, due to its negative effects regarding a decreasing overall stiffness and rising deflection” [66].

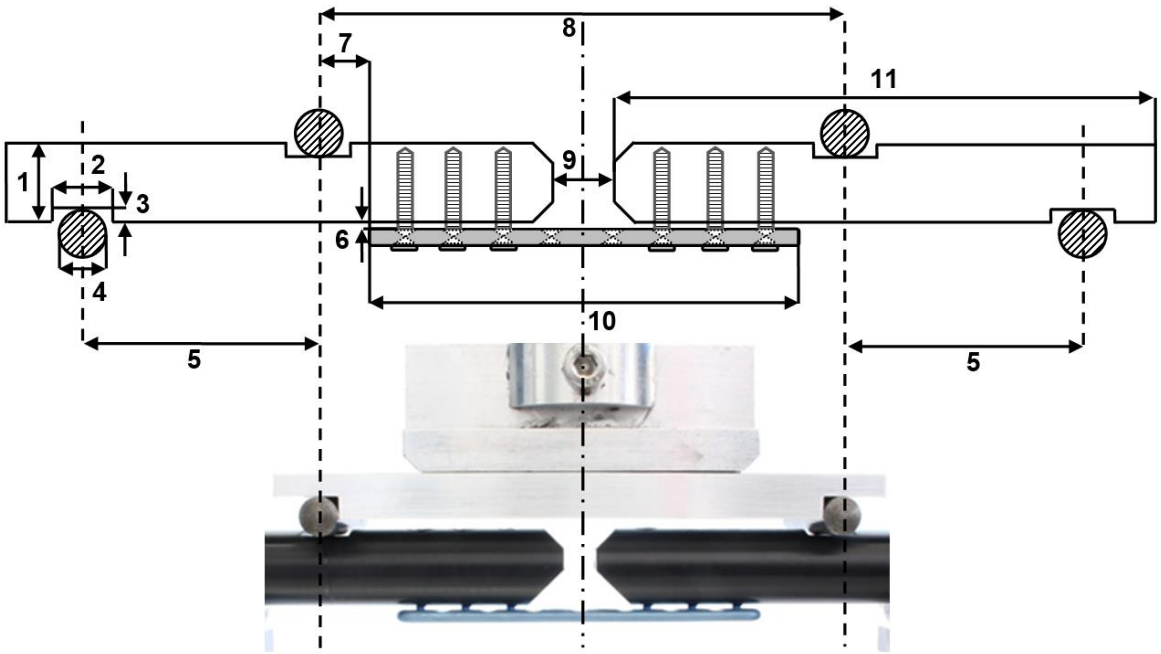


Fig. 16.: Detailed loading specification for static and dynamic testing of bone plate-screw constructs and realization of the 4-point bending setup showing the final setup for testing in the laboratory. 1. Diameter of bone substitute material (POM block): 25 mm, 2. Width of cutout: 20 mm, 3. Depth of cutout: 2 mm, 4. Diameter of support roller: 12 mm (applies to all four rollers), 5. Loading span distance: 70 mm, 6. Plate elevation: 2 mm, 7. Distance of bone plate to center span: 20mm, 8. Center span distance: 161 mm, 9. Simulated fracture gap: 10 mm, 10. Plate length: 121 mm, 11. Length of POM block: 200 mm. The resulting bending moment in Nm is calculated by $M_b = P * 0,5 * 0,07$ with P = proof load. Pictures provided by Endolab GmbH.

6.5.2 Loading specification as per ASTM F382

This test setup is well described in section 2.2.5. Many accredited test laboratories are using this setup in daily pre-clinical testing routine according to ASTM F382 [5]. The existing experimental setup at Endolab’s accredited mechanical laboratory has been used for this evaluation, located at Ahornweg 8, 83083 Riedering, Germany. A detailed loading

specification has been determined for this evaluation. ASTM F382 [5] recommends to locate “the two loading rollers at approximately the one-third points between the supporting rollers.“, A1.6.1.3.3 in [5], refer to section 6.5.1. This recommendation has been realized as Fig. 17 specifies the loading conditions in detail.

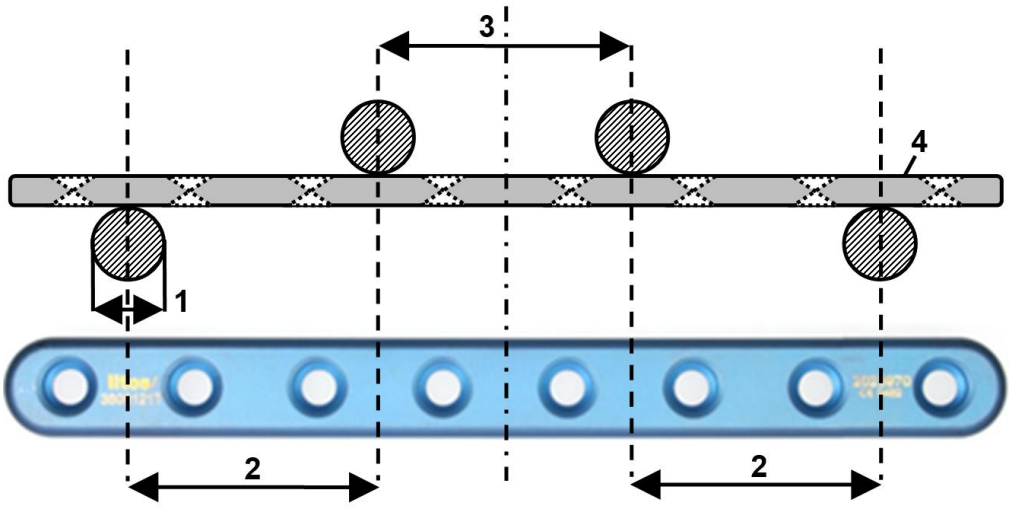


Fig. 17.: Detailed loading specification for static and dynamic testing as per ASTM F382 [5]. Specification of the 4-point bending setup. 1. Diameter of support rollers: 12 mm (applies to all four rollers), 2. Loading span distance: 30 mm, 3. Center Span distance: 30 mm. The bone plate has a defined length of 121 mm. The resulting bending moment in Nm is calculated as $M_b = P * 0,5 * 0,03$; P = proof load, 4. “Surface of the bone plate intended to be in contact with the bone” (A1.8.1.1 in [5]). Pictures provided by Endolab GmbH.

6.6 Summary of preliminary tests for bone plate-screw constructs

Preliminary static (n = 2) and dynamic tests (n = 3) have been conducted prior to the tests detailed below using a loading span of 35 mm instead of 70 mm. The mean construct (yield) strength has been determined as 4,38 ± 0,01 Nm. Furthermore, it was observed, that in dynamic testing the construct did not fail by bone plate or screw breakage, but shows a displacement change, i.e. a plastic deformation over the entire loading range at a load of 90 % proof load (or even at 120 % proof load). These preliminary test results together with the sensitivity analysis conducted by Halbauer et al. [66] led to the loading specifications detailed above in section 6.5.1.

6.7 Test planning

For the purpose of this evaluation, a test procedure for static and dynamic 4-point bending tests for each of the two groups has been developed.

6.7.1 Procedure for static and dynamic testing

Prior static and dynamic testing, a sequence of three test cycles under elastic conditions up to 80 % of the proof load prior to conduct static or dynamic testing (“pre-conditioning”) has been applied to remove any remaining loose conditions within the construct or between the construct and bone. Those conditions may result from the assembly and/or fixation process and may have an impact on the displacement measurement during testing. Pre-conditioning has been conducted on bone plate-screw constructs as well as on single bone plates for comparative purposes. Testing has been conducted in displacement-controlled mode and a vertical testing speed of 10 mm/min using a progressive load until failure of the bone plate-screw construct or the plate. All diagrams have been created from numeric data acquired during the test using Microsoft Excel for Office 365 MSO 32-Bit. The data analysis has been accomplished using MathWorks MATLAB, R2020a. Tab. 2 contains the test specification.

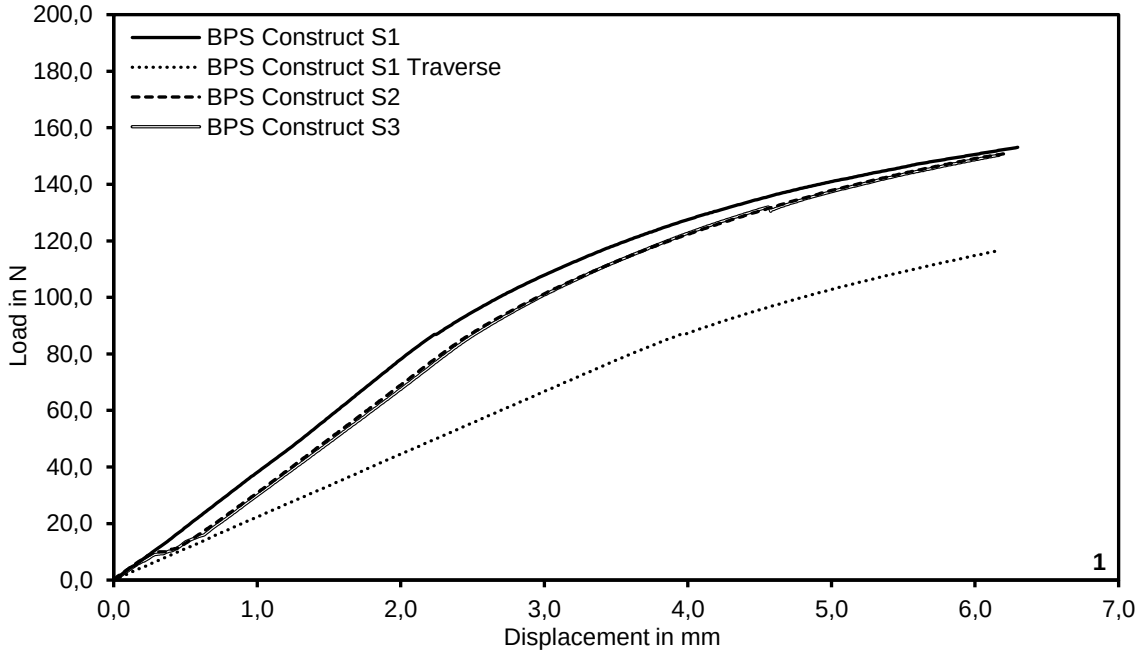
	Static testing	*Dynamic testing*
1 Pre-conditioning	• Load: 80 % proof load in N • BPS construct: 75 N • ASTM F382 [5]: 150 N • n = 3 cycles	• Load: 80 % proof load in N • BPS construct: 75 N • ASTM F382 [5]: 150 N • n = 3 cycles
2 Testing mode	• Vertical testing speed = 10 mm/min • Displacement-controlled	• Displacement-controlled • Sinusoidal waveform • Frequency = 5 Hz Duration: ~ 55,5 hours/test
3 Test range	• Progressive load until failure • three samples	• M-N diagram testing for one selected load: Constant amplitude test between 10 - 90 % of the proof load in N [5] • three samples as per ASTM F382, A2.7.4 [5] • five samples for bone plate-screw constructs
4 Test direction	• As to simulate a fracture gap closure	• As to simulate a fracture gap closure
5 Procedure	• Create load versus displacement curve using data acquired during the test • X-axis: displacement in mm • Y-axis: load in N	• Create displacement versus number of cycles graph using data acquired during the test • X-axis: number of dynamic loading cycles • Y-axis primary: displacement in mm • Y-axis secondary: bending moment in Nm
6 Additional Measurement	• Traverse displacement (Center displacement of the plate) using a video extensometer	• Static intermediate testing: stiffness measurement after completing a specified amount of cycles • Intervals: n = 1, 1.000 (R1), 5.000 (R2), 50.000 (R3), 500.000 (R4), 10^6 cycles (R5) • Stiffness BPS construct: 77 N • Stiffness ASTM F382 [5]: 180 N
7 Run-out	---	• One Million cycles
8 Result	• Proof load • Construct stiffness • Construct (yield) strength • Ultimate construct strength	• Number of cycles until failure at 90 % of proof load • Comparison of ASTM F382 [5] versus bone plate-screw construct testing results

Tab. 5: Test specification for static and dynamic testing. After termination of each test the test samples were visually analyzed for the presence of (construct) failure, including fixation failure or bone fracture.

6.8 Static testing results

6.8.1 Static testing of bone plate-screw constructs

Static testing for bone plate-screw constructs has been conducted on three samples using the loading specifications described in section 6.5.1 and applying the procedure outlined in section 6.7.1. The tests have been performed to determine the construct stiffness, proof load, construct (yield) strength and the proof point displacement. The bending structural stiffness cannot be calculated using the term given in ASTM F382 (A1.1 in [5]) due to the geometry of the construct sample. Based on the results obtained the dynamic testing load has been calculated. The results are summarized in Fig. 18. The bending curves show a linear increase leading to a mean construct stiffness of 36,68 ± 2,19 N/mm (measured in the linear portion until 83 N). The mean proof load has been determined as 112,46 ± 1,06 N with a corresponding mean proof point displacement of 3,40 ± 0,19 mm and an offset displacement q = 0,002 * 161 mm = 0,322 mm.



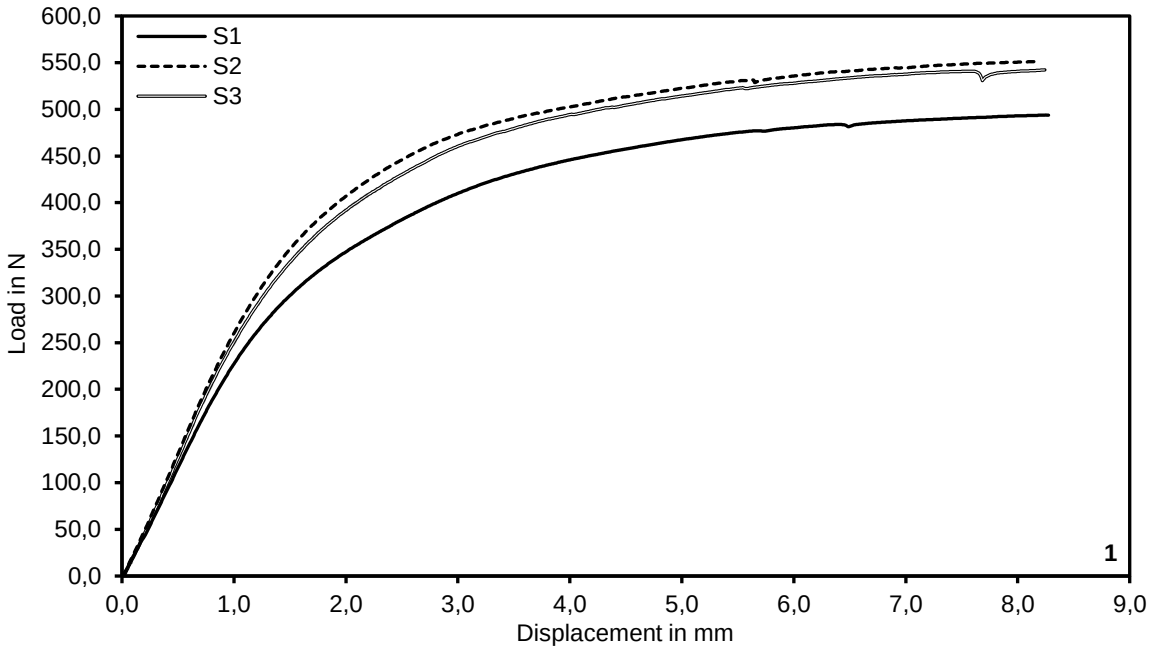
	Construct stiffness	*Proof point (Construct strength)*	*Proof point displacement*	*90 % Proof load displacement (mean)*
BPS Construct S1	39,20 N/mm	111,83 N	3,18 mm	Min: 0,33 ± 0,05 mm Max: 2,92 ± 0,18 mm
BPS Construct S2	35,63 N/mm	111,87 N	3,46 mm	
BPS Construct S3	35,22 N/mm	113,69 N	3,55 mm	
Mean ± SD	36,68 ± 2,19 N/mm	112,46 ± 1,06 N (3,94 ± 0,04 Nm)	3,40 ± 0,19 mm	**2**

Fig. 18.: Static testing results for bone plate-screw constructs and determination of construct properties. Part 1: Load versus displacement curves for three samples. The bending deformation of the plate in the center of the setup, has also been measured using a video extensometer (shown as BPS construct S1 Traverse). There is a calculated mean displacement factor of approximately 1,79 between the displacement measured by the testing machine compared to the traverse displacement. Part 2: Summary of the construct bending properties.

The calculated dynamic testing load is specified by 90 % of the proof load (101 N) which equals a bending moment of 3,54 Nm. The shape of the graph does not allow the determination of the construct ultimate strength.

6.8.2 Static testing as per ASTM F382

Static testing as per ASTM F382 [5] has been conducted using the loading specification described in section 6.5.2. The results are summarized in Fig. 19.



	Bending stiffness	*Proof load (Bending strength)*	*Proof point displacement*	*90 % Proof load displacement (mean)*
ASTM F382 S1	245,02 N/mm	217,06 N	0,95 mm	Min: 0,05 ± 0,01 mm Max: 0,84 ± 0,03 mm
ASTM F382 S2	278,12 N/mm	254,69 N	0,98 mm	
ASTM F382 S3	272,20 N/mm	230,88 N	0,91 mm	
Mean ± SD	265,11 ± 17,65 N/mm	234,21 ± 19,03 N (3,51 ± 0,29 Nm)	0,95 ± 0,04 mm	

2

Fig. 19.: Static testing results for the bone plate and determination of bending properties as per ASTM F382 [5]. Part 1: Load versus displacement graph for three samples. Part 2: Summary of the bending properties of the bone plate.

