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Biomechanical models: key considerations in study design

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Abstract

This manuscript summarizes presentations of a symposium on key considerations in design of biomechanical models at the 2019 Basic Science Focus Forum of the Orthopaedic Trauma Association. The first section outlines the most important characteristics of a high-quality biomechanical study. The second section considers choices associated with designing experiments using finite element modeling versus synthetic bones versus human specimens. The third section discusses appropriate selection of experimental protocols and finite element analyses. The fourth section considers the pros and cons of use of biomechanical research for implant design. Finally, the fifth section examines how results from biomechanical studies can be used when clinical evidence is lacking or contradictory. When taken together, these presentations emphasize the critical importance of biomechanical research and the need to carefully consider and optimize models when designing a biomechanical study.

Keywords: biomechanical study, experimental protocols, finite element modeling, implant design, synthetic bones

1. What are the most important characteristics of a good biomechanical study?

Biomechanical research can directly address a mechanical topic in a biological system, or it can help answer a clinical question that is related to load sharing, musculoskeletal performance, and/or implant design. As for any scientific study, the research question needs to be clearly defined and the study design needs to be adequate to answer the research question. For a biomechanical study, the research question (e.g., fracture stability) needs to be translated into the measurement of a biomechanical feature (e.g., relative fragment displacement).[1] This translation into a biomechanical feature is the key element of a worthwhile and effective biomechanical study. In order for a biomechanical study to be high quality, the biomechanical feature and the corresponding study design need to be appropriate, reliable, valid, and relevant.

"Appropriate" means that the study needs to identify a measurable biomechanical outcome that can answer the respective research question or address the research hypothesis. Frequent communications among clinicians and biomechanical engineers are essential for the identification of the appropriate biomechanical feature that best matches the research question.

"Reliable and valid" assessment of the outcome measures should guarantee that the findings of a study can be reproduced and that they actually measure what they are supposed to measure. There are several provisions in biomechanical studies to maximize reliability and validity. First, the choice of the test samples needs to be clearly defined and potential covariates need to be considered. Second, test setup and test conditions need to be well described and highly reproducible thereby minimizing variability in the data and increasing the power to detect differences. Third, data assessment and data analysis need to undergo stringent quality control measures to guarantee accuracy and precision of the outcome measure. This typically requires state-of-the-art measurement equipment that is regularly calibrated to provide consistency and control. Finally, the experiments should be performed with a sufficient sample size and with appropriate statistical methods. The statistical plan is part of the study design and should be done before the study is being conducted.[2]

"Relevancy" of the biomechanical study ensures that the findings are transferable to a clinical scenario and that the findings eventually support treatment decisions and help to improve outcome in patients.[3] There are several key provisions for a biomechanical study to be considered as relevant. First, the degree of model abstraction (e.g., loading experiment vs.

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numerical modeling) and the choice of test samples (e.g., human bone specimens vs. synthetic bones) need to balance representation of reality versus technical realizability.[4] Second, the loading conditions of the test setup should be geared to mimic real physiologic loads. The unavoidable simplifications that are often required to recapitulate in vivo loading have to be carefully considered. Third, the outcome measures should be chosen judiciously. In particular, care should be taken to produce results that can be readily compared with previous studies and easily transferred to the clinical arena. Finally, the limitations of the study should be taken into consideration and every endeavor made to minimize them. Importantly, this needs to be done during the design of the study—not when a manuscript review criticizes the adequate consideration of the study limitations.

Assuring a biomechanical study is appropriate, reliable, valid, and relevant improves the quality and transparency of the study and makes it findings reproducible. This approach not only facilitates the publication of the study findings, but more importantly, it enables transmission of the findings to clinicians, which ultimately results in improvement of patient care.

2. Choosing the appropriate model: human specimens versus synthetic bones versus finite element models

Currently, there is no consensus as to whether synthetic bone or cadaveric bone, or finite element models provide results that best recapitulate the clinical experience, represent relevant outcomes, or have the most potential to influence standards of care. The 3 models are fundamentally different from one another and it depends on the biomechanical feature to be measured as to the most appropriate to answer the respective research question. At a cursory level, synthetic bone and cadaveric models are simplified physical representations of a target system, which respond to external inputs, such as induced loads. Finite element models rely on theory-based principles, where assumed mechanical properties of bones and implants are assigned, virtual loads are applied, and resulting estimates of stresses and strains are compared with established standards. To provide a more thorough evaluation of the differences between models, a brief summary of the pros and cons associated with synthetic materials, cadaveric bones, and finite element models in orthopaedic trauma is outlined below.

