Experimentally tested computer modeling of stress fractures in rats

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A STRESS FRACTURE (SF) IS a partial or complete fracture of a bone, resulting from its inability to withstand cyclic subyield mechanical loads. It is a common injury in physically active individuals, particularly in track and field athletes, dancers, and military recruits (10, 20, 22). The epidemiological literature is less specific in regard to prevalence and incidence of SFs among athletes, but more solid data exist for military recruits. The incidence among soldiers is ~5%, but can vary, being 25% and even higher (1, 10, 13, 20, 29). Noteworthy, the incidence of SFs among female soldiers is reported to be at least three times higher than among male soldiers (2, 26). The incidence among soldiers is 5%, but can vary, being 25% and even higher (1, 10, 20, 29). Noteworthy, the incidence of SFs among female soldiers is reported to be at least three times higher than among male soldiers (2, 26).

The prevention of SFs is a major goal of sport and military medicine practitioners (11). To prevent this injury, there must be a clear understanding of its causative factors and the mechanisms by which they interact. To date, however, methodological limitations and expediency often lead to research designs that are inadequate for investigating in depth risk factors for SFs.

There is a large volume of literature regarding SFs, but most studies have been designed as clinical observations with limited control of their underlying factors. Additionally, there is no satisfactory animal model for investigating risk factors for SFs, which is why only a few studies used nonhuman in vivo models for studying SF etiology; these studies were conducted on various animal models, such as dogs, rabbits, turkeys, and rats (4, 6, 27, 39). In many of the studies, the number of the loading cycles causing a SF was normally reported, but the actual tissue-level loads causing the fracture (i.e., the bone strains, strain energy densities, stresses) were not standardized and, in many cases, were also not reported. Additionally, the anatomical locations where SFs occurred were not always identifiable.

Finite-element (FE) models were developed to evaluate strains and stresses within the bone in the context of SF etiology, particularly for long bones (19, 24). However, those studies were limited because they considered an isolated bone, while the overlying soft tissues were not incorporated in the modeling (7, 23, 24). These isolated FE bone models can be categorized as considering two-dimensional or three-dimensional (3D) bone geometry, but the constraining effect of the surrounding soft tissues, such as muscle and fat on bone deformations under loading, have not been accounted for in either type of studies (19, 24).

Based on the current state of knowledge, SF studies can benefit from the coupling of an animal model with an anatomically accurate 3D FE model. This approach is potent in providing information regarding peak strains/stresses, as well as the strain and stress distributions on the bone cortex. By running chronic animal experiments and comparing the outcomes with the strain/stress data obtained from the FE model, it will be possible to characterize anatomical and biomechanical factors contributing to SFs. Successful development of such methodology will further pave the way for systematic, objective, standardized, and quantitative analyses of proposed risk factors for SFs, as well as interventions, e.g., in the context of nutrition, pharmacological treatments, and environmental conditions.

The objective of this study was, therefore, to develop an experimentally validated FE modeling methodology for studying SFs. The present methodology can then be implemented in human studies as well, given respective MRI scans of subjects diagnosed with SFs.

METHODS

Computational model. In preparation for FE modeling of a rat’s shin, we employed the beam theory, assuming that the tibia behaves as a linear elastic hollow cylindrical curved beam (30°) subjected to bending by an axial load, to obtain a first approximation of the loads in a uniaxially loaded tibia. In our preliminary calculations, we assumed the following characteristics of the rat’s tibia: a length of 45 mm, an external diameter of 5 mm, an internal diameter of 2 mm, an elastic modulus of 10–20 GPa, and Poisson’s ratio of 0.3 (28). We then evaluated the axial loads that are required to induce midshaft tensile strains of ~2,000 με, which is at the high end of physiological
tolerance of cortical bone to repetitive loading (35). From these preliminary calculations, we deduced that the order of magnitude of the midshaft axial loads in the tibia of rats is 2–5 N.