The bending curve shows an anticipated linear increase leading to a mean bending stiffness of 265,12 ± 17,65 N/mm (measured in the linear portion until 177 N) and a bending structural stiffness of 2,98 Nm^2 (calculated as per A1.1 in [5]). The mean ultimate strength of the bone plate is 529,27 ± 31,01 N. The proof load to create a deformation of 0,2 % of the center span distance has been determined as 234,21 ± 19,03 N with a corresponding mean proof point displacement of 0,95 ± 0,04 mm and an offset displacement q with q = 0,002 * 30 mm

= 0,06 mm. The calculated dynamic testing load is 211 N, which equals a bending moment of 3,17 Nm.

6.9 Dynamic testing results

6.9.1 Dynamic testing of bone plate-screw constructs

Dynamic testing for bone plate-screw constructs has been conducted using the loading specification of section 6.7.1. A sinusoidal load alternates for n = 10^6 cycles at 5 Hz. In total four construct assemblies have undergone this procedure between 0,36 - 3,61 Nm (calculated mean using load data acquired during the test). After termination of each test, the specimens were taken off the materials testing machine and visually analyzed for the presence of failure modes. The BPS constructs showed plate bending across the bridge span, in particular no plate or screw breakage or signs of surface cracking was observed, neither screw bending, screw migration nor screw loosening. The raw data results are displayed in Fig. 20, showing several irregularities and effects mainly caused by the testing machine within the intermediate testing process. This is why the calculated mean displacement (min/max) using a logarithmic x-axis is presented in Fig. 21, which better illustrates the behaviour of the construct in the early loading phase. Generally, the construct shows a bilinear behavior with a first linear section until n = 10^3 loading cycles, followed by a non-linear one, and second linear section between n = 5*10^4 and n = 10^6 loading cycles.

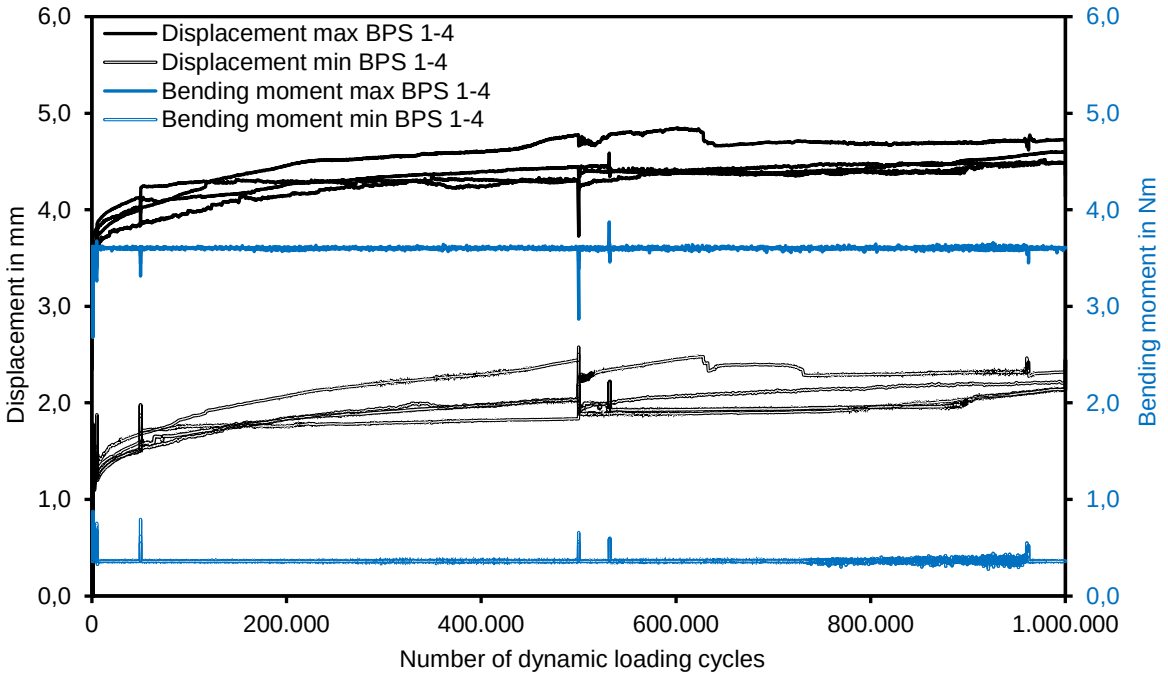


*Fig. 20.: Dynamic testing results for four bone plate-screw constructs. Raw data recorded during the entire loading range, displayed for the maximal and minimal displacement values versus number of dynamic loading cycles. The bending moment in Nm has been calculated by M_b = P * 0,5 * 0,07 with P = proof load (2nd y-axis).*

At the very beginning of the test, the construct exhibits a mean displacement change of 3,48 ± 0,10 mm (max) and 1,09 ± 0,05 mm (min). This displacement remains almost constant until n = 10^3 loading cycles (mean: 3,52 ± 0,10 mm (max); 1,12 ± 0,04 mm (min)) and steadily increases until n = $5*10^4$ cycles. A mean displacement change of 0,57 mm (max) / 0,62 mm (min) is detected between n = $5*10^4$ - 10^6 cycles. The starting point for the second regression analysis of n = $5*10^4$ cycles has been selected as it results in an acceptable coefficient of determination of R^2 = 0,97 (Annex 12.2). The resultant total plastic deformation is determined by the min-curve, in this case a calculated mean displacement change of **md = 1,11 mm** (2,20 mm - 1,09 mm). This value does not include the calculated offset of almost 0,29 mm caused by testing in a “non-linear section” of the static testing graph.

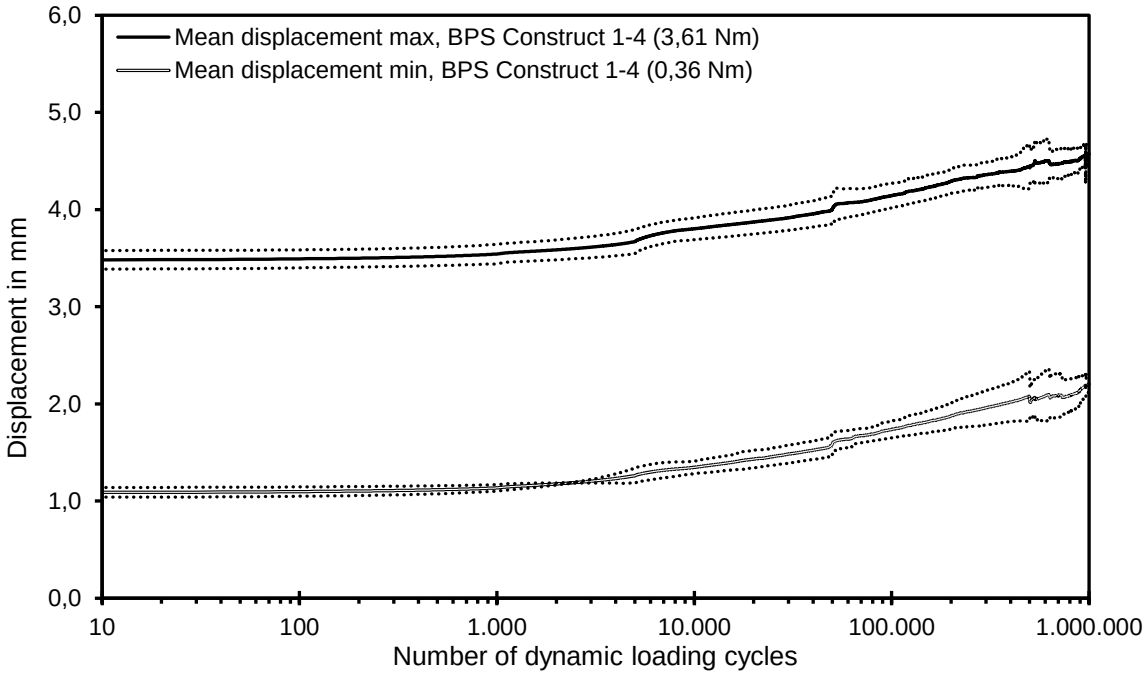


Fig. 21.: Analysis of dynamic testing results for four bone plate-screw constructs showing a bilinear behaviour. The raw data set has been smoothened using the ‘rloess‘-method [83] and interpolated using the ‘spline’-method in MATLAB (Data array 10, cubic interpolation for each data set). Mean displacement values versus number of dynamic loading cycles using a logarithmic x-axis. The error bar is the “running“ standard deviation for each data point.

6.9.2 Static intermediate testing of bone plate-screw constructs

During the dynamic testing routine, changes of the construct stiffness may indicate a construct failure, a loosening between construct components or a change of the mechanical properties of BPS construct. This is why static intermediate tests have been conducted after completing a specified amount of cycles in order to determine the current construct stiffness. The measurements were conducted at planned intervals of n = 1, 1.000, 5.000, 50.000, 500.000 and after n = 10^6 cycles. After completing each interval, the testing machine has been stopped and the actuator has completely been detached from the construct. Then a

single static bending test has been performed until reaching a specified limit of 77 N. Fig. 22 shows the results. There is a constant displacement change, if the construct exhibits further dynamic loading cycles, being in line with the results of the dynamic tests. In sum, the mean construct stiffness almost remains constant within n = $5*10^5$ cycles (with a slight tendency to a decreased stiffness over time).

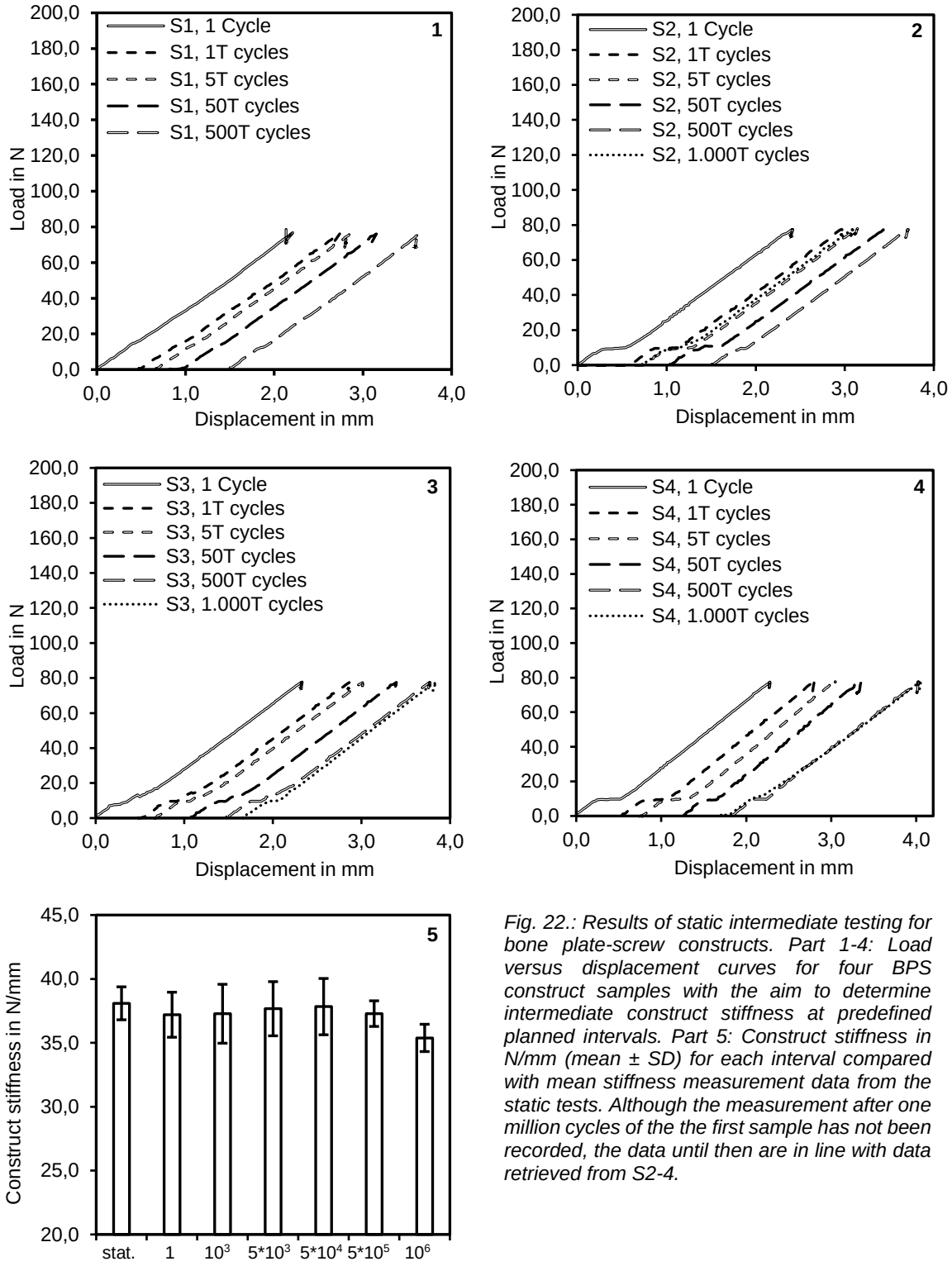


Fig. 22.: Results of static intermediate testing for bone plate-screw constructs. Part 1-4: Load versus displacement curves for four BPS construct samples with the aim to determine intermediate construct stiffness at predefined planned intervals. Part 5: Construct stiffness in N/mm (mean ± SD) for each interval compared with mean stiffness measurement data from the static tests. Although the measurement after one million cycles of the the first sample has not been recorded, the data until then are in line with data retrieved from S2-4.

6.9.3 Dynamic testing as per ASTM F382

Dynamic testing as per ASTM F382 [5] has been conducted using the loading specification as described in section 6.7.1. In this case a sinusoidal loading scheme alternates for one million cycles at a frequency of 5 Hz. In total three bone plates have undergone n = 10^6 cycles between 0,32 - 3,18 Nm (calculated mean using load data acquired during the test). The raw data results are shown in Fig. 23.

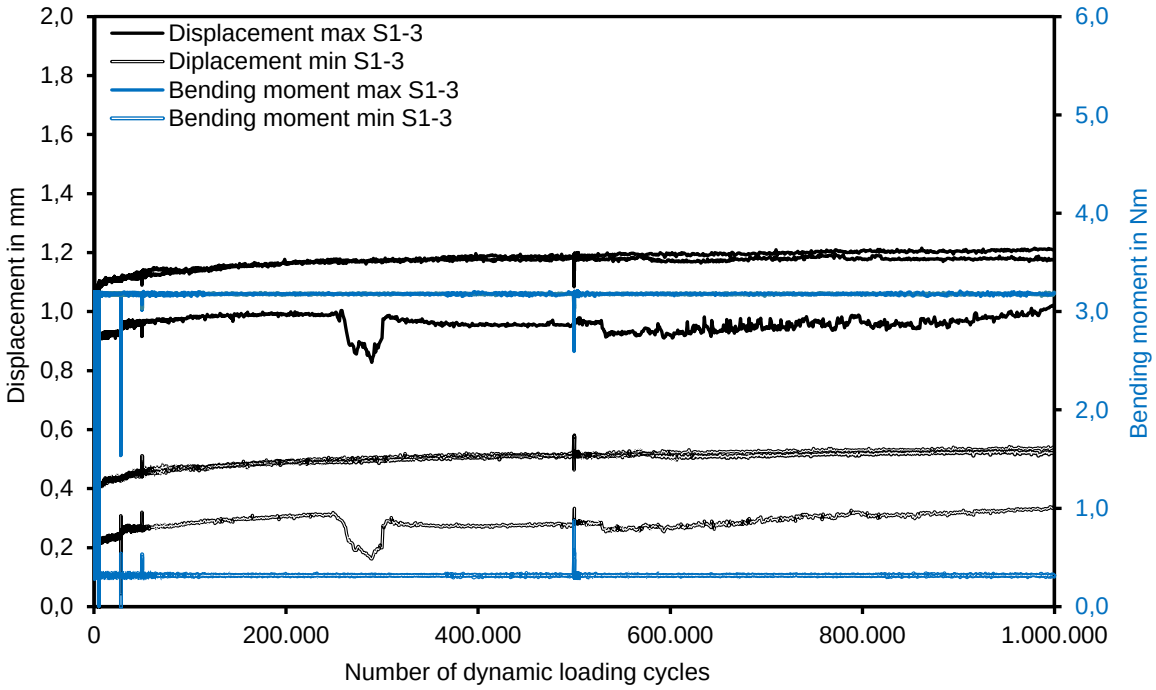


*Fig. 23.: Dynamic testing results for three bone plates as per ASTM F382 [5]: Raw data recorded during the tests, displayed for the maximal and minimal displacement values versus number of dynamic loading cycles. The bending moment in Nm has been calculated by M_b = P * 0,5 * 0,03 with P = proof load (2^{nd} y-axis).*

The calculated mean displacement max/min and the corresponding standard deviation using a logarithmic x-axis is shown in Fig. 24 while applying the same data assessment techniques as detailed in Fig. 21. At the beginning of the test (after n = 10 loading cycles) the bone plate exhibits an displacement change of 0,98 ± 0,11 mm (max) and 0,29 ± 0,11 mm (min). The resultant total plastic deformation is determined by the displacement min-curve, in this case a calculated mean displacement change of **md = 0,17 mm** (0,46 mm - 0,29 mm). This value does not include the offset of almost 0,05 mm. Apart from the data analysis, the bone plate itself shows a comparable (bilinear) behaviour, however, with a much lower magnitude compared to the bone plate-screw constructs (Fig. 21, factor 6.5). There is a first linear section until n = 10^3 cycles and a second linear one between n = 5*10^4 and n = 10^6 with a mean displacement change of 0,06 mm (max) / 0,07 mm (min). Over the entire loading range of n = 10^6 loading cycles a mean displacement of 0,43 ± 0,13 mm was calculated (min).