Cadaveric models have been used to train and educate clinicians and scholars with regularity since the 13th century.[5,6] The use of human specimens has distinct advantages, as evidence suggests that active exploration through cadaveric dissection contributes to improvement of knowledge[7] and provides the most high-fidelity simulation of the operative environment.[8] The use of cadaveric models in orthopaedic research has grown steadily in recent history.[9] A search of the terms "orthopaedic trauma cadaver" in PubMed indicates that 103 cadaveric studies were performed in 2000. Numbers of cadaveric studies peaked in 2017 at 422 and 292 cadaveric studies were performed in 2019. However, cadavers come with a considerable set of drawbacks, which includes high procurement costs,[10] issues with storage and preservation,[11] high variability,[12,13] biohazard and waste concerns,[10] and potential ethical issues. The cost of cadaveric specimens can vary widely, based on the segment size, prescreening requirements, and availability. Additionally, high variability between specimens often leads to studies that are either underpowered or financially burdensome due to high sample size requirements. Finally, donors are typically geriatric, which leads to a skew in the population that is modeled in these experiments.[10]

The use of synthetic bone models in biomechanical experiments has increased due to their potential for high biomechanical fidelity, low variability across specimens, decreased financial burden, and ease of use.[10] In their simplest form, bones can be represented with sheets or blocks of polyurethane foam, where composition can be adjusted to mimic differences in bone quality. Anatomically accurate, inexpensive models can be made with either a plastic or foam cortical material, which are more suitable for use in surgical simulations rather than biomechanical tests. The most recent generations of composite bone models have demonstrated the ability to recapitulate the biomechanical properties of whole human bone when placed under bending, axial, and torsional loads.[12–17] However, there are several disadvantages associated with synthetic bone models. Like cadaveric models, there is no healing response, and therefore analyses are limited to immediate postoperative behavior. Additionally, synthetic bone models lack soft-tissue components, which are used to apply controlled muscle loads to stabilized joints in the context of biomechanical experiments. Finally, although synthetic models may behave similarly to human bones when tested as a whole isolated specimen, local mechanical properties, and mechanical responses to orthopaedic implants may substantially differ from human cadaver bones and can lead to significantly different results between groups.[18,19]

Finite element (FE) modeling represents the most commonly used computational technique in orthopaedic research, which may be applied to almost any orthopaedic problem which is related to a biomechanical issue. These models are widely adjustable and do not suffer from the typical burdens associated with experiments involving cadaveric or synthetic bone models. Although FE models can be financially expensive to develop, a validated simulation model has the potential to be reused with minimal costs. For these reasons, the growth of FE analysis in orthopaedic research is on the cusp of outpacing cadaveric studies. A search of the terms "orthopaedic finite element analysis" in PubMed indicates that 33 studies were performed in 2000, while 286 studies were published in 2019. Some modern FE models, based on computed tomography or magnetic resonance imaging scans, have successfully accounted for variations in bone mineral density.[20–23] Other models include interactions between implants and bone, and have incorporated feedback loops with benchtop test results, thereby improving the validity of the computational model.[24,25] Recently, FE analysis has been used to evaluate fracture risk,[20,21] and healing progression. Studies are now able to accurately predict which patients will suffer a failure upon hardware removal[26] while other studies have proven to be more predictive of time to union than morphometric measures, pain scores, or radiographic scores.[27,28] FE models do have limitations. For example, they often do not incorporate the viscoelastic properties of bone and assume slow loading rates. Additionally, they are subject to errors caused by the "garbage in garbage out" phenomenon that is inherent with any computational model. Thus, for a FE model to be trusted, rigorous validation and corroboration measures are mandatory.

Cadaveric, synthetic bone, and FE models are all an abstraction of reality, which can be used as tools to explain complicated behaviors with a biomechanical background. These models possess a unique set of advantages and disadvantages and it is important to keep them in mind when interpreting the findings. Given the limitations associated with each approach, future studies should be designed with parallel experiments that utilize different methodologies so that direct comparisons can be

made and a more thorough understanding of the question at hand can be provided.