The 3D anatomy of the un-deformed rat shin was obtained from axial MRI scans (General Electric, Fairfield, CT), 3-T, T2-mode, of a euthanized Sprague-Dawley male rat (age: ~7 wk, weight: 170 g). The MRI scans were loaded into parallel planes that were 1 mm apart. The contours of cortical bone, trabecular bone, and bone marrow of the tibia and fibula, the enclosing muscle and fat, and distal and proximal cartilage tissues were manually drawn for each slice and lofted into 3D bodies (Fig. 1) by means of a solid modeling software (SolidWorks 2008, SolidWorks). The 3D geometrical model obtained from the MRI scan, which is further referred to as the reference geometrical model configuration, was imported to an FE solver (ABAQUS version 6.9, SIMULIA), where a skin layer was added on top of the fat using the “Skins” function in ABAQUS (Fig. 2). We used the automatic meshing feature of ABAQUS with manual adjustments that were required to achieve convergence, and all tissue components were meshed using tetrahedral elements, excluding the skin, which contained triangular elements. To provide a more solid relationship between anatomy, tissue mechanical properties, loads delivered to the tibia, and internal cortical bone strains and stresses, we developed anatomically realistic 3D FE models of the rat shin, which represent several anatomical variants and biological variability in tissue mechanical properties (detailed later).

The models were solved using the nonlinear large deformation strain/stress analyses features of ABAQUS. Specifically, bone and cartilage tissues were considered isotropic linear-elastic materials, whereas soft tissues other than cartilage were considered hyperelastic homogeneous isotropic solids. For the reference model configuration, the cortical and trabecular bone tissues were assigned elastic moduli of 18 and 5 GPa, respectively, and both were assumed to have a Poisson’s ratio of 0.3 (28). Cartilage was assigned an elastic modulus of 10 MPa and a Poisson’s ratio of 0.4 (28). Muscle, fat, and skin were all assumed to behave according to the generalized Mooney-Rivlin solid strain energy density function $W$ as follows (33):

$$ W = C_{10}(\lambda_1^2 + \lambda_2^2 + \lambda_3^2 - 3) + C_{11}(\lambda_1^2 + \lambda_2^2 + \lambda_3^2 - 3)\left(\lambda_1^{-2} + \lambda_2^{-2} + \lambda_3^{-2} - 3\right) + \frac{1}{D_1}(J - 1)^2 \quad (I) $$

where $\lambda_i$ are the principal stretch ratios; $J = \det(F)$, where $F$ is the deformation gradient tensor; and $C_{10}$, $C_{11}$, and $D_1$ are constitutive parameters that were adopted from the literature for each tissue type and are specified in Table 1 for the reference model configuration.

The boundary conditions that were applied were as follows. Based on the above-mentioned analytic modeling, as well as on preliminary analyses with the present FE models, we applied a uniformly distributed force of 3.4 N on the distal surface of the cartilage of the shin (ankle joint) (Fig. 2). The proximal end of the shin was constrained to prevent any translational or rotational motions, which corresponded with the animal studies described in Animal experimentation section below.

In regard to the numerical method, for the reference model configuration, we used 8,207 and 4,288 elements of the type C3D10M in ABAQUS to mesh the tibia and fibula, respectively. The bone marrow and cartilage tissues contained 4,294 and 3,352 elements of the same type, respectively. Muscle tissue contained 73,750 elements, again of the same type, Muscle, fat, and skin were meshed using 171,911 elements of the type C3D4 in ABAQUS. Lastly, skin was meshed using 36,421 elements of the type M3D3 in ABAQUS. Given the above mesh densities, the runtime of the reference model and of the variant models described below was ~48 h each, using a Linux-based server with a CPU containing Intel core i-7 2.67 GHz 4 cores and 8 threads, and 12 GB RAM. The size of a single model file (.cae suffix in ABAQUS) was ~20 MB, and the size of the results file (.odb suffix in ABAQUS)