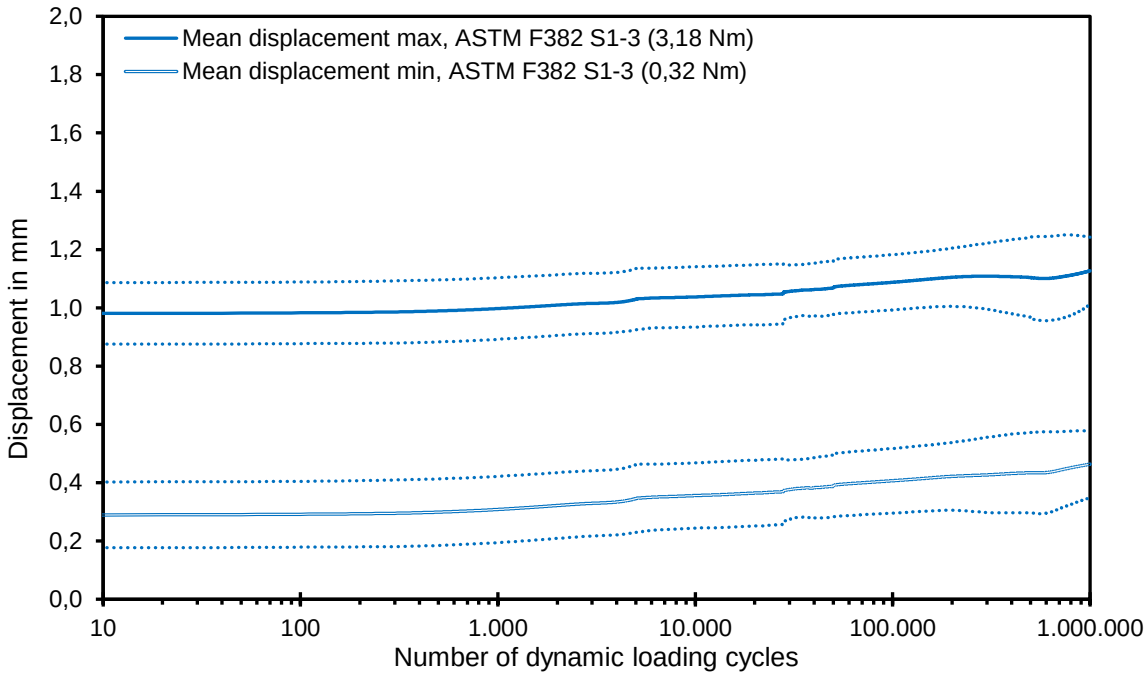
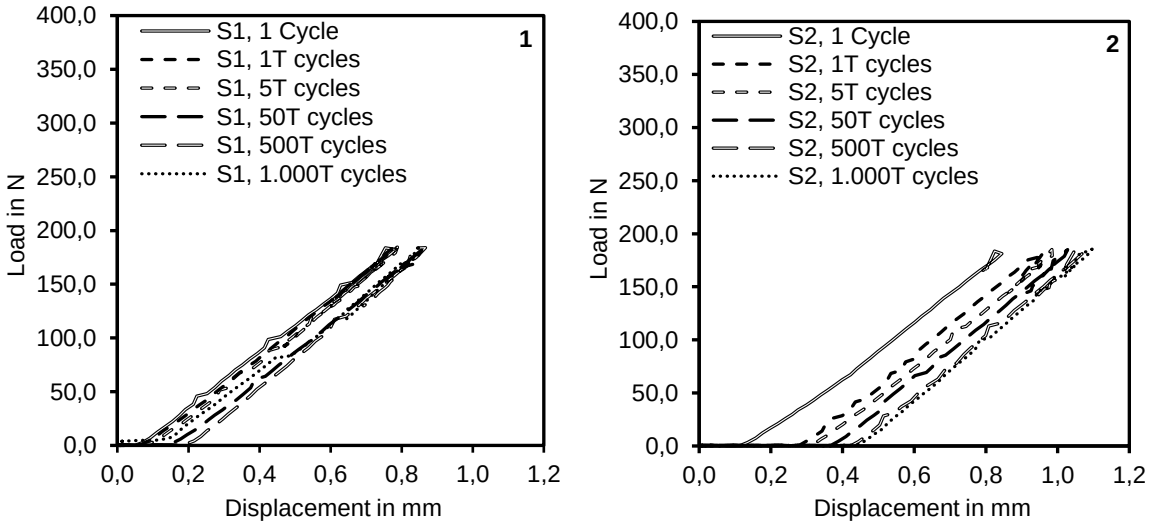


Fig. 24.: Analysis of dynamic testing results for three samples as per ASTM F382 [5]: The raw data set has been smoothed and data points interpolated using the same principles as for the BPS constructs (Fig. 21). Mean displacement max and -min values versus number of dynamic loading cycles using a logarithmic x-axis. The error bar is the "running" standard deviation, calculated for each data point.

6.9.4 Static intermediate testing as per ASTM F382

The measurement intervals chosen were identical to the ones for the BPS construct. After completing each interval, a single static bending test has been performed using a specified limit of 180 N. Fig. 25 shows the results. In this case, there is a constant displacement change over time, confirming the results of the dynamic test. However, the displacement change is relatively low compared to the behaviour of the BPS construct (Fig. 22). In contrast to the results of the BPS construct, the mean bending stiffness of the bone plate steadily (but slightly) increases within n = $5*10^5$ cycles by 5.6 %.



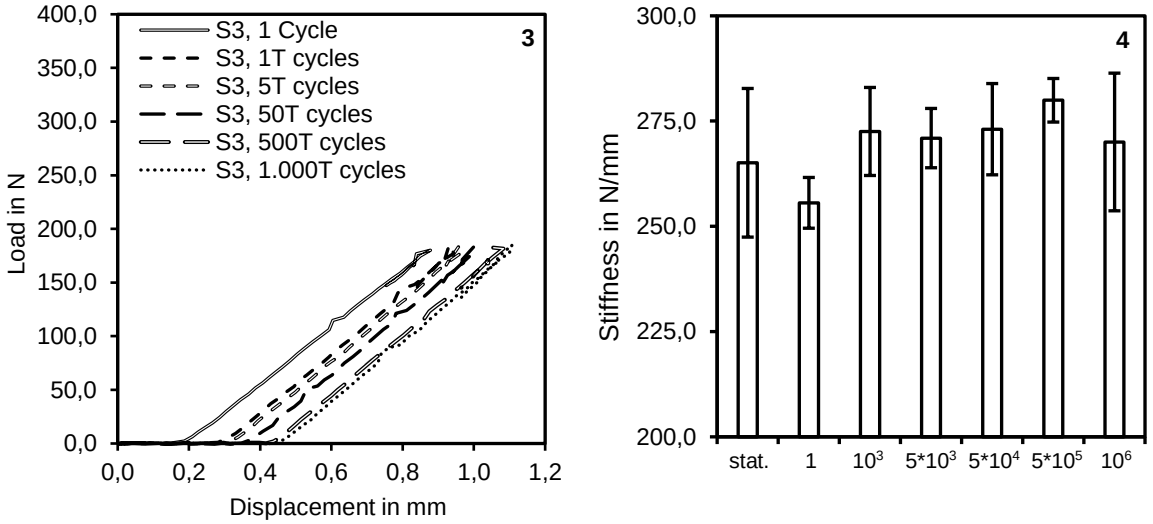
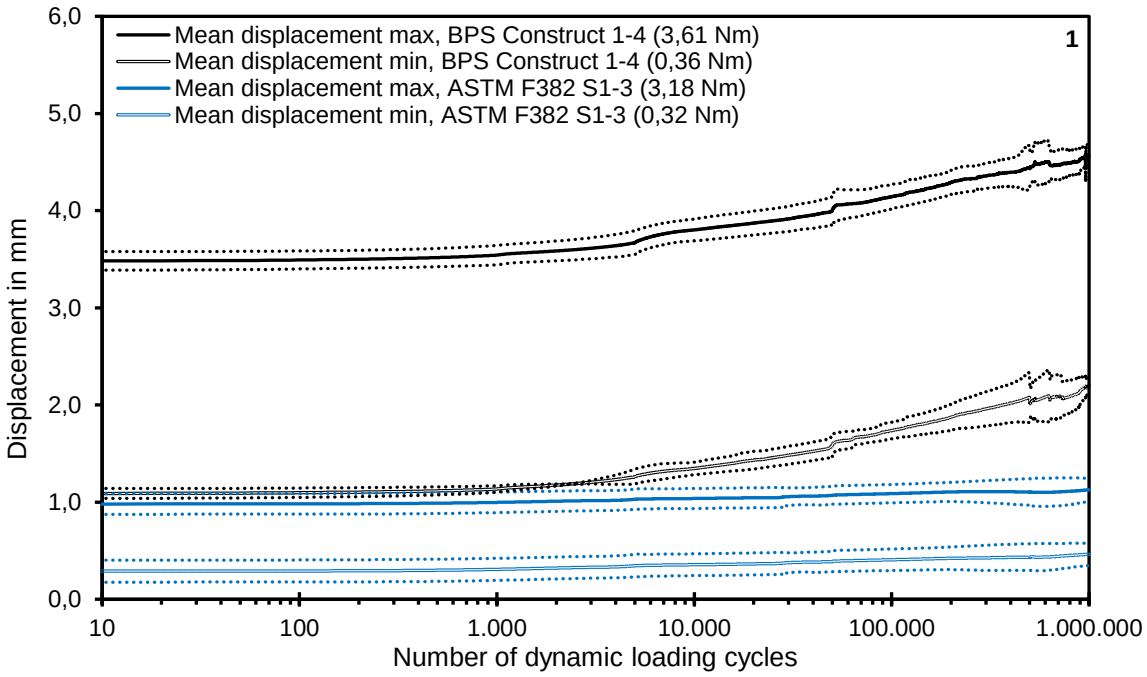


Fig. 25.: Results of static intermediate testing as per ASTM F382 [5]. Part 1.-3.: Load versus displacement curves for three samples after finishing a specified amount of loading cycles. Part 4: Calculated mean bending stiffness in N/mm compared to the initial mean static stiffness of the bone plate. Generally, an increasing stiffness over the entire loading range has been observed. The error bar is the standard deviation.

6.10 Comparison and summary of the testing results

In total six static tests were conducted, three as bone plate-screw construct and three as defined in ASTM F382 [5]. The test samples generally showed an equal bending behaviour among each group. The static deflection curves of the bone plate-screw constructs include a linear section to determine plate stiffness, as well as a non-linear section to determine the bending strength. The curves are comparatively flat at the beginning of the load, leading to a low(er) stiffness of 36,68 ± 2,19 N/mm (mean ± SD). The proof load was determined at an offset of 0,322 mm as 112,45 ± 1,06 N, the yield point at 2,91 ± 0,07 Nm. Dynamic testing was then conducted at 101 N which equals a bending moment of 3,54 Nm. The bone plates tested as per ASTM F382 [5] showed the anticipated stiff behaviour of a straight bone plate tested in static 4-point bending mode. There is a slight deflection at a given and relatively high load. The proof load was determined using the 0,2 % offset method (0,06 mm) as being 234,21 ± 19,03 N (mean ± SD), the bending stiffness was 265,11 ± 17,65 N/mm (mean ± SD). The proof load was used to determine the alternating, sinusoidal load for dynamic testing at 211 N which equals a bending moment of 3,17 Nm. The static and dynamic displacement results over the entire loading range and mechanical characteristics for each group are summarized in Fig. 26. In total seven dynamic tests were conducted, four as bone plate-screw construct and three as defined in ASTM F382 [5]. The samples showed an equal bending behaviour among all tested samples per group.



2

Static testing	***Bone plate-screw construct***		***ASTM F382***	
Stiffness	36,68 ± 2,19 N/mm		265,12 ± 17,65 N/mm	
Proof load	112,46 ± 1,06 N		234,21 ± 19,03 N	
Proof point displacement	3,40 ± 0,19 mm		0,95 ± 0,04 mm	
90 % Proof point displacement (min, max)	0,33 ± 0,05 mm 2,92 ± 0,18 mm		0,05 ± 0,01 mm 0,84 ± 0,03 mm	
Calculated dynamic testing load	101 N (3,54 Nm)		211 N (3,17 Nm)	
Measured dynamic testing load	0,36 - 3,61 Nm		0,32 - 3,18 Nm	
Yield Load	83,15 ± 2,10 N		176,92 ± 12,28 N	
Yield Point	2,91 ± 0,07 Nm		2,65 ± 0,18 Nm	
Strength	3,94 ± 0,04 Nm		3,51 ± 0,29 Nm	
Ultimate strength	Not determined		529,27 ± 31,01 N	
Dynamic testing	*min*	*max*	*min*	*max*
Total mean displacement change	1,11 mm	1,09 mm	0,17 mm	0,15 mm

Fig. 26.: Summary of the testing results for both groups. Part 1: Comparison of displacement results determined during dynamic testing under displacement-controlled conditions. The error bar represents the standard deviation. Due to the sample size no statistical analysis has been performed. Part 2: Summary of the mechanical characteristics of the bone plate-screw construct and the bone plate as per ASTM F382 [5].

The bone plate-screw constructs showed a bilinear behaviour under dynamic testing conditions. There is a first linear section until n = 10^3 loading cycles, and a second one, a linear increase roughly between n = 5*10^4 and n = 10^6 cycles (Fig. 21 and Fig. 26, part 1), leading to a total mean displacement change of md = 1,11 mm. The fifth sample, that was excluded from the analysis, showed an equal bending behaviour until n = 10^5 loading cycles (data shown in annex 12.3). In order to roughly determine the starting point for the additional displacement change a regression analysis of both sections has been conducted. The analysis led to an intersection of both graphs at x = 3.268 cycles for the bone plate-screw

constructs. (Annex 12.2 contains its calculation). Bone plates tested as per ASTM F382 [5] showed the anticipated behaviour of a straight bone plate tested in 4-point bending mode under constant dynamic loading conditions. There is a relatively low displacement change at the beginning (0,02 mm after $n = 10^3$ cycles) and throughout the entire loading scheme. Looking closer to the changes of the displacement, a comparable bilinear behavior (with comparable linear sections) can also be observed in this case (Fig. 24 and Fig. 26), however with a much lower magnitude. A linear regression analysis of both sections led to a calculated intersection of both regression lines at x = 870 cycles (Annex 12.2). This calculation is affected by the low slope of the regression curve, but seems suitable for a rough approximation. All three samples were able to complete $n = 10^6$ loading cycles, however, a mean displacement of change of md = 0,17 mm was detected after the run-out criteria had been reached. The total displacement change (plastic deformation) is the applicable failure mode in both cases, no plate or screw breakage was visually observed, neither a breakage of the bone substitute material nor any other failure.

7 Discussion

This dissertation explores the possibilities and constraints when modern bone plate-screw constructs are subject to pre-clinical testing under standardized conditions.

7.1 Regulatory requirements and literature review results

For many years ASTM F382 [5] has been (and still is) the most appropriate mechanical testing reference for metallic bone plates, however, the latest standard updates did not sufficiently consider various design changes including anatomically shaped, pre-contoured or angle-stable, locked type constructs with significant changes in biomechanics compared to conventional fracture fixation methods. The analysis of applicable regulatory requirements revealed, that the majority of modern bone plates cannot be sufficiently evaluated prior to marketing. Pre-clinical testing of bone plate-screw constructs is insufficiently regulated and shall be harmonized to enhance confidence of testing. This circumstance applies to a variety of testing standards, since the latest research results are not systematically included [121]. A systematic literature search on n = 159 publications revealed, that standardized testing of bone plate-screw constructs (whether for regulatory purposes or) as applied in biomechanical research, remains an unsolved regulatory and pre-clinical opportunity since many years. Consequently, the main goal of this thesis was set to develop and to apply standardized pre-clinical testing methods for straight or pre-contoured, conventional or locked-type bone plate-screw constructs and to assess the results in a clinical context.

7.2 Development of standardized test methods

Starting with an assessment of different standardization methods, two separate approaches to test or evaluate a medical device for osteosynthesis were taken into consideration. Biomechanical testing for research purposes, as applied in various scientific studies, and mechanical testing for regulatory purposes. Although often used synonymously, both terms cover different pre-clinical testing concepts [206].

7.2.1 Standardized biomechanical testing

Standardization of biomechanical testing in terms of standardized test setups seemed almost impossible and the reason for that is obvious. Biomechanical testing for research purposes aims to explore a specific research question. The pre-clinical evaluation of the

construct is often not the primary goal of the study, the test setups serve the purpose of biomechanical research. However, standardization in that area would be beneficial to directly compare research results, not only for regulatory purposes. Although there is an ongoing demand to counteract “a lack of standardization in the methods used and a lack of consistency in both the testing procedures and the measurements” [33], standardization in this case can only be achieved by specifying a general biomechanical testing process, defining criteria for the development of a specific testing procedure, which then would be unique for a single anatomical region. In this context, three requirement groups subdivided into several requirements (1. Biomechanical modelling, 2. Sample preparation, 3. Testing methodology and performance assessment) were identified, that need to be considered, interpreted and applied when designing a procedure e.g. for the distal radius [174], proximal humerus [124], distal humerus [191], or the ulnar coronoid process [125]. Each output would be unique for a specific location. This process approach is not necessarily effective in terms of standardization. It would also not fit into current concepts of level 3 testing standards and it would still be quite unlikely that the output would deliver testing results, that are directly comparable, thus standardization potentially ineffective. However, such biomechanical setups (“customized test models taking into account the characteristics of the implant” [112]) likely serve the purpose of testing under anticipated biomechanical (clinical) conditions.

7.2.2 Standardized mechanical testing

Mechanical testing of implants for osteosynthesis is different. It shall be performed by applying published internationally recognized standards. Mechanical testing is mainly conducted for regulatory purposes and inherently serves the purpose of physical testing under standardized conditions. Regulators are used to working with specified testing setups and a limited number of unspecified variables in the test procedure. Consequently, and bearing the biomechanical assessment above in mind, a more promising standardization approach is the development of a (i.e. level 3) testing guidance for straight and pre-contoured conventional and locked-type constructs for osteosynthesis.