3. How do I select an experimental test and FE analysis protocol?

When selecting a test protocol for a physical experiment, or an analysis protocol for a virtual test (*in silico*) such as FE analysis, current testing standards should be used. Testing standards are useful not only for regulatory purposes but can also help to evaluate accurately the performance of a device. To support scientific progress and exchangeability among working groups, the description of test protocols in manuscripts and the definition of standards have evolved to be a relevant element in translation-oriented research and in preclinical testing. Hence, sufficient details should be included in any scientific publication. Substantial standardization has been reached for endoprosthetic[29,30] and spinal implants,[31,32] and there is a committee for standards on osteosynthesis, the ASTM Subcommittee F04.21 (https://www.astm.org/COMMIT/SUBCOMMIT/F0421.htm). Testing standards do not always exist for specific research questions, and therefore other experimental protocols may be developed. However, knowledge of existing test standards for approval processes should not be overlooked.

When selecting an appropriate experimental test scenario, it is necessary to start by defining the research question. The PICO method[33] is a useful tool to help with this process. It consists of defining the target Population, the type of Interventions to be compared with a Control group, and the Outcome measures. This represents the basis for any later comparisons, which must be defined *a priori*. Next, a hypothesis should be generated. Within this setting, the comparison groups are picked and ideally, a positive and a negative control group are added to strengthen the evaluation. Based on this foundation, one should determine the actual test parameters (Table 1),[34] their associated measurement accuracy and sensitivity, and how they might affect the measurement outcome. Once there is an estimate of the main outcome and an expected difference between groups, a power analysis should be conducted to estimate the number of required samples. Tests should be kept as simple as possible for easier execution, validation, and repetition, while maintaining the appropriate complexity to answer the research question.

Historically speaking, benchtop test results have not always matched the clinical experience. For example, experimental studies showed that stiffer plates could bear more loading cycles because of lower plate stress, while clinical results indicated that stiffer plate constructs tended to lead to plate failures. An explanation was suggested by MacLeod et al.[35] (Fig. 1). In the physiological setting, stiffer plates maintain higher strain over a long time in later healing phases due to load sharing with callus according to their stiffness ratio. Additionally, it has been shown that plates that are more flexible lead to faster callus formation. Therefore, the variation in time with healing,[35–37] degeneration, corrosion, or degradation needs to be considered in some cases.

If too many parameters change, a computer simulation might be indicated instead of idealized, simple models often used in experimental tests. Prioritizing which parameters can be idealized often requires more sophisticated methods. For example, in a study that simulated cadaveric and synthetic bone in an experimental test, a complex material mapping model was compared with a 2-phase material model. The evaluated interfragmentary movement for both material models in the simulation explained over 90% of the variation in the test data. When using over-simplified boundary conditions, only about 72% of the variation could be explained. Thus, for the outcome measure interfragmentary movement, the type of bearing that was chosen for the test was much more critical than the material used to represent bone.[38,39]

For FE analyses, standards are being established[40,41] and should be rigorously applied. This is especially important if the FE findings are to be applied in clinical trials or for regulatory purposes.[42,43] However, limitations exist when extracting clinically relevant data from such models[44] as realistic, physiological mechanical conditions need to be considered in

Table 1

Test parameters to consider when selecting an experimental test and FE analysis protocol for bone healing

Test parameter	Examples	Remark
Time-scale	Fracture event (fall incident) versus fatigue loading during daily activities	Strain rate influences bone and implant strength
Spatial-scale	Tissue-level versus macroscopic biomechanics	Hierarchical modeling is also possible, enabling both models in parallel with a homogenization step in between
Loading model	Generic loads (axial compression, torsion) versus physiological load (muscle and joint loading)	Simplicity, generalizability versus accuracy, relevance
Boundary conditions	Fixed bearing at one end (constraining all degrees of freedom, i.e., no translation and no rotation) versus cardan joint or ball bearing, x-y-table, etc.	Boundary conditions in terms of displacement constraints need to be considered in conjunction with applied loads and reaction forces caused within the bearings
Environmental conditions	Standard laboratory conditions (25°C, dry, 1 bar) versus physiological conditions (higher temperature, pressure, corrosive medium)	Corrosion and fatigue strength are strongly influenced by the environmental conditions
Material model	Cadaver bone versus synthetic bone	More realistic failure modes versus less variability
Fracture configuration	Gap size, fracture plane orientation, degree of comminution, empty gap versus filled gap	Fracture type, size, and slope will influence the local tissue deformation
Support model	Contact, tissue bridging, grafting, scaffolds, large fracture gap versus small fracture gap, also contact bone-plate or bone-nail	Bony support or support through grafts or scaffolds will influence the stiffness nonlinearly and lead to different results as a function of load
Fixation configuration	Type (intramedullary nail versus plate), position (medial, anterior, etc), material (titanium, steel), screw configuration (short plate working length, large plate working length)	Exact fixation configuration influences stiffness and strength and should be reported in detail