were \( \approx 2 \) GB. Simulations were then designed to test the effects of biological variability in rat shin anatomy and in mechanical properties of tissues with respect to the reference model configuration. For this goal, we built variant model configurations, where the shin length was varied by \( \pm 30\% \) to represent longer or shorter limbs. The change in shin lengths was obtained by artificially altering the distance between the axial planes of the magnetic resonance images, which caused the axial slices to become closer together (\( -30\% \)) or further apart (\( +30\% \)), resulting in a correspondingly modified 3D shin geometry. Boundary conditions and mechanical properties of tissues in the modified shin-length model configurations were the same as in the reference model. We further built model configurations, which simulated altered tissue mechanical properties with respect to the reference configuration, to represent biological variability in tissue stiffness. For that, the elastic modulus of cortical bone, and the instantaneous shear modulus of muscle (\( C_{10} \) parameter of muscle tissue in Eq. 1) were varied, each by \( \pm 30\% \), an extent typical to biological variability in tissue mechanical properties (15, 37). In these modified tissue-stiffness models, geometry and boundary conditions, as well as mechanical properties of other tissues, were kept the same as in the reference model configuration. Accordingly, seven model configurations were built and analyzed: one reference model configuration, two model configurations with altered shin length, two model configurations with altered bone stiffness (high/low), and two model configurations with altered muscle stiffness. Each such model configuration was analyzed for the distributions of principal tensile strains and stresses in the cortical bone of the tibia. The strain and stress distributions in cortical bone were plotted along a path, which was defined by the site at which peak principle tensile strain occurred and by the proximal and distal bone edges (see Fig. 5C).

### Animal experimentation.

The corresponding animal studies were approved by the Institutional Animal Care and Use Committee at Tel Aviv University (approval no. M-09–070) and conformed to the national guides for care and use of laboratory animals. Four young adult Sprague-Dawley male rats (age: \( \sim 7 \) wk and weight: 170–180 g at study onset) were used as an in vivo model for inducing a SF. Animals were housed in a controlled environment at the Animal House of the Tel Aviv University. They were given free access to food

<table>
<thead>
<tr>
<th>Soft Tissue</th>
<th>( C_{10} ), kPa</th>
<th>( C_{11} ), kPa</th>
<th>( D_{1} ), MPa(^{-1} )</th>
<th>Species</th>
<th>Ref. No.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Muscle</td>
<td>4.25</td>
<td>0</td>
<td>2.36</td>
<td>Porcine</td>
<td>37</td>
</tr>
<tr>
<td>Fat</td>
<td>0.143</td>
<td>0</td>
<td>70.2</td>
<td>Ovine</td>
<td>15</td>
</tr>
<tr>
<td>Skin</td>
<td>9.4</td>
<td>82</td>
<td>( \ast )</td>
<td>Human</td>
<td>21</td>
</tr>
</tbody>
</table>

\( \ast \)Skin is assumed to be incompressible, hence the term containing the \( D_{1} \) parameter in Eq. 1 is nil.
and water and gained weight (~3 g/day). Any altered behavior of the animals during caging was documented.

Before each experimental session, the animals were weighed and were then anesthetized using 90 mg/kg ketamine and 10 mg/kg xylazine by intra-abdominal injection. Maintenance doses, during the experimental sessions, which lasted ~30 min each, were 30 mg/kg of ketamine that was injected, if necessary, based on a pinch response.

During the experimentation, the anesthetized rat was laid on a horizontal rigid surface. Its posterior left knee was flexed, so that the tibia was perpendicular with respect to the femur. No other constraints were used to restrict motion of the tibia (Fig. 3).

Cyclic loading was delivered through the hind foot, using a custom-made electromechanical apparatus that was previously designed in our laboratory (by A. Gefen) (Fig. 3). The device comprised a linear actuator (IMS M-Drive 17, Schneider Electric, Rueil-Malmaison, France), at the tip of which a load cell (Honeywell Model 31, by Sensotec, Morristown, NJ) with force capacity of 10 N and accuracy of 0.3% was installed. The operating code for the device was written using the Labview software (National Instruments, Austin, TX). The loading tip of the device, made of stiff stainless steel (17–4 PH), was designed specifically for the present protocol, so that it would fit the size of the hind foot of the animals and would deliver axial forces to the tibia through the ankle joint, without producing a substantial moment.