Standardized mechanical torsion and bending tests have been developed to serve that purpose, alongside with detailed test setups for straight and contoured bone plate-screw constructs, requirements for positioning of the construct, specific testing requirements, failure criteria and a definition of outcome parameters for static and dynamic testing. This proposal is based on the methods applied by Bottlang et al. [19] and Fitzpatrick et al. [47], and follows the well-accepted testing philosophy of ASTM F382 [5], section A1.6.2.1 [5]. It contains both, torsion and bending tests and therefore modifies and extends the methods proposed by ASTM F382 [5], while incorporating worst-case test conditions [89] and reducing the number of potential independent variables, as found in the literature. Torsion

and bending tests in a static and dynamic loading mode are established test methods in various international standards for comparable, implantable orthopedic medical devices [5, 9, 10, 13]. Derogating from the methods proposed by Bottlang et al. [19] implant testing is conducted across the “implant axis” and not across the physiological “bone axis”. The bone plate (= the test object) is centered within the setup, thus reduces potential variables of bone (e.g. bone mineral density), its anatomy (e.g. load transfer mechanics) or biomechanical aspects (e.g. testing under 20° abduction [180]). This technical approach seems suitable to align the construct in a standardized manner to serve the purpose of standardized test conditions, however, the alignment may cause a mechanical load to the construct that does not necessarily represent worst-case (or physiological) loads at this anatomical area.

While bending is regulated in ASTM F382 [5], torsion tests were added, since torsional loads are likely to occur at the skeletal system and are likely to contribute to certain types of fractures. Compressive loads in an isolated test scenario across the “implant axis” would not deliver additional information. The second option, to test along the physiological “bone axis” using rigid bone substitutes (a typical compression test found in the literature, but using cadaver bone instead), would also not add information as it just represents a certain “type of a bending test”. Therefore compressive testing was not included. The determination of certain characteristics, such as e.g. construct stiffness, construct strength or number of cycles until failure, has been adopted from ASTM F382 [5] and also transferred to torsion testing, as (already regulated) torsion testing follows the same principle (A2 in [9]). The test methods are suitable to test the complete construct assembly under the condition that it is rigidly fixed to “healthy bone”. Bone is replaced by suitable rigid, artificial material that is capable to transfer the applied load/moment without inherent plastic deformation. The failure is expected to occur at the construct. This test scenario excludes various *in-vivo*-situations such as e.g. osteoporotic bone of the elderly. However, it is the intention to mechanically evaluate the construct and not to explore its ability to treat complex fracture types of e.g. osteoporotic bone. Both test methods ensure that the complete bone plate-screw construct fits into the test setup and that there is no further structural limitation for testing. Any bone plate fulfills its intended purpose only in combination with corresponding bone screws, making it indispensable to test those devices assembled together, i.e. as a bone plate-screw construct. This aspect is particularly important in order to test the final implant and to avoid any mechanical manipulation of the plate as discovered in daily testing routine.

The test setups presented are applicable for the majority of currently available devices, especially those for upper and lower extremities, including straight linear, anatomically shaped, locked-type or conventional systems. However, due to the extensive variety of

plates, the test setups are maybe not appropriate for all implant constructs available. There are existing irregular construct designs that may not directly fit into the setups or that have one or more design features making it considerably difficult to align them in the test setups, e.g. as for constructs intended for the calcaneus. However, the test setups are valid for the majority of available bone plate-screw constructs having at least a linear fixation part, e.g. for the humerus, tibia or distal radius. Small bone plates e.g. those intended for fingers and toes or the upper face may not fit in the setup and are potentially excluded [82]. These plates are used in minimally load bearing anatomical areas of the far extremities and shall therefore be tested differently [82]. Additional guidance for positioning the construct and specific testing requirements are considered indispensable to further serve the purpose of standardization. However, it remains a proposal that requires validation on several bone plate-screw constructs for different anatomical areas. The specification of specific testing requirements addresses major questions (and thus requirements) that need to be interpreted and implemented when testing a construct under worst-case conditions [89]. Worst-case conditions must represent “clinically relevant worst-case scenarios” using devices that “represent worst-case design” [89]. This is an important aspect when developing pre-clinical testing methods, parameters and boundary conditions, and explains, why specific testing requirements such as “plate elevation” or “bridge span and number of applied screws” have been introduced and specified. The variation of these requirements may have an impact of the mechanical behaviour of the construct, e.g. a plate elevation of > 0mm impacts construct stiffness and strength [2, 163], or the number of screw holes occupied (versus left empty) in the bone plate likely impacts bending stiffness, strength and its fatigue behaviour [81], but serves the principle of a “flexible” fixation. However, at the same time it must be ensured, that the specifications are in line with basic clinical procedures [53]. Additionally, worst-case test conditions are expected by regulators and typically assumed and scientifically justified by the study designer, when there is a lack of specification. Defining boundary conditions limits potential variables and thus contributes to standardization.

However, these testing procedures have several limitations. Many of them are determined by the nature of mechanical testing and are already captured by ASTM F382 [5]. “The standard does not define levels of performance or case-specific clinical performance for bone plates, as insufficient knowledge is available to predict the consequences or their use in individual patients for specific activities of daily living” (1.2 [1]). In the current absence of relevant performance related design specifications (e.g. strength level for bending), testing against the predicate (a well-established device with a proven clinical history, “the golden standard”) is a valid alternative to demonstrate equivalence and to receive market clearance, e.g. in the US. However, the (implant specific) values obtained using isolated

torsion and bending tests may be compiled in a data source, which once may serve as a fundamental basis to define such levels of (clinical) performance [121]. These data need to be properly linked to available data from the manufacturer's "post-market surveillance system" (combination of technical and PMS data). This practice is currently not systematically established or followed, however, in line with the requirement of the MDR for implantable medical devices, this data will have to be systematically collected, documented, evaluated and published in the "periodic safety update report" (PSUR) and the "summary of safety and clinical performance" (SSCP) when the MDR is set into force and provided that the European database on medical devices ("EUDAMED") is "fully functional" [86]. As the intention is to define test methods to "conduct relative comparisons of different construct designs" (A2.5.2 in [1]) this procedure does not address biomechanical aspects sufficiently, nor does it intend to replace biomechanical testing or testing against the requirements of any other standard or jurisdiction. Biomechanical testing under anticipated physiological loading conditions, i.e. methods and procedures applied in biomechanical research, has not been considered and addressed sufficiently, but at the same time appears to be also not fully compatible with testing under standardized conditions. Four-point bending or torsion testing simplifies test conditions by isolating basic loading modes. This method eases the standardization process, but neglects the fact, that any load at the skeletal system is by far isolated or that simple. In many cases these loads are combination loads *in vivo*. As detailed above, any possible solution to standardize e.g. physiological loading conditions including specific load transmission modalities would introduce a number of independent variables to the testing procedure, a circumstance that seems contradictory to standardization [5, 9, 10, 13].

Compression testing along the bone axis simulating the load that is expected to occur at the skeletal system is only partially covered as compression testing is often applied as compressive bending. This is maybe the most appropriate disadvantage from a clinical perspective. Compressive loads are most frequently used in biomechanical research to simulate physiological loading for upper and lower extremities. However, under the condition that the construct is rigidly fixed to bone substitute material, compressive testing would not deliver additional information as not already received under 4-point bending mode.

Mechanical torsion and bending tests (using solid POM bone replacement bars) are not capable to evoke all possible clinical failure modes, e.g. screw failure due to shear forces acting on the screw during axial loading, simulation of the complex fixation in metaphyseal bone. The clinical relevance using rigid bone substitute material is generally limited. But this is not the intention of mechanical testing, nor of any other testing standard containing requirements for implants for osteosynthesis [5, 9, 10]. At this time, it is also not intended

to predict the in-vivo performance of the implant based on the measurements results obtained. However, the results can be used for direct construct comparison.

Furthermore, not all boundary test conditions are specified. It remains unspecified which test methods are applicable per anatomical area, although the literature search revealed methods that are commonly applied per fracture location. There are also no specific requirements about how the measurements shall be taken, or which bone plate variation per anatomical area shall be tested, including which plate length, width or thickness, or how many specimens shall finally be used for the evaluation. There are also no set requirements for the POM diameter or the screw length applied. Comparable regulatory requirements include only a justification of the chosen implant, referring to worst-case test conditions [104]. Additionally, the choice of three screws on each fracture side, applied in a right angle of 90° between the plate and the screw must not necessarily represent worst-case test conditions [120, 215]. However, it serves the purpose of standardization and is line with surgical guidance published by the AO [94]. It should be noted, that not every single detail is or can be standardized in form of a “recipe”, especially when such a variety of devices is within the scope of its application [121]. The application still requires basic (bio-) mechanical knowledge to avoid any misinterpretation of the test results [121]. That is common practice and in line with other published standards for non-active implants for osteosynthesis [5, 9, 10, 13].

Dynamic testing has been specified using a run-out criteria of $n = 10^6$ cycles for comparative purposes as it is standardized by ASTM F382 [5] and may represent “state of the art” in mechanical testing [5, 86]. However, due to the extensive variety of BPS constructs, not all devices must resist the same amount of dynamic loading cycles the implant has to withstand clinically. The literature review revealed differences between upper and lower extremities, plate sizes and their load bearing capabilities, or maybe there is no requirement to test certain devices dynamically at all [82]. It still remains unspecified, how many loading cycles shall be anticipated for any rehabilitation phase until bone healing occurred, as no measurement data exist that would scientifically justify any specification at this time. However, based on the results of the practical application of standardized tests (for this type of construct), dynamic testing shall be conducted on a sufficient number of loading cycles ($n > 3.268$ cycles, as per regression analysis in annex 12.2) in order to evoke additional displacement changes caused by the construct assembly (section 7.4).

Moreover, no requirements were defined for the “pre-conditioning” of the construct, i.e. a defined loading scheme prior static or dynamic testing to eliminate loose conditions within the setup. This aspect is not regulated in ASTM F382 [5], likely because single items are intended to be tested and typically, nothing is assembled or fixed prior loading. The pre-

conditioning applied here is for the sake of completeness and does not serve any further purpose.

Pre-clinical testing itself bear several practical and clinical limitations. During the surgical intervention of the physician, it is common practice to bend or mechanically adapt (certain) plates to local needs. Intraoperative adaptation of the plate prior implantation (“contouring”) using appropriate bending tools -typically supplied by the manufacturer- is commonly applied by physicians with an undefined and unpredictable impact on product *in-vivo*-performance [91, 94]. In essence, not only the designer of the plate has an impact on the clinical performance of the device, but also the surgeon. Moreover, it is common sense, that certain devices for osteosynthesis are not only used according to their intended purpose, but applied in an “off-label-use” [53]. In this context, especially straight and small, thin plates might be used at multiple anatomical areas. If, for instance, a small, straight bone plate can be used for many fracture types and (minimal load-bearing) locations, pre-clinical testing will always remain a challenging topic.

Finally, the test methods and specific testing requirements presented are not capable to adress all three major inconsistencies found during the systematic literature review (3.5.). While the test methods are clearly defined, it remains unclear which construct shall be tested using which test method and how many dynamic loading cycles are applicable for which device or which anatomical area. In this context, a table that combines a classification of the construct (selection based on “extremity”, “AO-classified bone” and “anatomical area”) and basic testing methods such as torsion or bending test (comparable to the approach found in ISO 10993-series of standards [106]) in order to define mandatory tests for each bone (and applying performance limits for strength and cycles to failure), remains a potential (future) goal of this standardization framework.

7.3 Application of standardized test methods

The standardized tests for bone plate-screw constructs have initially been applied on a locked-type construct intended for the diaphyseal ulna, a device, that is already available on the market for many years. The intention was to evaluate and assess the behaviour of the implant under those standardized testing conditions and to explore the differences between the standardized construct tests proposed and the established isolated plate tests of ASTM F382 [5] in a static and constant dynamic loading test.

Generally, all planned tests were completed successfully and in a replicable pattern. However, one dynamic test result of the BPS construct was excluded from the analysis, since data acquisition accidently stopped at n = $5*10^5$ cycles (showing an identical displacement change until then, as shown in Annex 12.3). Descriptive instead of explorative

statistics has been applied due to the low number of test samples. The variance of data obtained led to the conclusion, that the test setups are principally suitable to mechanically characterize the construct under test and to deliver plausible test results for direct product comparison. Each of the test samples (and independent from the setup chosen) shows a uniform failure pattern, a plastic deformation (“displacement change“) without any breakage of the components involved. Since the bone plate is made of unalloyed titanium, grade 1, this behaviour is plausible and as expected (as being in line with pre-testing results, 6.6). The E-modulus of titanium is lower by the factor of two compared to stainless steel, however, the fatigue strength is around twice as high as that of stainless steel or casted CoCr-alloys [64].

Studies on other bone plates (made of different materials, conventional and locked-type devices) containing dynamic tests on at least n = $6x10^3$ cycles, indicate, that not all test specimens break under dynamic loading conditions, but show a variety of failure modes including, e.g. plate bending (”displacement change“) [1, 60, 176, 187, 188, 194, 198], plate breakage [74, 81, 170], or screw loosening [230]. A direct comparison with other testing results remains impossible due to the heterogeneity of the applied methods and materials. The static test of the BPS constructs revealed differences in applied loads, stiffness and proof load, caused by a different loading span distance (30 mm versus 70 mm). This result was as expected. However, the yield point of both tests (as well as the bending strength, although slightly affected by the shape of each deflection curve) remains comparable with 9 % difference, which indicates, a.) that initial structural failures, i.e. plastic deformation, appears under the same static load condition, unaffected by the test setup chosen, and b.) that the bone-plate-screw construct likely displays the mechanical behaviour of the bone plate itself. For the BPS constructs, however, no side effects could be observed, such as loosening between any of the assembled components (plate, screw, POM, Epoxy resin) or any deformation of the POM block, which might have contributed to the result.

The behaviour of the construct assembly revealed major differences compared to bending tests using single plates. When assembled and tested as a construct, the implant shows a first initial constant displacement change and an increasing plastic deformation, leading to a mean displacement change of md = 1,11 mm after finishing the test (0,17 mm for the bone plate alone with a comparable starting point for the displacement change). This effect of the construct, which might be crucial for the overall performance assessment, can be described as additional ”creeping plastic deformation“. While the bone plate itself shows a much lower magnitude of additional mechanical deformation, it must be assumed, that the effect is caused by other components of the construct test, e.g. due to a potential screw deformation (near the plate) or a micromovement within the bone plate-screw head-interface. Since the second moment of inertia of the POM bar is higher by the factor of 1.000 compared to the

bone plate, potential side effects of the bone substitute are considered negligible. The epoxy resin can also be excluded as a potential cause of the effect, since it would end up in a brittle fracture and not in a creeping behaviour [96]. Although the applied bending moment is higher for the bone-plate-screw constructs (13 %), the difference of the displacement changes encountered between the groups cannot be explained by the difference in applied bending moments alone. And, however, although the bending moment is mechanically comparable, the stress at the device (assembled construct versus single plate) is not necessarily identical. This circumstance may have also contributed to the results.

The results of the static intermediate tests also revealed differences between the groups. Testing as bone plate-screw construct showed a mean stiffness, which remains almost constant with a slight positive trending. On the contrary, when tested as per ASTM F382 [5], the mean bending stiffness rises by 5,6 % (until $n = 5*10^5$ cycles) compared to the mean bending stiffness of the static test. This effect is well-known as strain hardening of titanium [64]. It is assumed that, for the constructs, the effect is compensated by previous deformations of the creeping effect leading to an overall constant bending stiffness.

7.4 Assessment of the results in a clinical context

Following the requirements of the MDD [85], MDR [86] and ISO 14602, 7.2 [112] a pre-clinical evaluation shall be conducted in a biomechanical and/or mechanical environment and shall ideally be combined with an assessment of relevant clinical data (if already available). Standardized mechanical bending tests have been applied on bone plate-screw constructs and as per ASTM F382 [5]. In this context, mechanical testing in an assembled state is considered superior compared to single bone plate testing for the following reasons. Construct testing follows its clinical application and is the logical extension of existing, already standardized test procedures. It represents a more realistic testing approach, which is closer to the actual clinical application, especially for locked-type bone plate-screw constructs. Construct testing is the only possible approach to test the entire implant and includes the function of angular stability into the test setup (and thus an essential performance feature). In line with other applicable standards, its application intends to determine characteristic mechanical parameters of the construct, which allow a direct device comparison.

The testing results revealed a different testing outcome compared to single bone plates, in particular, an additional creeping deformation over time has been observed. This additional creeping plastic deformation encountered can only be detected when tested in an assembled state and thus offers essential information when assessing the implants mechanical resistance to repetitive loading scenarios. This is considered to be a major

advantage of construct-testing and represents a gain in information for a pre-clinical evaluation.