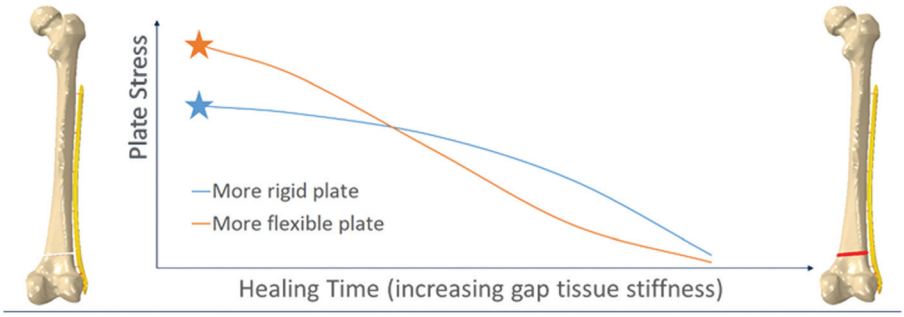

Figure 1. Schematic showing that locking plate stress accumulation over time and thus fatigue failure can be inaccurately predicted by in vitro testing (*star) when comparing the performance of different implants or materials in a static setup ignoring the healing tissue (Compare MacLeod et al., 2015). Courtesy of Dr Mark Heyland, Berlin Germany.

such test protocols. The test parameters need to be justified and validated[45,46] with respect to the specific clinical outcome measure and its variation.

The potential risk of scientific models to provide false findings can be minimized by using different models and creating synergies between *in silico,* experimental and clinical observations.[47] Clinical data can be used as input for test protocols and for validation of experimental tests[48] and simulations.[49] Experimental tests and simulations can then be used to perform parameter studies.[49] It should be taken into account that such FE simulations can also directly integrate models of cell stimulation for instance.[50,51]

Biomechanical research in trauma care often concerns fracture stability and progression of healing at the same time. Experimental tests can answer specific research questions for a particular patient population. Virtual testing using FE models can be applied for specific populations but may also allow for patient-specific tests, but uncertainty quantification and validation for computer models are critical.

4. Biomechanical research for implant design: pros and cons

The history of implant design is full of examples of implant failures caused by a design process driven by expert opinion rather than by biomechanical data and clinical evidence. Lord Kelvin properly stated: "When you can measure what you are speaking about and express it in numbers, you know something about it; but when you cannot measure it, your knowledge is unsatisfactory."[52] Data for implant design can be derived from both clinical and biomechanical studies but clinical studies are more realistic than biomechanical experiments. Therefore, biomechanical studies must be carefully designed to simulate clinically relevant and reproducible test conditions without inappropriate over-simplifications.[53] Compared with clinical studies, biomechanical studies provide several powerful advantages.[54] The cost and time of biomechanical studies are typically one order of magnitude lower compared with clinical studies. Biomechanical studies provide highly controlled and reproducible test conditions, in stark contrast to the inherent variability of clinical studies due to uncontrolled factors such as differences in injury mechanisms, comorbidities, and patient compliance. Furthermore, results of biomechanical studies are typically assessed in direct, quantitative measures, while clinical studies are often limited to indirect measures and outcome scores.

By providing a highly controlled and reproducible test condition and direct, quantitative outcome measures, biomechanical studies typically have a higher sensitivity to detect a true difference between groups compared with clinical studies. The development of hip arthroplasty provides a historic example of the power of biomechanical research.[55] Sir Charnley stated "*it took us some 300 operations and 3 to 4 years to arrive at the conclusion that Teflon was unsuitable*" for acetabular cups. Three surgeon colleagues advised Charnley that "*We have come to the same conclusion that the operation should be abandoned.*" In contrast, biomechanical data generated by Craven, Charnley's research engineer, had predicted that Teflon would wear poorly and would not last. Craven developed a wear tester, discovered an alternative material, and generated positive wear data in only 3 weeks.

Despite the high sensitivity to quantify differences in implant performance in a timely and cost-effective manner, biomechanical studies are greatly outnumbered by clinical studies. For example, in 2018 the Journal of Orthopedic Trauma published 146 clinical studies, but only 21 biomechanical studies. Moreover, 2/3 of the biomechanical studies compared the performance of existing implants to retrospectively demonstrate their potential benefits. While important, data from these retrospective biomechanical studies were generated after implants had been released and may only be of help for future design iterations.

The impact of biomechanical research greatly depends on timing. If research precedes implant design, the results can lead to innovative solutions in a systematic, evidence-based strategy. However, if research follows implant design, its impact is mostly limited to exploring hypothesized benefits of new designs. This research strategy is often motivated by marketing interests rather than an objective desire to resolve clinical challenges.