The cyclic loads, with a triangle wave shape, frequency of ~1.2 Hz, which is typical for physiological gait of a man or a rat, and preset peak of 7 N, were delivered for ~30 min per session, 3 times/wk, for a period of 2 wk up to 12 wk, depending on the survival of the individual animal. Selection of the peak load was based on the described FE model, indicating an axial tibial force of ~3.4 N that induces tensile strains of ~2,500 με in cortical bone at the tibial midshaft. This is considered to be the high end of the physiological tolerance of cortical bone to repetitive loading in long bones (5, 35). In an attempt to induce a SF in the tibia of the animals within a feasible experimental time period, i.e., weeks to months, we used a preset peak load of 7 N, which is approximately twice the load predicted by the model. This load still kept the tensile strains at the midshaft of the tibia substantially below the yield strain of cortical bone (~10,000 με in tension) (41).

Outcome measures of the animal model studies were the presence or absence of a tibial SF based on X-ray scans taken approximately every 2 wk and interpreted by an experienced musculoskeletal radiologist (N. Shabshin). The contralateral (right) shin was used as a self control. The anatomical location of an established SF was documented to compare its location to that of maximal strains on and within the tibial cortical bone, as predicted by the FE models. In addition, during loading sessions, we recorded the load waves and the number of loading cycles delivered each day to each animal, enabling the calculation of the total number of loading cycles delivered to each animal.

RESULTS

FE models. Overall, strains and stresses were found to peak between the mid- and proximal thirds of the tibia for the reference model and all the model variants, excluding the one depicting a shorter shin (Figs. 4 and 5). Peak tensile and compression strains and stresses in tibial cortical bone for the reference model and for all model variants were <3,000 με and <70 MPa, respectively (Figs. 4 and 5); for example, tensile strains and stresses in the reference model peaked at ~2,200 με and 29 MPa, respectively (Fig. 4).

Tensile strain and stress distributions in tibial cortical bone for the model variants representing different shin lengths are shown in Fig. 4, in which the data from each model variant are superimposed using a normalized scale for the tibial length (the position along the tibial path is normalized with respect to the tibial length for each model variant). The longer shin model variant produced an ~14% increase in peak cortical tensile strain with respect to the reference model (Fig. 4A). In this shin, additional localized elevated strains were evident, and the average of strains along the tibia path was approximately three times greater than in the
The location at which maximal strains appeared was similar to that in the reference model (mid- to proximal tibia) (Fig. 4A). Consistent with these findings, in a 30% shorter-than-normal shin, the peak strain in the tibial cortical bone was \( \sim 46\% \) lower than in the reference model (Fig. 4A), and strains were <500 \( \mu \varepsilon \) along the entire tibial path. In the shorter shin, the site of elevated strains shifted toward the distal tibia. In this case, in the mid- and proximal tibia, strains were substantially more uniform with respect to the corresponding distributions in both the 30% longer shin and the reference model variants (Fig. 4A).

Trends of the tensile stress data were similar overall to those of the above-described strain data (Fig. 4B). The highest and most inhomogeneous stresses were found in the longer shin model variant (\( \sim 138\% \) increase in peak stress with respect to the reference). The region of elevated inhomogeneous stresses was in the mid- and proximal tibia, similar to the reference model (Fig. 4B). In the shorter shin, a \( \sim 38\% \) decrease in peak stress with respect to the reference was evident (Fig. 4B). In this shin, the site of maximal stresses was shifted toward the distal tibial end, inducing a more uniform stress distribution at the mid- and proximal tibia (Fig. 4B).