Many existing test specifications were developed on the basis of relevant clinical failure reports indicating potential device weakness [121]. Preventing harm to the patient by identifying previously unknown clinical failure has only been achieved in a few cases [121]. An analysis on “why and how locking plates fail“ has recently been published by Gueorguiev et al. [63]. This article contains potential causes for implant failure. The authors concluded that „most locking plate failures are related to technical errors (i.e. surgical errors, errors related to the application), such as undersizing of the implant, too short working length, and imperfect application of locking screws“. They recommend “a meticulous preoperative planning“ … “under consideration of the principles of the internal fixator technique to avoid technical errors“ … “leading to early implant failure“ [63]. The article also includes radiographs with failed screw heads and shafts (amongst other failures) close to the bone plate, indicating at least a potential failure in that implant region [63]. Another summarizing review by Strauss et al. included an analysis on reported failures on locked plate systems [203]. Typical failures found were ”implant breakage“, ”intraoperative technical errors“, ”fracture of the implant“, ”improper plate placement“, ”plate breakage“ and ”screw breakage at the screw-plate interface“ (4 of 6 reported clinical failures, 46 samples total). The authors summarize four mechanisms of locked plate failures: plate bending, plate fracture, plate pull-off and locking screw failure. Obviously, there are various contributing factors that may result in implant failure. However, it can be concluded, that, although no direct correlation between the construct testing results obtained and the above mentioned clinical failure mechanism can be found, there is at least an indication that strengthens the hypothesis, that the creeping plastic deformation of the construct is caused by stress accumulation and deformation in the screw-head/screw-shaft area, which might lead to a failure in this construct region. The slope of the creeping plastic deformation can be interpreted as an indicator for possible construct failure(s). The analysis by Gueorguiev et al. [63] and Strauss et al. [203] also revealed, that not all possible construct failures observed clinically can be tackled by rigorous pre-clinical testing. “Technical errors” [63] (including ”intraoperative technical errors“ [203], “improper plate placement” [203], a.o.) may be reduced by the surgeon through “meticulous preoperative planning“ [63]. The failure criteria defined in section 5.2.6. and applied within this work essentially corresponds to what has been summarized by the authors [63, 203]. However, the criteria “screw breakage” may be enhanced to include special emphasis on “screw breakage at the screw-plate interface”. A “plate pull-off” would constitute a failure of the test (although its occurrence is considered unlikely during mechanical testing), but is generally not associated to the mechanical integrity of the construct.

It can also be concluded, that (for this type of titanium plate) it is crucial to carry out dynamic tests with a sufficient number of loading cycles. Based on the regression analysis, the mean displacement change of the constructs starts after completing almost n = 3.268 loading cycles. This value may deviate between constructs and device types, caused by different materials, locking mechanism, dimensions, geometries and surfaces, so that a general conclusion about sufficient loading cycles cannot be drawn. However, and that is an important finding, more than 50 % of the biomechanical studies identified in the literature were not capable to evoke such a plastic deformation as insufficient dynamic loading cycles were applied (median for upper extremity = 2.000 cycles).

The total displacement change (plastic deformation) is the applicable failure mode in this case, no plate or screw breakage was visually detected, neither a breakage of the bone substitute material nor any other failure. Whenever implants for osteosynthesis fail by plastic deformation, the “degree“ of such a deformation expressed in mm shall be assessed from the clinical perspective. Typically, a local displacement change of 2 mm (dehiscence) of the fractured bone is considered clinically relevant as it impacts bone healing [31, 57, 171]. A vertical plastic deformation dislocates the fractured elements, thus becomes clinically relevant. The measured value in this case is the vertical displacement of the loading rollers and not that of the deflection in the center of the plate. There is a calculated mean displacement factor of 1,79 ± 0,076 mm (mean ± SD) between the displacement measured by the testing machine compared to the traverse displacement. Consequently, a total mean dislocation of md = 1,99 mm for the BPS construct (and md = 0,65 mm for the isolated bone plate, if the same factor is applied) can be assumed in the fractured region, which is clinically relevant. This value is quite conservative as it does not consider the offset already caused by 90 % proof load. However, this assessment seems only applicable to a limited extent (if at all) as it is only valid under certain (biomechanical) testing conditions, which are, in essence, those listed as requirements for biomechanical testing (section 5.1.1.). Transferring biomechanical performance criteria to mechanical testing results should generally be avoided, instead comparative testing seems appropriate.

Although construct testing is considered superior compared to single bone plate testing as per ASTM F382 [5], the testing results obtained do not constitute (or allow) a complete pre-clinical assessment from the clinical perspective. The testing essentially addresses regulatory requirements for comparative purposes and is not sufficient to ensure a complete, pre-clinical evaluation. In particular, it is not possible to conclude on the fulfillment of the intended purpose of the medical device. The testing results only provide mechanical parameters to enable direct comparability with other bone plate-screw constructs.

From the clinical perspective, the testing methods and results obtained when applying them do not meet the requirements of biomechanical testing under physiological boundary conditions. Such an assessment shall be conducted using a different, a specific testing procedure, which addresses three major requirement groups as detailed in section 5.1.1. The following explains to what extent these requirements have been addressed and met in this case.

The test setup does not fulfill the requirements of an adequate biomechanical model, the choice of the bone substitute material only fulfills the purpose of a rigid fixation and does not simulate physiological bone. A plausible assessment of local forces and moments acting at the (diaphyseal) ulna, including functional aspects, has not been performed, and thus the testing methods do not necessarily represent physiological loading conditions. The intended use of the implant did not affect the determination of testing characteristics, such as testing methods and parameters, or the number of dynamic loading cycles the implant shall withstand. The fracture modelling remains simple, the setup does not include a specific, i.e. more complex fracture simulation *in vitro*. However, the fracture types at the ulna are typically of “lower“ complexity. In sum, many requirements concerning biomechanical modelling have not been taken into consideration.

The construct sample selection, that has been performed, addresses several requirements specified in section 5.1.1. Although possible plate variations have been taken into consideration, the number of test samples is relatively low and is not based on appropriate statistical techniques with rationale for sample size [108]. The screw inclination and fixation type chosen seems valid for ”healthy bone“, which is the case here. The assembly and embedding process is standardized, but not clinically relevant. However, it allows the elimination of stress encountered during the fixation process. In sum, the sample preparation is adequate to meet several requirements listed in section 5.1.1, but not necessarily in a biomechanical manner.

The specified requirements set for test methodology and performance assessment in section 5.1.1 have been met, however, they have been interpreted for mechanical testing. The test results do not allow a direct comparison with published testing results in the biomechanical literature. At least a plausibility check on the magnitude of failure loads or displacement values and cycles to failure seems possible within certain limits. For the implant under test this plausibility check is limited as seven out of eight publications (Annex 12.1) contain studies at the olecranon using different devices and loading scenarios. Sanders et al. have investigated “the biomechanical effect of number of screws and plate length” while applying 4-point bending tests at the diaphyseal ulna [185]. In this article the bending moment at failure (“Ultimate moment” at bone fracture) ranges from 11,0 to 26,2 Nm. However, the difference compared to the construct testing within this work may have

been caused by multiple factors, e.g. by the different setup (de facto a 3-point bending test), the usage of donor bone, different plate material and size (stainless steel) a.o.
The outcome variable(s) have been specified as well as associated failure criteria. The testing parameters and the testing method mainly address regulatory requirements obtained from ASTM F382 [5], biomechanical aspects, such as compressive bending tests were justifiably not taken into account. There are no other specified requirements for the number of dynamic loading cycles available except those documented in ASTM F382 [5] and other personal assumptions published in the literature. Although of highest importance, defined criteria for a pre-clinical performance assessment are not available (neither for mechanical nor for biomechanical tests) thus the determination of a successful test remains a scientific task for the manufacturer of the construct.

Consequently, the standardized testing methods presented seem suitable to close the “regulatory testing gap“ for bone plate-screw constructs, but they are not capable to replace a biomechanical assessment nor do they constitute a complete pre-clinical evaluation. The mechanical testing results need to be statistically verified and compared with competitive devices. Finally, torsion tests have not been covered at all.

7.5 Assessment of goal achievement

The main goal of this dissertation was the development and application of standardized pre-clinical testing methods for straight and pre-contoured, conventional or locked-type bone plate-screw constructs and to assess the results in a clinical context.
It could be demonstrated that this goal has been achieved. Standardized pre-clinical testing methods have been developed, that are principally suitable for the majority of conventional or locked-type bone plate-screw constructs. The testing results (using a titanium construct sample) revealed a different testing outcome compared to already standardized testing methods, and underline the advantages and superiority of construct testing with respect to regulatory and clinical requirements. However, those testing methods are associated with the general clinical limits of mechanical testing and remain a theoretical recommendation, that should be applied in full and validated on several bone plate-screw construct samples for different anatomical areas using different device constructs.

8 Outlook

This dissertation contains the development and an exemplary, initial application of test methods for standardized testing of bone plate-screw constructs for osteosynthesis. Further research activities are necessary to provide proof of the concept and to further develop standardized testing methods for bone plate-screw constructs: It is common sense, that new standardized test methods need to be applied by various stakeholders, as they “are often developed through extensive round-robin testing in multiple laboratories around the world, with the testing parameters scrutinized by multiple interested parties - industry, government, independent research laboratories, and academic researchers” [206].

Since performance levels for strength and cycles to failure remain unspecified, the values obtained using the test methods proposed herein once may serve as a fundamental basis to define such levels. These test data provided by research groups or accredited test laboratories may statistically be evaluated to define performance criteria for the mechanical part of the pre-clinical evaluation of bone-plate screw constructs [121]. These performance criteria shall to be aligned with a biomechanical assessment.

This dissertation is therefore succeeded by a BMWi third-party funded research project, led by Prof. Capanni, Ulm. Prospectively, the following research goals are set: 1. Investigation of the physiological (i.e. biomechanical) loading mechanics of a (selected) pre-contoured bone plate-screw construct in order to define (clinically relevant) performance criteria for testing, and 2. Investigation of the source of the creeping plastic deformation encountered during dynamic testing, combined with the hypothesis, that there is relative change in the screw-head/screw-shaft region, e.g. a micromovement between screw head and bone plate.

While researching and compiling the results of this dissertation, the international organization for standardization (ISO) has initiated, finally adopted (dated: 2017-08-21) and therefore supported a new work item proposal, entitled “ISO/WD 22771 Implants for surgery - Metal bone plates - Standard test methods for anatomic locking bone plates” [90]. Apparently, there is a new project registered in the working program of the responsible technical committee. It shows the importance and relevance of this topic and clearly confirms the need to develop and publish standardized, pre-clinical testing procedures for those devices. At the time of this dissertation a working draft has been formulated and has been circulated to ISO members for comments, including DIN for Germany (“NA 027-02-15 AA Endoprothetik und Osteosynthese”). Following the general ISO-principles for developing standards, each project is divided in several development stages [121]. Each step may

include suggestions for improvement and changes of requirements, and a final review (an international adoption) of all ISO member states. It usually takes many years until a standard is officially published. The technical content of the standard manuscript is usually set with the final draft international standard (FDIS) as editorial changes are possible, but technical changes are excluded [121]. Consequently, any discussion about, or evaluation of the current drafted content seems not appropriate. It is very likely that this standard (if ever) will not be published before 2024. Furthermore, publication does not equal international recognition or harmonization under the MDR [86].

This evaluation also applies to a “new specification”, that is currently being developed by the American Society for Testing and Materials (ASTM) for “Metallic Bone Plates Used in Small Bone Fracture Fixation” [82]. This standardization effort underlines the assumption, that a uniform standard for all variants of bone plate-screw constructs (i.e. load-bearing versus minimal load-bearing devices) seems not feasible. The work item is currently in draft form and is under development by ASTM Committee F04 on medical and surgical materials and devices, Subcommittee F04.21 on osteosynthesis [82].

9 Abstract

The majority of modern bone plates (i.e. locked type constructs with different biomechanics compared to conventional fixation) cannot be sufficiently evaluated prior to marketing as insufficient standardized test methods exist. A literature review on n = 159 publications revealed, that standardized testing of bone plate-screw constructs (whether for regulatory purposes or) as applied in the biomechanical research, remains an unsolved regulatory challenge. The main goal was to develop and to apply standardized testing methods for straight or pre-contoured, conventional or locked-type bone plate-screw constructs and to assess the results in a clinical context.

Standardization of biomechanical testing in terms of standardized test setups seemed almost impossible as it mainly intends to explore a specific research question. Therefore standardized mechanical torsion and bending tests (for regulatory purposes) have been developed, together with detailed test setups for straight and contoured bone plate-screw constructs, requirements for positioning the construct, specific testing requirements, failure criteria and outcome parameters for static and dynamic tests. This proposal is based on the methods applied by Bottlang et al. [19] and follows the well-established testing philosophy of ASTM F382 [5]. It contains torsion and bending tests and extends the methods proposed by the standard [5], while incorporating worst case test-conditions [89] and reducing the number of potential independent variables. The test setups are applicable for the majority of currently available devices, especially those for upper and lower extremities.

Testing has been conducted on a locked-type construct intended for the diaphyseal ulna, with the intention to evaluate the implant-behaviour under standardized testing conditions and to explore the differences between those tests and the established methods of ASTM F382 [5] in a static and constant dynamic 4-point bending test using 90 % proof-load.

The static test of the constructs revealed (expected) differences in applied loads, stiffness and proof load, caused by a different loading span distance. The yield point of both tests remains comparable, thus plastic deformation appears under the same static load condition. In a constant dynamic loading test the constructs exhibit a bilinear behaviour, showing an additional creeping deformation over time between $n = 5*10^4 - 10^6$ cycles. The magnitude of the deformation of the single bone plate is much lower. The effect is potentially caused by screw deformation near the plate or a micromovement within the bone plate-screw head-interface. The mechanical testing results are suitable for regulatory purposes to enable direct product comparison, but they do not constitute a complete pre-clinical evaluation. The results need to be statistically verified and applied on various constructs, including torsion tests. Further research activities are necessary to provide proof of the concept. This dissertation is therefore succeeded by a BMWi third-party funded research project.

10 Ausführliche Zusammenfassung

I Knochenplatten-Schrauben-Konstrukte im regulatorischen Kontext

Knochenplatten und Schrauben werden regulatorisch als separate Medizinprodukte betrachtet. Eine Knochenplatte erfüllt Ihren medizinischen Zweck jedoch nur in Verbindung mit Knochenschrauben, sodass diese Kombination zwangsläufig als funktionelles Konstrukt getestet werden sollte [49, 60, 130, 217, 218]. Derzeit gültige Standards beinhalten keine spezifischen Testanforderungen für solche Konstrukte. Während Biegeprüfungen erforderlich sind [5], bleibt unklar, warum Torsions- oder Kompressionstests nicht anwendbar sind. Ferner hat sich das Design von Knochenplatten seit der Einführung der Testung erheblich verändert. Konventionelle und winkelstabile Knochenplatten-Schrauben-Konstrukte sind mehrheitlich keine geraden Platten mehr, sondern fast immer der lokalen Anatomie angepasst. Zudem stellen verblockte Konstrukte eine funktionale, starre Kombination dar, die mechanisch tragfähig ausgelegt ist [193, 234]. Dies ist eine wesentliche Funktionsänderung. Die Anwendung verfügbarer Standards für Konstrukte ist nicht ausreichend geregelt und die Testung damit nicht gewährleistet. Es besteht folglich eine regulatorische Lücke zwischen den verfügbaren Medizinprodukten und den anwendbaren Testmethoden. Diese Dissertation untersucht die Möglichkeiten und Einschränkungen, Knochenplatten-Schrauben-Konstrukte unter standardisierten Testbedingungen vorklinisch zu testen.

II Eine systematische Literaturanalyse der Testmethoden und Testparameter

Es wurde eine systematische Literaturanalyse (n = 159 biomechanische Publikationen) durchgeführt, mit dem Ziel, den Stand der Technik verwendeter Testmethoden und Testparameter zu ermitteln. Generell ist die biomechanische Literatur für Knochenplatten äußerst vielfältig, inkonsistent und heterogen. Es wurden folgende Schlüsse gezogen: 1. Testmethoden und Testparameter werden nicht einheitlich pro anatomischer Region angewendet. Einige Methoden wurden häufig identifiziert (Kompression: Radius, Femur, Tibia; Biegung: Ulna, Metacarpale; Torsion: Fibula). Die Testparameter variieren erheblich, insbesondere bei Biege- und Torsionstests. 2. Es wurde eine signifikante Vielfalt von abhängigen Variablen beobachtet, was einen Vergleich zwischen einzelnen Studien nahezu unmöglich macht. Die ermittelten, maximalen Testparameter können nur als grobe Richtwerte verwendet werden, keinesfalls sind sie als medizinische Leistungsparameter zu interpretieren. 3. Dynamische Tests werden nicht systematisch angewendet. Die Anzahl dynamischer Zyklen variiert zwischen n = 3 bis n = 10^6. Der Spezifikation liegen häufig individuelle Annahmen über die Anzahl postoperativer Körperbewegungen zugrunde. Die

Anzahl dynamischer Zyklen für die unteren Extremitäten ist im Median drei bis vier Mal höher als für die oberen Extremitäten.

III Ziel der Arbeit

Basierend auf dem regulatorischen Stand der Technik (I) und der Literaturanalyse (II) besteht Bedarf an einer Verbesserung verfügbarer Testmethoden für Knochenplatten-Schrauben-Konstrukten. Folglich besteht das Hauptziel der Arbeit darin, standardisierte Testmethoden für gerade und vorkonturierte, konventionelle oder winkelstabile Knochenplatten-Schrauben-Konstrukte zu entwickeln und anzuwenden, und die Testergebnisse im klinischen Kontext zu bewerten.