In summary, biomechanical research is underutilized, is essential and it has the most impact when initiated before implant design. Biomechanical research relies on a close collaboration between surgeons and scientists, as stated in the Orthopaedic Research Society presidential address of Dr. Thomas Brown: "If we are to realize the tremendous potential of orthopaedic research, we need to enthusiastically promote an equal partnership between orthopaedic clinicians and scientists."[56]

5. How to use the results of biomechanical research in clinical practice

In the modern era of evidence-based medicine, when presented with challenges in practice, clinicians are able to refer to an ever-growing pool of orthopaedic evidence. In various areas of

interest, clinicians can critically appraise relevant literature to make individualized management decisions to optimize patient care. However, as clinical practice continues to evolve, a number of clinical problems either remain unsolved or lack sufficient clinical evidence to support a favorable management protocol. In these areas that require further investigation or when clinicians seek answers to the technical issues of fracture fixation, biomechanical evidence offers valuable insight that can be used to aid clinical decision making and guide areas of future investigation.

For example, with an aging patient population and increases in the number of total hip arthroplasty and revision arthroplasty procedures, there has been a subsequent increase in periprosthetic femur fracture prevalence.[57,58] Vancouver B1 fractures, which are characterized as a fracture around a stable prosthesis, represent a large proportion of periprosthetic femur fractures, accounting for approximately 30% of cases.[59,60] Despite this increase in prevalence, there remains a lack of clinical evidence regarding Vancouver B1 fracture fixation. Synthesis of the available evidence has demonstrated that an optimal treatment strategy has yet to be identified.[61,62] As a result, there is a clear lack of consensus within the orthopaedic community regarding the treatment of Vancouver B1 fractures. A recent cross-sectional survey completed by Bates et al.[63] highlighted this divide between surgeons as open reduction and internal fixation with locked plating fixation was favored only slightly over open reduction and internal fixation with lateral cable plating ± anterior cortical strut allograft (51.1% vs. 45.5%).

Given the dearth of clinical evidence and lack of consensus in clinical practice, evidence comparing the biomechanical properties of current periprosthetic fracture fixation strategies represents a strong source that can be used to tease out potential differences between treatments. A study by Zdero et al.[64] demonstrated significantly greater axial, lateral, and torsional stiffness in specimens treated with lateral cable plating and an allograft strut when compared with various single implant fixations. A study by Lewis et al.[65] which compared various cable, unicortical locked, and bicortical locking screw fixation techniques, showed significantly greater maximum torsional and axial force in specimens treated with bicortical fixation. From this evidence, clear biomechanical advantages were identified using both biplanar plating and bicortical fixation.[64,65] Beebe et al.[66] compared various bicortical single plane fixations with unicortical + anterior strut fixation. Significantly higher axial and torsional stiffness was observed in unicortical + anterior strut fixation when compared with bicortical screw fixations.[66] Similarly, Lochab et al.[67] found that a locking compression plate with anterior strut allograft fixation demonstrated significantly higher compressive abduction, torsion, and medial-lateral 4-point bending stiffness when compared with combined uniplanar bicortical locking plate and 2 locking attachment plate fixation. Another biomechanical consideration, in the context of periprosthetic femur fracture fixation, is the spacing of the fixation. Dubov et al.[68] found greater axial stiffness with increasing spacing of proximal and distal cable-screw pairs. These findings demonstrated biomechanical advantages in periprosthetic fracture fixation using biplanar fixation with appropriate spacing of fixation points.

In summary, biomechanical evidence can be used to evaluate fracture management options when clinical evidence is lacking or in conflict and when the clinical performance strongly depends on the biomechanical performance of the fixation method. In the case of periprosthetic femur fracture management, biomechanical evidence has played a role in informing current practice and current clinical investigations. Presently, an ongoing randomized control trial comparing isolated locked compression plating with cable plating and strut allograft will provide much needed clinical evidence in the management of Vancouver B1 periprosthetic femur fractures.

6. Conclusions

A good biomechanical study may take a number of forms, but steps must always be taken to ensure the design is appropriate, reliable, valid, and relevant. These foundational elements allow the findings to be transmitted to clinicians to improve patient care. Biomechanical research also plays an important role in implant design and allows differences in implant performance to be quantified in a time and cost-effective manner. Given the critical importance of biomechanical research, the model utilized needs to be carefully considered and optimized when designing a biomechanical study.

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