IV Entwicklung standardisierter Tests für Knochenplatten-Schrauben Konstrukte

Gemäß regulatorischer Vorgaben besteht eine vollständige präklinische Evaluierung aus biomechanischen und/oder mechanischen Tests [5, 86, 105, 111, 112]. Eine Standardisierung biomechanischer Tests für eine Vielzahl solcher Konstrukte erscheint (wenn überhaupt) nur als prozessorientierter Ansatz realisierbar. Zu diesem Zweck wurden die wesentlichen Anforderungen ermittelt, die es bei der Anwendung, d.h. der Herleitung eines bestimmten Verfahrens (z.B. für den distalen Radius) zu betrachten gilt. Mechanische Tests für regulatorische Zwecke, die in erster Linie eine Vergleichbarkeit mit anderen Implantaten ermöglichen, sind daher Gegenstand dieser Arbeit. Bei jeder Frakturfixierung ist das Implantat axialen, Biege- und Torsionsbelastungen ausgesetzt. Folglich ist jeder Belastungsmodus für vorklinische Tests zu berücksichtigen. Basierend auf den Forschungsmethoden von Bottlang et al. [19] und Fitzpatrick et al. [47], und dem etablierten Standard ASTM F382 [5] folgend, wurden mechanische Biege- und Torsionstests für gerade und vorkonturierte Knochenplatten-Schrauben-Konstrukte entwickelt. Torsionstests wurden hinzugefügt, da Torsionsbelastungen musko-skelettal übertragen werden und an der Entstehung bestimmter AO-Frakturtypen beteiligt sind [95]. Torsions- und Biegetests im statischen und dynamischen Belastungsmodus sind ferner etablierte Testmethoden für vergleichbare orthopädische Implantate [5, 9, 10, 13]. Abweichend von Bottlang et al. [19] stellen die Testaufbauten und -anforderungen einheitliche, standardisierte Test-bedingungen (i.W. Worst-Case Bedingungen [89]) her. Zwecks einheitlicher Implantat-Positionierung wird der lineare Anteil des Implantats an der vertikalen (Torsion) oder horizontalen (Biegung) Belastungsachse ausgerichtet und -im Falle einer verblockten Verschraubung- mit einem Abstand von 1-2 mm (“plate elevation“) zur Kortikalis rigide an eine POM Rundstange spannungsfrei montiert, und zwar so, dass zwei Plattenlöcher nicht besetzt sind und gleichzeitig die frakturierte Stelle (“bridge span“) überbrücken. Generell ist

die Fixierung in der Diaphyse mit drei Schrauben und in der Metaphyse mindestens mit drei Schrauben zu realisieren (bei großen Platten mit vier metaphysär). Große Platten sind mit vier Schrauben in der Diaphyse zu fixieren. Unter diesen Testbedingungen, insbesondere durch die rigide Fixierung, erzielt eine zusätzliche singuläre axiale Testung keinen Erkenntnissgewinn, es wäre lediglich eine besondere Biegebelastung. Es wurden zudem einheitliche Fehlerkriterien aufgestellt, sowie Ergebnisparamater für statische und dynamische Tests definiert, i.W. der ASTM F382 [5] folgend. Das vorgestellte Konzept dient dem Zweck der mechanischen Charakterisierung des Implantats und ermöglicht so einen direkten Vergleich zwischen mehreren Implantaten mit gleicher Indikation.

V Anwendung standardisierter Tests für Knochenplatten-Schrauben Konstrukte

Insgesamt wurden sechs statische 4-Punkt-Biegetests an verblockbaren Ulna-Platten (121 mm, längste Knochenplatte im Sortiment) der Fa. litos, Ahrensburg, durchgeführt, drei als Konstrukt (montiert am 25 mm POM Rundstange, Plattenabstand 2 mm [2], Center span 161 mm, Loading span 70 mm) sowie drei gemäß ASTM F382 [5] (Center span, Loading span 30 mm). Die statischen Konstrukttests ergaben eine mittlere Steifigkeit von 36,68 ± 2,19 N/mm (SD) mit einer vergleichsweise flachen Kurve zu Beginn der Belastung. Die mittlere Prüflast wurde mit 112,46 ± 1,06 N (SD) bestimmt. Es wurde anschließend dynamisch bis 101 N getestet (90 %, M_b = 3,54 Nm). Die Endlast konnte nicht bestimmt werden. Die konventionell getesteten Knochenplatten zeigten ein zu erwartendes Testverhalten. Die mittlere Biegesteifigkeit betrug 265,12 ± 17,65 N/mm (SD). Die mittlere Prüflast wurde mit 234,21 ± 19,03 N (SD) bestimmt (0,2 % Offset-Methode [5]). Daraus ergab sich eine dynamische Wechsellast bis 211 N (90 %, M_b = 3,17 Nm). Die Endlast betrug im Mittel 529,27 ± 31,01 N (SD). Insgesamt wurden sieben dynamische Tests durchgeführt, vier als Konstrukt sowie drei gemäß ASTM F382 [5]. Die Konstrukttests zeigten ein bilineares Verhalten (1. Linearität zwischen n = 0 - 10^3 Zyklen, 2. zwischen n = $5*10^4$ - 10^6 Zyklen) mit einer mittleren plastischen Gesamtverformung von **md = 1,11 mm**. Die konventionell getesteten Knochenplatten zeigten eine vergleichsweise geringe, mittlere Gesamtverformung von **md = 0,17 mm**. Auch hier kann das gleiche bilineares Verhalten beobachtet werden, jedoch in weitaus geringerem Maße. Bei allen Testungen wurde eine plastische Verformung beobachtet, jedoch kein Platten- oder Schraubenbruch oder andere Fehlerarten registriert. Die während der dynamischen Testung durchgeführten statischen Zwischentests zeigten ein unterschiedliches Verhalten. Die Steifigkeit der Konstrukte verlief nahezu konstant, die der Platten nahm um 5,6 % zu.

VII Diskussion

Regulatorische Anforderungen und Ergebnisse der Literaturanalyse. Die Analyse regulatorischer Anforderungen ergab, dass die meisten modernen Knochenplatten nicht ausreichend präklinisch getestet werden können. Eine systematische Literaturrecherche (n = 159 Publikationen) ergab, dass standardisierte Tests von Knochenplatten-Schrauben-Konstrukten (ob für regulatorische Zwecke oder in der biomechanischen Forschung) seit vielen Jahren eine ungelöste, regulatorische und präklinische Herausforderung darstellen.

Entwicklung standardisierter Testverfahren. Es wurden standardisierte, mechanische Tests für assemblierte Knochenplatten-Schrauben-Konstrukte entwickelt und praktisch mit etablierten Testmethoden verglichen. Die mechanische Testung von Konstrukten entlang einer (imaginären) Implantatachse reduziert potentielle Variationen im Setup, beinhaltet jedoch eine Reihe von klinischen Limitierungen, größtenteils determiniert durch die Natur mechanischer Testungen. Der Einsatz eines künstlichen Knochenersatzmaterials schließt verschiedene *in-vivo*-Situationen aus (z.B. osteoporotischer Knochen). Die Testaufbauten gelten für die meisten derzeit verfügbaren Konstrukte, möglicherweise jedoch nicht für alle verfügbaren Varianten, einschließlich kleiner Knochenplatten. Einige biomechanische Aspekte sind nicht ausreichend adressiert, z.B. achsiale Kompressionstests. Dies ist aus klinischer Sicht der vermutlich größte Nachteil. Ferner sind nicht alle Randbedingungen spezifiziert, z.B. welche Prüfmethoden pro anatomischem Bereich anzuwenden sind oder welche Knochenplattenvariation zu testen ist. Dies ist jedoch gängige Standardisierungspraxis. Präklinische Tests selbst unterliegen praktischen, klinischen Einschränkungen. Intraoperatives Anbiegen der Platte vor der Implantation oder “Off-Label“-Anwendungen haben möglicherweise einen Einfluss auf die klinische Leistung des Produkts [53].

Anwendung standardisierter Testverfahren. Die statischen Konstrukttests ergaben Unterschiede in den aufgebrachten Lasten, der Steifigkeit und der Prüflast, hervorgerufen durch eine größere Lastspanne. Die plastische Verformung tritt jedoch unter vergleichbaren Biegemomenten auf, unabhängig vom gewählten Testaufbau. Dynamische Tests ergaben einen deutlichen Unterschied zwischen den Platten und den Konstrukten nach $n = 10^6$ Zyklen (errechnete Durchbiegung der Platte von md = 1,95 mm bei den Konstrukten zu md = 0,29 mm konventionell). Die Konstrukte zeigten eine kriechende plastische Verformung, die möglicherweise durch Schraubenverformung oder eine mechanische Veränderung (z.B. Mikrobewegung) zwischen Knochenplatte und Schraubenkopf verursacht wurde, und die so nur im zusammengebauten Zustand festgestellt werden kann.

Bewertung der Ergebnisse im klinischen Kontext. Die Testung im zusammengebauten Zustand, d.h. als Knochenplatten-Schrauben-Konstrukt ist aus folgenden Gründen dem Testen einzelner Knochenplatten überlegen: Konstrukttests folgen der klinischen Anwendung und sind die logische Erweiterung bestehender, bereits standardisierter

Testverfahren. Die Testung orientiert sich an der tatsächlichen klinischen Anwendung, insbesondere für Konstrukte mit verriegelten Knochenschrauben. Konstrukttests ermöglichen, das gesamte Implantat zu testen und beziehen so die Funktion der Winkelstabilität mit ein (und damit ein wesentliches Leistungsmerkmal). In Übereinstimmung mit anderen anwendbaren Normen ist beabsichtigt, mechanische Parameter des Konstrukts zu ermitteln, die einen direkten Produktvergleich ermöglichen. Die Konstrukt-Testergebnisse zeigten ein anderes Testergebnis als die der Platten, insbesondere wurde eine Kriechverformung beobachtet. Diese zusätzliche plastische Verformung kann so nur im zusammengebauten Zustand festgestellt werden und bietet daher wichtige Informationen für die Beurteilung der mechanischen Beanspruchbarkeit des Implantats gegenüber dynamischen Belastungsszenarien. Dies ist ein wesentlicher Vorteil von Konstrukttests und stellt einen Informationsgewinn für eine vorklinische Bewertung dar. Eine Analyse möglicher Ursachen für das Versagen von Konstrukten von Gueorguiev et al. [63] ergab, dass die meisten Fehler auf technische Fehler zurückzuführen sind (Anwendungsfehler), z.B. zu geringe Größe des Implantats, zu kurze Arbeitslänge oder unvollständiges Anbringen der Verriegelungsschrauben. Die Autoren empfehlen “eine sorgfältige präoperative Planung“ … “unter Berücksichtigung der Prinzipien interner Fixationstechnik, um technische Fehler zu vermeiden“…“die zu einem frühen Implantatversagen führen“ [63]. Die Röntgenaufnahmen dazu zeigen u.a. Schraubenbrüche in unmittelbarer Nähe der Knochenplatte, die auf einen möglichen Ausfall in diesem Implantatbereich hindeuten. Obwohl keine direkte Korrelation zwischen den Testergebnissen und dem abgebildeten klinischen Versagensmechanismus hergestellt werden konnte, gibt es zumindest einen Hinweis darauf, dass die kriechende plastische Verformung des Konstrukts durch Spannungsakkumulation und Verformung im Bereich der Schraubenkopf-Verbindung verursacht werden könnte, die zu einem Versagen in diesem Konstruktionsbereich führen könnte. Die Steigung der kriechenden plastischen Verformung kann als Indikator für ein mögliches Konstruktversagen interpretiert werden. In diesem Zusammenhang könnte das Fehlerkriterium „Schraubenbruch“ um den Passus „Schraubenbruch an der Schrauben-Platten-Grenzfläche“ erweitert werden.

Für diesen Titan-Implantattyp ist es ferner entscheidend, dynamische Tests mit einer ausreichenden Anzahl von Belastungszyklen durchzuführen. Die mittlere Verschiebungsänderung der Konstrukte beginnt rechnerisch im Mittel nach ca. 3.268 (die der Platten nach 870) Zyklen. Dieser Wert kann zwischen Konstrukten abweichen (unterschiedliche Materialien, Verriegelungsmechanismen, Abmessungen u.a.), sodass eine allgemeine Schlussfolgerung über ausreichende Belastungszyklen nicht getroffen werden kann. Mehr als 50 % der biomechanischen Studien jedoch wären rückblickend nicht in der Lage, eine solche plastische Verformung hervorzurufen, da nicht ausreichende

Belastungszyklen appliziert wurden (median obere Extremität = 2.000 Zyklen). Die Testmethoden erfüllen nicht die Anforderungen standardisierter, biomechanischer Tests unter physiologischen Randbedingungen. Eine solche Bewertung kann nur unter Verwendung eines spezifischen Prüfverfahrens durchgeführt werden, das drei ermittelte Anforderungsgruppen mit jeweiligen Unterpunkten in Betracht zieht (1. Biomechanische Modellierung, 2. Probenauswahl und -vorbereitung, 3. Testmethodik und Leistungsbeurteilung). Die vorgestellten standardisierten Testmethoden erscheinen geeignet zu sein, die Lücke regulatorischer Tests für Knochenplatten-Schrauben-Konstrukte zu schließen, aber sie können weder eine biomechanische Testung ersetzen, noch stellen sie eine vollständige vorklinische Bewertung dar. Insbesondere lässt sich keine vollständige Aussage zur Erfüllung der Zweckbestimmung ableiten. Die Testung liefert mechanische Kennwerte um eine direkte Vergleichbarkeit mit anderen Produkten zu ermöglichen. Die mechanischen Testergebnisse müssen statistisch verifiziert und mit Konkurrenzprodukten verglichen werden. Torsionstests kamen nicht zur Anwendung.

Bewertung der Zielerreichung. Das Ziel der Arbeit wurde erreicht. Der standardisierte Testvorschlag ist mit den allgemeinen klinischen Grenzen mechanischer Tests assoziiert und verbleibt ein theoretischer Ansatz, der vollständig angewendet und mit Hilfe mehrerer Knochenplatten-Schrauben-Konstrukte validiert werden muss.

VII Ausblick

Dieser Dissertation folgt ein gefördertes Forschungsprojekt mit folgenden Zielen: 1. Untersuchung der physiologischen (d.h. biomechanischen) Belastungen eines vorkonturierten Knochenplatten-Schrauben-Konstrukts, um klinisch relevante Leistungs-parameter für Testzwecke zu definieren. 2. Untersuchung der plastischen Verformung, kombiniert mit der Forschungshypothese, dass es zu einer relativen Änderung zwischen Knochenplatte und Schraubenkopf kommt. Während der Anfertigung dieser Dissertation hat die internationale Standardisierung-Organisation ISO den neuen Arbeitstitel ISO/WD 22771 “Standardprüfverfahren für anatomische Knochenplatten mit spezieller Verriegelung“ verabschiedet [90]. Dieses Projekt zeigt die Relevanz des Themas und bestätigt die Notwendigkeit, vorklinische Testverfahren für diese Produktgruppe zu entwickeln und zu publizieren. Der technische Inhalt wird jedoch erst mit dem finalen Entwurf (FDIS) in ferner Zukunft festgelegt. Zum jetzigen Zeitpunkt erscheint jede inhaltliche Diskussion daher nicht angemessen. Dies gilt auch für eine neue Spezifikation der ASTM für „Metallische Knochenplatten zur Fixierung kleiner Knochenbrüche“, die derzeit entwickelt wird [82]. Offensichtlich erscheint ein einziger, einheitlicher Standard für alle Varianten von Knochenplatten-Schrauben-Konstrukten nicht realisierbar. Diese Dokumente werden (wenn überhaupt) vermutlich nicht vor 2024 öffentlich verfügbar sein.

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12 Annex

12.1 Data of the systematic review

C	Test method: Compression
B	Test method: Bending
T	Test method: Torsion
Te	Test method: Tensile
P	Number of preconditioning cycles
X	No upper test limit, Test to failure
--	No information provided, No test conducted
M	Metallic test setup, No bone is used
Ca	Cadaver bone
S	Synthetic bone substitute
PU	Polyurethane
Max.	Maximum, upper test limit specification
Min.	Minimum, lower test limit specification
Sawtooth	Sawtooth loading profile
stepwise	Increasing-amplitude test
combine	Combination test, simultaneous test
AP	Anteroposterior
ML	Mediolateral

Static test		Dynamic test			
Test method	**Test parameter Information**	**Test method**	**Test parameter Information**	**Number of cycles**	Source
Clavicle					
C,B	0-X(B), 0.5mm/s **10-500N(C)**, 5N/s	C,T	**10-500N(C)** 5N/s(C) ±5° (T), 0.5deg/s	100 (C,T)	[30] S
Outcome: Stiffness (C,T), Load to failure (B), Failure stiffness (B)					
C	0N-X 0.5mm/sec	C,T	stepwise: 5-58.5N(C) +28N per 1 cycle 310Nmax. stepwise: ±0.7°(T) ±0.7° per 1 cycle ±7°max.	10 Sawtooth (C,T)	[68] Ca
Outcome: Stiffness (C,T), Load to Failure (C)					
B	3Pt-bending 0mm-X, until 30 mm 0.5mm/s Lever arm 12cm	C,T	**10-500N(C)**, 5N/s ±5°(T), 0.5deg/s	100 (C,T)	[178] S
Outcome: Stiffness (C,T,B), Load to failure (C,T,B)					
--	--	C,Te,T	stepwise: +10% per 1 cycle 120Nmax.(C) **300Nmax.(Te)** ±7°max.(T)	8 (C,Te,T) Sawtooth	[160] Ca
Outcome: Stiffness (C,Te,T)					
T	0deg-X	--	5P with 80% of torque failure 0.8 deg/s	--	[227] S
Outcome: Stiffness, Load at failure, Deflection at failure, unconstrained plate motion					
B	3Pt-Bending 0N-X	C,B,T	0-100N(C) **±10°(T)** 3Pt-Bending 0-80N(B)	20 (C,T) 1.000(B)	[0] S
Outcome: Stiffness (C,B,T), Load to failure (B)					
--	--	C,T	±1 - ±50N/s (C,T) 0N-X (C,T) +10% per cycle	10 (C,T)	[59] Ca
Outcome: Stiffness (C,T)					
Te	0N-X 0.5mm/s, ramp mode	C,Te,T	10-75N (C,Te) + 2°(T) combined	5.000 (C, Te, T)	[176] Ca
Outcome: Stiffness, Load to failure (C, Te)					
B	3Pt-Bending 0mm-X	--	--	--	[147] Ca
Outcome: Failure load, Bending stress, Bending stiffness, Young's modulus					
B	0mm-X 60mm/min	--	--	--	[197] S
Outcome: Failure torque, Energy (J)					
B,T	0N-X (B) 15mm/min(B) 0Nm-X (T) 15°/min(T)	B,T	3Pt-Bending **143N(B)** **4.97Nm(T)**	1.000 (B,T)	[37] Ca
Outcome: (Percentage of) stiffness (B,T), Failure load (T), Failure moment (B)					
B,T	0mm-X (B) 2 mm/min 0°-1°(T), 2°/min	--	--	--	[41] Ca
Outcome: Stiffness (B,T), Load to failure (B)					
Proximal humerus					
C	0N-X, 5mm/min	C	10-80N	100.000	[194] Ca
Outcome: Stiffness, Load to failure, Deformation					
--	--	T	stepwise: 2, 3.5, 5, **7.5Nm** 0.5°/s	100 each 1.200 max	[179] Ca
Outcome: Survival rate					
C	0N-X, 10cm/min	C	2-120N, 50mm/min	100	[180] Ca
Outcome: Interfragmentary Rotation and Translation, Load to failure					
T	0N/m-X, 30°/min	T	0.25-1112 N/m	10.000	[48] Ca
Outcome: Interfragmentary motion, Stiffness, Torque to Failure					
C,T	10-120N(C) 0.1-2.5Nm(T) **0-500N (C)** in 45s	C,T	10-120N(C) 0.1-2.5Nm (T)	200 (C,T)	[76] Ca
Outcome: Stiffness (C,T), Load to failure (C)					
C,T	50N-X(C) 5mm/min 0-1°(T), 1deg/s	--	--	--	[141] Ca
Outcome: Stiffness (C,T), Shear failure load (C)					
C,B	**100N(C,B)** 230mm length	--	--	--	[142] Ca
Outcome: Stiffness (C,B)					
C,T,B	0,5mm (C) **4°(T)** **4mm (B)**	B	4mm (B) Lever arm 100mm	1.000	[144] Ca
Outcome: Stiffness (C,T,B)					
C	0N-X, 20N/s	C,T	± 2Nm(T), ± 5Nm(T) each for 3.000cycles +30-50N(C) combined	6.000 max	[188] Ca
Outcome: Rotational displacement (T), Load to failure (C)					
B,T	**7.5Nm(B)** **8.3Nm(T)** 1mm/min (B,T)	--	--	--	[52] Ca
Outcome: Stiffness (B,T)					
C	0N-X, 1N/s	C	90N,180N,**450N** each for 200 cycles 450N for 2.000 cycles	200 min 2.600 max	[239] Ca
Outcome: Plastic deformation, Crash test					
B,T	0mm-X(B), 1mm/s 0°-X(T), 1°/s	B,T	**±5mm(B)** Lever arm 12cm **0-8°(T)1°/s**	100 (B,T)	[98] S
Outcome: Load to failure (B,T)					
--	--	B (Tensile load)	Load applied to 3 rotator cuff tendons Abduction/Adduction 15-45°	500 min 1.000 max	[124] Ca
Outcome: Resulting force acting at the glenoid					
B (Tensile load)	Load applied to 3 rotator cuff tendons 30° Abduction 0.5mm/s	--	--	--	[219] Ca
Outcome: Force to failure					
C	Specific test bench 200N, 0.02 mm/s	C,T	stepwise: 200N-X(C) +0.05 N/cycle pulling force acting on the anchor torque detectors + 1-3 Nm(T) combined	--	[23] Ca
Outcome: Displacement (C,T), Stiffness (C), Load at failure criterion (T)					
--	--	B,T	±2Nm(T) **0-7.5Nm(B)**	5.000 (T) 10.000 (B)	[195] Ca
Outcome: Displacement (B,T)					
B,T	5mm(B), 1mm/s 0,2-6.5Nm (T), 0.5°/s 0mm-X(B, Valgus)	--	--	--	[128] Ca
Outcome: Stiffness (B,T), Load to failure (B)					
--	--	B,T	Varus Bending **0-7.5Nm(B)** ± 2Nm(T)	5.000 (B,T)	[45] Ca
Outcome: Displacement (B,T), Stiffness (B,T)					
--	--	B	stepwise: 0-2,5kg +2,5Kg per 1cycle 4mm/min,lever arm 7cm	--	[153] Ca
Outcome: Relative displacement, Initial stiffness, Failure load					
--	--	B (Tensile load)	40-200N applied to supraspinatus tendon 2.75kg at dist. humerus Abduction: 10-60°	5.000	[181] Ca
Outcome: Interfragmentary displacement					
--	--	B (Tensile Load)	125-200N applied to 3 rotator cuff tendons 35-65° Abduction	400	[196] Ca
Outcome: Intercyclic fracture motion, Displacement, Load to failure					

Diaphyseal humerus

C,B,T	**100N(C)** excentrically loaded 4Pt-Bending **200N(B)** **4.5Nm(T)** external rotation 0Nm-X(T)	T	**0-4.5Nm**	1.000	[65] Ca
Outcome: Stiffness (C,B,T), Load to Failure (T)					
C,T	0N-X (C,T)	C,T	**5-250N(C)**, 5N/s **0-5N(T)**	1.000 max.(C,T)	[2] S
Outcome: Load to failure (C,T)					
T	--	T	±10Nm	1.000	[56] S
Outcome: Stiffness					

Distal humerus

C,B	10-150N(C) **10-120N(B)** Cantilever bending	C,B	**10-150N(C)** 10-120N(B) 0.1Hz	5.000 (C,B)	[158] Ca
Outcome: Stiffness (C,B)					
C,B	Flexion: 75° (C) Extension: 15° (B) ramp 15N/s (C,B) 0N-X, +0.1N/cycle	C,B	Flexion (C):15-100N Extension (B):15-150N	2.500 (Flex) 5.000 (Exten)	[231] Ca
Outcome: Stiffness, Cycles to failure					
C,B,T	**250N(C)** ±1.6Nm(T) 4Pt-Bending: 4.5Nm 0Nm-X (B)	B	**4Pt-Bending: 4.5Nm** AP Bending	4.000	[135] Ca
Outcome: Stiffness (C,B,T), Strength (B)					
C,B	Flexion (C) Extension (B) Stiffness: 0-50N 0,1mm/s Yield: 25N-X 0,1mm/s	C	stepwise: 20-150N +10N per 5.000 cycles	1P 5.000 min.	[211] S
Outcome: Stiffness (C,B), Yield strength (B), Fracture motion					
C,B	60% of Yield strength Ext:5°(B),0.1mm/s Flex:75°(C), 0.01mm/s	B	Extension: 5°(B) 50%Yield strength +10% per 250.000 cycles	3P 250.000 min.	[170] S
Outcome: Stiffness (C,B), Median fatigue limit as per ASTM STP 731 (B)					
C,B,T	**250N(C)** 0Nm-X(B), 0,1mm/s ±1.6Nm(T)	B	**4Pt-Bending: 4.5Nm**	4000	[134] Ca
Outcome: Stiffness (C,B,T), Load to failure (B)					
C,B	0N-X (C,B)	C,B	stepwise: 0-20N(B) +20N after 10cycles 60N max. lever arm 15cm stepwise: 0-20N(C) +20N after 20cycles 100N max. axial/sagittal	10-30 max. (B) 20-100 max.(C)	[237] Ca
Outcome: Stiffness (C,B), Load to Failure (C,B)					
C,B	Flexion: 5°(C) Extension:85°(B) 20-40N (C,B)	C	Flexion (C) **20-150N**	5.000	[190] S
Outcome: Stiffness (C,B), Alpha-Angle, Plastic deformation, Cycles until failure					
C,B	Flexion: 5°(C) Extension:85°(B) 0-50N (C,B), 0,1mm/s	C	Flexion(C) **15-150N**	5.000	[191] Ca
Outcome: Stiffness (C,B), Cycles until failure					
C,B,T	120N(C) 120N(B), AP bending **0-9Nm(T)** 0N-X (B), 5mm/s	B	60N(B) Posterior bending	4.000	[205] Ca
Outcome: Stiffness (C,B,T), Strength (B)					
C,B	Flexion: 0-200N(C) **Extension: 6Nm(B)** 0-X	B	**Extension (B): 0-200N**	5P 5.000	[29] Ca
Outcome: Stiffness (C,B), Strength (C,B)					

Diaphyseal radius

--	--	C,B,T	**4Pt-Bending:10-75N** **10-200N(C)** **± 2Nm(T)** **0-X (B), 0.7mm/s**	20 (C,B,T)	[167] S
Outcome: (Failure) Stiffness, Failure displacement, Failure load					

Distal radius

C,B	250N(C) 50N(B),5mm/min 0N-XN (C)	--	--	--	[133] S
Outcome: Gap motion (C,B), Force to Failure (C)					
C	150N	C	5-150N	5P 5.000	[174] Ca
Outcome: Stiffness, Range of motion, Secondary loss of reduction					
C	0-90N· 1N/s	C	0-80N	5.000	[146] Ca
Outcome: Stiffness, Fracture displacement					
C	100N 0N-X	C	--	--	[183] Ca
Outcome: Stiffness, Load to Failure					
C	0N-X, 10mm/min	C	100N	10.000	[198] S
Outcome: Stiffness, Load to Failure					
B	10N-X	--	--	--	[28] Ca

Outcome: Stiffness, Load to yield 5 mm displacement, Strength					
C	0N-X 800N max.	C	80N / 200N 2x4 cycles 10-150N 2.000 cycles	8 2.000	[27] Ca
Outcome: Stiffness, Load to failure					
C	0N-X, 2N/s	C	stepwise: 10-100N + 100N per 2.000 cycles 300N max.· 2N/s	2.000 min 6.000 max	[35] S
Outcome: Stiffness, Yield strength, Displacement					
--	--	C	**800N**	10P 2.000	[222] S
Outcome: Stiffness, elastic deformation, elastic tilt angle, plastic deformation					
C	0N-X, 1mm/s	C	10-150N	5.000	[61] Ca
Outcome: Stiffness, Displacement, Failure strength					
C	0N-X, 0.1mm/s lever arm 20mm	C	stepwise: 0-0.2Nm +0.2Nm per 5.000cycles	5.000 min	[80] M PU
Outcome: Strength, Elastic limit, Number of cycles, Load level at failure					
C	0-250N, 4N/s 0N-X	C	0-250N	3.000	[122] Ca
Outcome: Elastic limit, Failure load					
C	5-250N	C	5-250N, 0,15mm/s	5P 2.400	[131] Ca
Outcome: Stiffness, Displacement					
C	**0-300N** 0N-X, 2mm/min	C	0-300N, 1N/s	5.000	[129] Ca
Outcome: Stiffness, Failure peak load					
C	0-X, 10mm/min	--	--	--	[154] S
Outcome: Rigidity, Strength					
C	0N-X, 1mm/s	--	--	--	[208] Ca
Outcome: Stiffness, Failure strength					
C,B	250N(C) **80N(B)** lever arm 11cm 0-X(C)	C	150N	1.000	[156] Ca
Outcome: Stiffness (C,B), Load to failure (C)					
C,T	20N(C) ± 1.5Nm(T) combined 1,5Nm-X(T) +20N(C) combined 130N(C) 0N-X(T)	C,T	**0.5-1.5Nm (T)** +20N(C) combined static	1.000 (T)	[157] Ca
Outcome: Stiffness (C,T), Load to failure (T)					
B	4Pt-Bending 40N, 20mm/s, 6cycles 3 directions 0-X, 400N max.	--	--	--	[169] Ca
Outcome: Stiffness, Deformation angle, Gap size					
C	20-100N, 1N/s 0-X, 1mm/s	--	--	--	[200] S
Outcome: Stiffness, Load to failure					
C,B	10-250N(C) 50N(B), 0.5mm/s lever arm 12,5cm 0-X(C)	C	0-250N	1.000	[218] S
Outcome: Stiffness (C,B), Load to failure (C), Load to catastrophic failure (C)					
C	--	C	stepwise: 10-100N +0.025N per 1 cycle	6.000 min	[230] Ca
Outcome: Stiffness, Plastic deformation, Gap displacement, Cycles to failure					
C	0N-X, 1 mm/s	--	--	--	[18] Ca
Outcome: Stiffness, Strength					
C	15-X, 1 mm/s 61N applied to flexor and extensor tendons	--	--	--	[62] Ca
Outcome: Angular displacement, Range of motion, Load to failure					
C,T	100N(C), 10N/s 0N-X(C) 2.0Nmm(T)	C	40-100N	5.000	[123] Ca
Outcome: Stiffness (C,T), Load to failure (C)					
C,B	10-100N(C) **± 1.5Nm(B)** 0Nm-X(B)	B	**0.5 -1.5Nm**	1.000	[130] Ca
Outcome: Stiffness, Load to failure					
C	200N	C	10-200N	500	[71] S
Outcome: Displacement					
B,T	0N-X (B,T)	B,T	4Pt-Bending AP:250N, $5.6x10^{-3}$ Nm ML:500N, $1.1x10^{-2}$ Nm +0.5Nm after 2000 and 3000 cycles 0.5Nm(T)	10.000(B) 2.000 min. (T)	[55] Ca
Outcome: Stiffness (C,B), Cycles to failure (C,B), Energy absorption					
--	--	C	Stepwise: 10-100N +25N per 1.000 cycles	1.000 min.	[79] Ca
Outcome: Load to failure, Stiffness, Fracture gap movement, Screw cutting distance					
C	90N, 1N/s	C	80N	5.000	[146] Ca
Outcome: Stiffness, Fracture displacement					

C,B	250N(C), 0.5mm/s 3Pt-Bending 50N(B), 0.5mm/s	--	--	--	[152] S
Outcome: Stiffness (C,B), Displacement (C,B)					
--	--	C	150N	5P 5.000	[175] Ca
Outcome: Stiffness, ROM, Subsidence					
C	0-100N(C), 5mm/min 0-75N(C) 20mm Axial Offset	C	0-100N	10.000	[209] S
Outcome: Axial and eccentric load stiffness					
C,B	250N(C) 50N(B), 0.5mm/s	--	--	--	[228] S
Outcome: Stiffness (C,B)					
--	--	C,T	5N(C) +1,5mm/10s(C) 0.3Nm(T) + 1Nm/° in 10s (T)	8 (C,T)	[26] Ca
Outcome: Stiffness, Strength					
C	0N-X, 2mm/s	C	100-250N, 100N/s	5.000 20.000	[21] Ca
Outcome: Stiffness, Load to failure					
C	0N-X(C)	C	400N	2.000	[148] Ca
Outcome: Stiffness, Strength, Screw angulation					
C	0N-X, 1mm/s	--	--	--	[136] Ca
Outcome: Stiffness, Yield load, Maximum load					
C	0N-X, 10mm/min	C	**50-800N**	2.000	[40] S
Outcome: Stiffness, Displacement, Load to failure					
C	**300N**	C	300N	1.000	[201] S
Outcome: Stiffness, Load to failure					
C	20-200N, 40N/s 0N-X, 0.5mm/s	--	--	10P	[221] S
Outcome: Stiffness					

Proximal ulna

C	**5-30N**, 0.1mm/s Extension: 0° Valgus:5° 0N-X, 0.1mm/s Proc. coronoideus	C	**20-100N**	5.000	[125] S
Outcome: Stiffness, Strength					
B	Specific test bench: vertical distal ulnar displacement of 60mm, 2mm/s Olecranon	--	--	--	[25] Ca
Outcome: Stiffness, Strength					
B (Tensile load)	6.6kg-X 90° Flexion	B (Tensile load)	stepwise: 0.18kg + 0.5kg until 1.6Kg + 1kg until 6.6kg 30 cycles, 30-90° with hanging load Olecranon	1.240 (6.6kg was cycled 1.000)	[3] Ca
Outcome: Displacement, Load to failure					
--	--	B (Tensile load)	25-200N 200N in 50% Flexion + elbow motion 0-90° combined Olecranon	300	[164] Ca
Outcome: Fracture gap movement					
--	--	B (Tensile load)	**10-300N** simulate pull of triceps brachii on the olecranon 90° Flexion	50.000	[212] Ca
Outcome: Angular displacement in the region of the humeral trochlea					
B (Tensile load)	1mm/s loading ramp applied to the triceps arm fixed in 90° flexion Olecranon	--	--	--	[225] Ca
Outcome: Load to failure					

Diaphyseal ulna

B	4Pt-Bending: 0-X	--	--	--	[185] Ca
Outcome: Stiffness, Peak loads, Ultimate moments					
B (Axial load)	0mm-X, 1mm/min No bone interface	--	--	--	[75] M
Outcome: Force at 1mm flexion, Maximum Force					

Metacarpale

B	3Pt-Bending 5-X 100mm/min	--	--	--	[39] Ca
Outcome: Stiffness, Maximum load					
B	3Pt-Bending 1-10N preloading 0N-X	B	10N to 20-50% of the maximum load of the native bone.	1.000	[39] Ca
Outcome: Displacement, Stiffness, Maximum load					
B,T	apex-dorsal bending 10mm/min 4.5cm lever arm 0°-X(T), 2°/s	--	--	--	[54] S
Outcome: Load to failure (B), Torque to failure (T)					
B	3Pt-Bending, 0mm-X	--	--	--	[161] Ca
Outcome: Stiffness, Peak load					
B	0mm-X, 10mm/min 4.5cm lever arm	--	--	--	[199] S
Outcome: Load to failure					

Proximal femur

C,B,T	50-500N(C) **10-50N(B)** 100N(T) 100N-X(C) Periprosthetic Fracture fixation	--	--	--	[238] Ca
Outcome: Stiffness (C,B,T), Load to failure (C)					
C,T	50-500N(C),30N/s 0.3-4.0Nm(T), 0.2N/s Periprosthetic Fracture fixation	C	**50-1000N(C)** For 10.000 cycles +0.1N/cycle	10.000 min.	[143] Ca
Outcome: Stiffness (C,T), Load to failure, Cumulative survival rate to failure (C)					
C	0-1000N	--	--	--	[164] S
Outcome: Displacement					
C	0N-X Periprosthetic Fracture fixation	--	--	--	[22] S
Outcome: Load to failure					
C,T	500N(C), 5mm/min **5-20Nm(T)**, 25°/min	C	stepwise: 100-300N +100N per 10cycles 0.75mm/s	10 min. 80 max.	[32] S
Outcome: Stiffness (C,T), Loading to failure (C)					
--	--	B	4Pt-Bending 10N(P) 10mm displacement	100	[15] S
Outcome: Moment to displace the constructs by 10 mm					
C	500,1000,1500, **1868N** for 10s, 10mm/min Inter-trochanteric fracture fixation	--	--	--	[43] S
Outcome: Interfragmentary rotation, Strain on implant, Stiffness					
B	4Pt-Bending 0.1mm/s Interprosthetic fracture fixation	--	--	--	[140] Ca
Outcome: Strength					
C	0-100N +100N, 1.000N max.	--	--	--	[165] S
Outcome: Loads at the intertrochanteric fracture line					
--	--	C	stepwise: 100-750N +0.1N/cycle Periprosthetic fracture fixation	--	[216] Ca
Outcome: Stiffness, Cycles to failure					

Diaphyseal femur

--	--	C,B,T	stepwise: 0-50N (C) +100N per 100 cycles 4pt-bending: 0-1Nm +1Nm per 100 cycles 0-1Nm(T) +1Nm per 100 cycles	100 min. (C,B,T)	[47] S
Outcome: Stiffness (C,B,T), Strength (C,B,T)					
--	--	C ASTM F382-99	20-689N (C) (65% yield load)	100.000	[207] S
Outcome: Cycles until failure					
--	--	C,T	**100-1.000N (C)** **±20Nm(T)** 0Nm-X(T)	5.000 (C,T)	[229] S
Outcome: Fracture gap motion (C,T), Stiffness (C,T), Cycles to failure					
C,B,T	**500N(C)** **36Nm(B)**, Lateral **11Nm(T)** periprosthetic Fracture fixation	C	400N(C)	10.000	[51] Ca
Outcome: Stiffness (C,B,T), Strength (T)					
C,T	0N-X(C), 0.20mm/s 3000N max 0deg-X(T), 0.1deg/s +70lbs combined	--	--	--	[172] S
Outcome: Stiffness (C,T), Load to failure (C)					
--	--	B	stepwise: cyclic bending ±250N +10% per 1.000cycles	1.000 Min.	[182] Ca Al
Outcome: Stiffness, Load sustained, Cycles to failure					
C,B,T	18° abduction (C) 10m/min Coronal, sagittal bending	--	--	--	[204] S
Outcome: Stiffness (C,B,T), Load to failure (C)					

Distal femur

--	--	C	stepwise: 100-1000N +400N after 10 cycles 2200Nmax.	10min. 30max.	[151] Ca

Outcome: Subsidience, Reversible defomation					
C,T	100-500N(C) 10mm/min **5-20Nm(T)**, 20°/min	C	stepwise: 100-300N(C) +100N after 10cycles 1700N max., 0.75mm/s	10min. 140max.	[226] S
Outcome: Stiffness (C,T), Load to failure (C), Strength (C)					
C,T	± 10Nm(T) ext-int. Rotation +20N (C) combined	C	stepwise: 20-200N + 100N per 500 cycles	500 min.	[213] S
Outcome: ROM (T), Displacement (C), Stiffness (C), Cycles to failure (C)					
C	**134 - 1.790N(C)**	C	**134 - 2.640N** Preload:2.224N, 8cycles	80.000	[75] S
Outcome: Stiffness, Micromotion across fracture gap, Cycles to failure					
C	0N-X, 0.1mm/s	C,Te	**-20N (Te)** 265N (C) Titanium Plate **-20N (Te)** 420N (C) Steel Plate	80.000 (C,Te)	[81] M
Outcome: Strength, Elastic limit, Cycles to failure, Load level at failure					
C,T	± 10Nm(T) +20N(C)combined 0Nm-X(T), 1Nm/s	C	stepwise: 20-200N +100N per 500cycles	10P 500 min.	[214] Ca
Outcome: Stiffness (C,T), Cycles to failure (C)					
C,T	100N-X(C) 10mm/min Preload 3Nm **±10°/min(T)** +200N (C) combined	C	stepwise: 100-300N(C) +100N per 10 cycles	10 min.	[239] Ca
Outcome: Plastic deformation, Crash test until defined breakup criteria					
--	--	C,T	50-700N (C) **± 5°(T) cyclic combined**	50.000	[60] S
Outcome: Stiffness, Deformation, Remaining torque					
C,T	0N-X(C), 0.1mm/s 0°-X(T), 0.1°/s Elastic testing: 0.2mm/s(C), 60%Yield 0.15°/s(T)	C	stepwise: 70% Fmax. +10% per 25.000cycles 0.2mm/s Preload: 50% Fmax.	25.000 min.	[187] S
Outcome: Stiffness (C,T), Cycles to failure, Peak load at failure (C)					
C,T	150/800N(C) 0N-X(C), 1mm/s 0°-X(T), 0.25°/s	C,T	Internal rotation 5Nm(T) +150/800N (C) Combined	100	[24] S
Outcome: Stiffness (C,T), Displacement/Rotation (C,T), Load to failure (C,T)					
C	200-800N	C	stepwise: 190-735N 290-1180N	100.000 each 200.000	[4] Ca
Outcome: Stiffness, Subsidience					
C,B	1.000N(C), 100N/s **300N(B)** AP Bending valgus/varus medial/lateral	C	1.000N	10.000	[117] Ca
Outcome: Stability (resistance to displacement in newtons per centimeter, C,B)					
C	0N-X(C) 10mm/min Knee arthroplasty	C,T	200-500N(C) **±8Nm(T)** +200N (C) combined	10 (C,T)	[149] Ca
Outcome: Stiffness, Yield strength, Ultimate Strength					
C	100N-X, 5mm/min Preload: 25-500N(C) 5cycles, 10N/s	--	--	--	[166] S
Outcome: Stiffness, Load to failure, Peak force					

Proximal tibia

C	0-300N Loaded eccentrically	C	stepwise: 100-300N +100N per 10 cycles 1000N max. 30N/s	10 min. 80 max	[34] S
Outcome: Stiffness, Plastic deformation, Load to failure					
C	100N-X	C	stepwise: **100-1000N** +100N per 10cycles 1200N-X +400N per step	10 min.	[46] Ca
Outcome: Subsidence, Deflection, Load to failure (fracture gap closure)					
C	0N-X, 0.5mm/s	C	40-670N	1.000	[173] Ca
Outcome: Displacement, Load to failure					
C	100N-X, 100N/s	C	**100-1000N**	10.000	[77] Ca
Outcome: Subsidence, Force to fallure					
--	--	Ca	stepwise: 50N-400N +400N per 5 cycles 1600N max. 0.5mm/min	5 min. 20 max.	[58] Ca
Outcome: Vertical plastic deformation at the end of each cycle					
C	0N-X	C	stepwise: 0-500N +500N per 3 cycles 1500N max., 1mm/min	3 min. 6 max.	[118] S
Outcome: Stiffness, Load to failure, Subsidience of the medial plateau					
C	10-250N +50N per 1 load 400N max., 10N/s Force applied to the medial-tibial plateau	--	--	--	[17] S

Outcome: Elastic/plastic shear, Elastic/plastic deformation					
C	0N-X 1mm/s	C	150/800N(P), 60 cycles stepwise: 800N +10% per 20.000 cycles 1.600N max.	20.000 min. 180.000 max.	[1] S
Outcome: Load to failure, Cycles to failure					
C	**600N, 1112N** 25mm/min	--	--	--	[168] S
Outcome: Stiffness, Displacement					
C	500N, 100N/s 500N-X	C	50-500N	10.000	[72] S
Outcome: Displacement, Load to failure					
C	0N-X 20mm/min	C	stepwise: 0-500N +500N per 5 cycles 1500N max.	5min. 15max	[139] S
Outcome: Reversible/irreversible displacement, Horizontal diastasis, Stiffness, Load to failure.					

Distal tibia

C,T	0-350N(C) 10mm/min -5 to 10Nm(T) 18°/min	--	--	3P (C,T)	[78] S
Outcome: Interfragmentary movement (C,T), Stiffness (C,T)					
C,B,T	250N(C) 2cm ax. Offset **12.5Nm(T)** **15Nm(B)**, 2.5N/s	C	Preload: 750N, 5min. **0-750N**	11.110 total	[202] Ca
Outcome: Stiffness (C,B,T), Fracture displacement (C)					
C,T	**10N-400N(C)**,0.1mm/s excentrically loaded 0.5°/s(T) + 10N combined	--	--	--	[236] S
Outcome: Stiffness (C,T)					

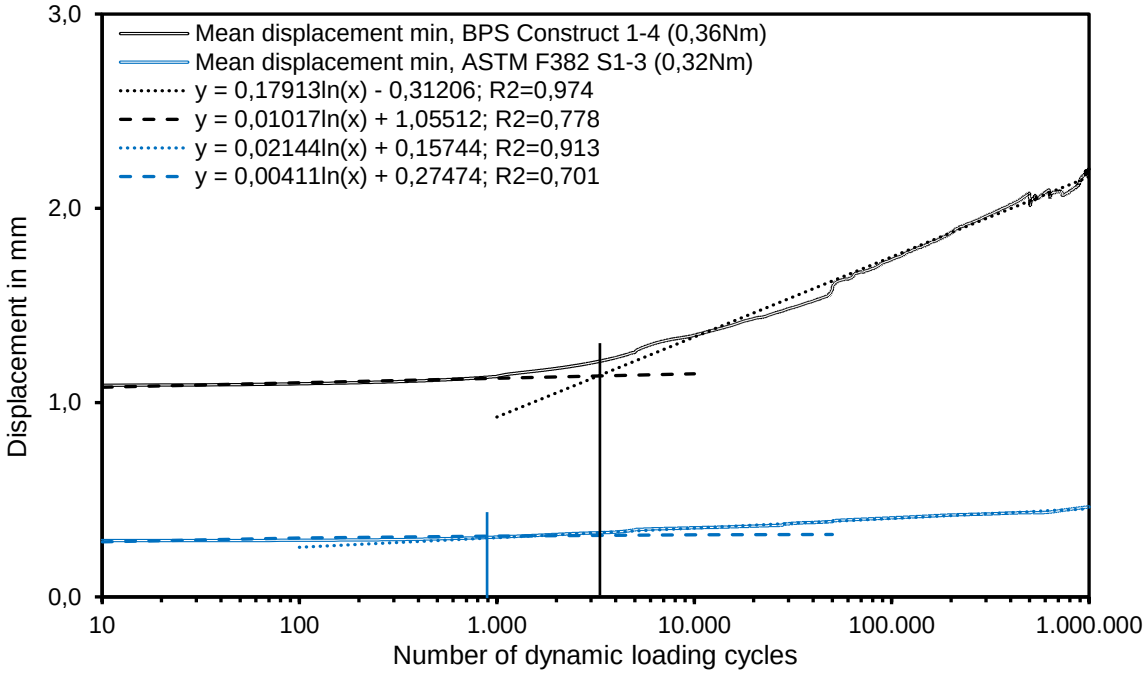
Distal fibula

T	0°-X(T) 5°/s 90° Rotation	T	static Preload: 1N (C) + 1Nmm (T) 20% yield (T), 10°/s	4.000	[186] S
Outcome: Stiffness, Energy, Load to failure, Maximal moment					
C,T	700N (C) +60deg/s to an excursion of 90° (T) Combined	--	--	--	[159] Ca
Outcome: Torque to failure, Angular rotation at failure, Stiffness					
--	--	B	stepwise 4Pt-Bending 10N-X +10N per 1.000 cycles	1.000 Min. 500.000 max.	[189] S
Outcome: Fatigue strength, Cycles to failure					
T	stepwise: 10% of yield load +10% per 3 cycles ASTM F1264	T	**0-422N** (=65% mean yield)	--	[16] S
Outcome: Stiffness, Peak load, Displacement at failure					
C,T	**0-720N(C)**, 20N/s 0deg-X(T), 1deg/s +720N (C) combined	--	--	5P 0-500N 20N/s	[36] Ca
Outcome: Stiffness (C,T), Strength (C,T)					
B,T	1.5Nm(B), 1mm/s **2Nm(T)**, 1deg/s	T	**2Nm(T)**	1.000	[42] Ca
Outcome: Fracture site angulation (B) and rotation (T) under Load, Stiffness (B,T)					
B,T	1.8Nm(T) **3.9Nm (B)**	--	--	2P	[67] Ca
Outcome: ROM (B,T), Stiffness (B,T)					
T	1.0Nm, 0.1Nm/s 0Nm-X	T	± 1Nm	2.000	[126] Ca
Outcome: Stiffness, Torque to failure					
B,T	**±4N (B)** lever arm 25mm ±0,24Nm(T) lever arm 60mm **100N (B)**	--	--	3P	[132] Ca
Outcome: Stiffness (B,T), Neutral Zone in mm, Load to failure (B), Displacement at 100N					

Metatarsale

B	0mm-X, 1mm/s	B	**5-90N**	250.000	[99] Ca
Outcome: Plantar gapping during fatigue testing, Stiffness, Load to failure					
B	0mm-X, 120mm/min	B	27N (70% of static failure load) lever arm 7.5cm	1.000	[119] S
Outcome: Dorsal displacement, Stiffness, Load to failure					
--	--	B	0-31N linear ramp, 7.75N/s	1.000	[192] Ca
Outcome: Stiffness					

12.2 Regression analysis



Determination of the intersection of two linear sections within the dynamic testing protocol for BPS constructs (1) and bone plates (2). A logarithmic regression has been conducted between n = 0 - 10^3 and between n = 5*10^4 - 10^6 cycles. The intersection is calculated by:

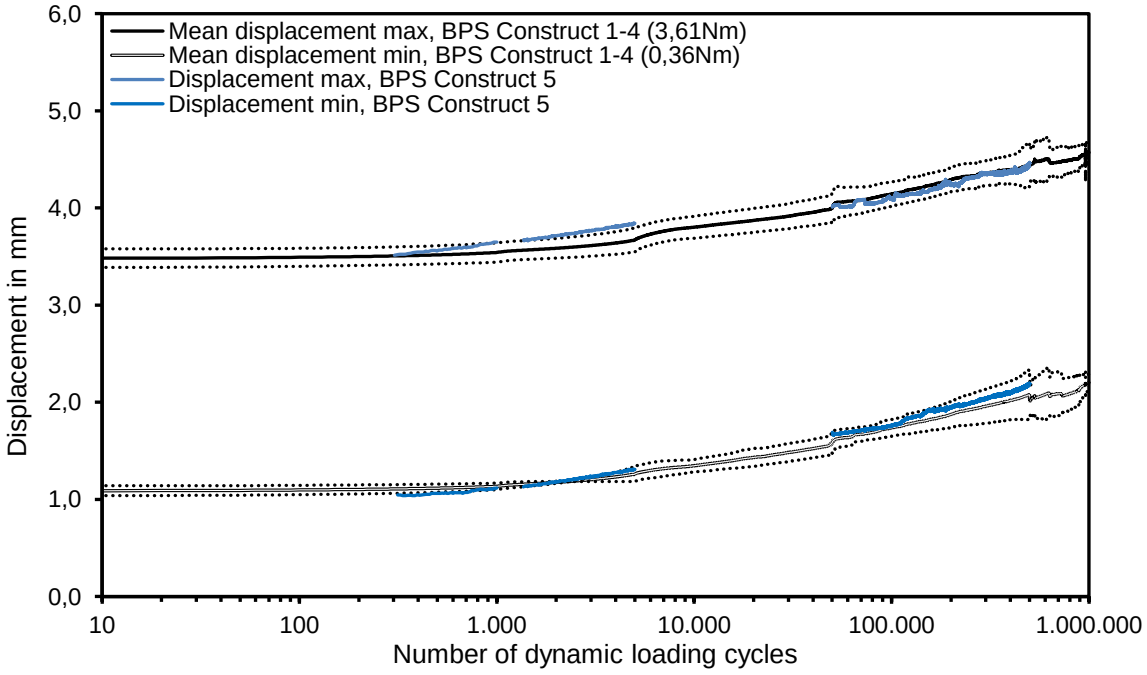
(1) $\ln(x) = \frac{1{,}05512 + 0{,}31206}{0{,}17913 - 0{,}01017} = \frac{1{,}36718}{0{,}16896}$

$e^{8{,}092} = 3.268$ cycles

(2) $\ln(x) = \frac{0{,}27474 - 0{,}15744}{0{,}02144 - 0{,}00411} = \frac{0{,}1173}{0{,}01733}$

$e^{6{,}769} = 870$ cycles

12.3 Excluded data - 5th bone plate-screw construct sample



List of tables

List of figures

Acknowledgements

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Publications (peer-reviewed)

1 Schorler H, Capanni F, Gaashan M, Wendlandt R, Jürgens C, Schulz AP (2017) Bone plates for osteosynthesis - a systematic review of test methods and parameters for biomechanical testing. Biomed Tech (Berl) 62, 235-243

2 Schorler H, Wendlandt R, Jürgens C, Schulz AP, Kaddick C, Capanni F (2018) Bone plate-screw constructs for osteosynthesis - recommendations for standardized mechanical torsion and bending tests. Biomed Tech (Berl) 63, 719-727

3 Halbauer C, Schorler H, Liberto L, Capanni F (2021) Comparison of a standardized four-point bending test to an implant system test of an osteosynthetic system under static and dynamic load condition. Biomed Tech (Berl), doi: 10.1515/bmt-2020-0228

Conference presentations, posters, lectures

1 Schorler H, Capanni F (2018) Towards standardized testing of bone plate-screw constructs for osteosynthesis. Vortrag DIN-Normenausschuss Feinmechanik und Optik, NA 027-02-15 AA Endoprothetik und Osteosynthese, Technische Universität Hamburg-Harburg

2 Schorler H, Halbauer C, Wendlandt R, Schulz AP, Jürgens C, Capanni F (2019) Recommended mechanical testing of bone plate-screw constructs for regulatory purposes. Poster, Deutsche Gesellschaft für Biomechanik

Curriculum vitae

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