The effects of variations in mechanical properties of bone and muscle tissues on the distributions of strains and stresses in the cortical tibial bone were milder overall with respect to the effects of altering the shin length. In particular, mechanical property changes did not affect the location of elevated strain/stress sites, nor did they induce considerable changes in inhomogeneity of the strain/stress distributions (Figs. 4 and 5). For example, a 30% increase in the elastic modulus of cortical bone resulted in a very small reduction (<1%) in the peak cortical tensile strain, whereas a 30% decrease in the elastic modulus of the bone caused an \( \sim 8\% \) rise in the peak cortical tensile strain (Fig. 5A). Likewise, a 30% increase and 30% decrease in the
shear modulus of muscle tissue caused a negligible change and ~6% rise in peak cortical tensile strains, respectively (Fig. 5A). Cortical bone stresses were affected to a greater extent than strains by changes in tissue mechanical properties. Specifically, a 30% increase and 30% decrease in the elastic modulus of cortical bone caused an ~32% rise and ~27% drop in peak bone stresses, respectively; 30% increase and 30% decrease in the shear modulus of muscle caused a negligible and ~6% rise in cortical bone stresses, respectively (Fig. 5B). Altogether, when comparing the relative sensitivity of cortical bone strain/stress data to changes in bone tissue vs. muscle tissue stiffness, it appears that changes in bone tissue properties are more influential than changes in properties of the surrounding tissues.

In summary, the results from the FE modeling indicated that 1) in longer shins, more inhomogeneous and higher tensile strains/stresses, which were concentrated between the mid- and proximal thirds of the tibia of the animal, were evident; 2) anatomic variants in shin length influenced the strain/stress distributions to a greater extent with respect to changes in mechanical properties of tissues; and 3) bone tissue stiffness was more dominant than muscle tissue stiffness in affecting the strain/stress distributions in tibial cortical bone.

Animal model. The four animals were subjected to loading cycles in a range between 8,894 and 47,957 cycles (Table 2). Peak forces delivered to the ankle joint varied only mildly between the animals. Peak loads delivered to each animal are specified in Table 2. The animal that was exposed to the highest number of loading cycles and to the highest peak force (animal 1; Table 2) was diagnosed as suffering a SF in the proximal third of its left tibia, based on the routine X-ray scans. This occurred following ~35,000 loading cycles that were delivered during 9 wk of testing. The diagnosis was confirmed by a second X-ray ~4 wk afterwards. The X-rays of the other three animals, which were exposed to fewer loading cycles and lower average peak forces (Table 2), did not demonstrate SF.

**DISCUSSION**

This study introduces a new approach for studying SFs. The novelty of the model is that it is the first SF-related computer model to consider a very detailed 3D anatomical bone, including its cortical and trabecular components, and the bone marrow in the medullar cavity. The model considers for the first time the soft tissues enveloping the bone, their nonlinear constitutive properties, and also bone-loading conditions. The present FE model enables a full mapping of the strain/stress distributions within the tibia, showing that the engineering data are comparable to the actual location of a SF occurring in a respective animal model.

Strain distributions in bones are highly inhomogeneous under physiological loading, and the extent of strain inhomogeneity can be associated with the risk for bone cracking and mechanical damage (14, 16, 17). Hence, the full mapping of strain and stress distributions within the tibia is a major advantage of the present model. In the past, direct approaches to determine bone strains during physiological cyclic loading were investigated by surgically attaching strain gauges to the bone cortex (7, 25, 30). Besides being invasive, these studies are limited in several other aspects, compared with the FE model described herein. First, strain gauges, which provide only point measurements (as opposed to mapping the entire strain/stress distributions), cannot fully account for strain/stress inhomogeneity, even if several locations are monitored. Second, it is difficult to predict a priori where a SF will develop, and, hence, strain-gauge measurements can easily miss the developed SF. Third, the presence of a strain gauge biases the fields of strains/stresses around it, since there are stiffness

<table>
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<th>Table 2. Characteristics of the load cycles delivered to each animal</th>
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<td><strong>Animal No.</strong></td>
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Data of the animal diagnosed with a stress fracture are in bold.
differences and geometrical irregularities at the points of strain-gauge attachments. Soft tissues, which might be damaged during the surgical insertion of the strain gauge(s), could further affect biomechanics and the mechanical role that the soft tissues play in locomotion.

The peak tensile strains that were modeled in the present study were higher than those measured by means of strain gauges attached in vivo (12). This suggests that a single or even several points of measurement using strain gauges cannot accurately allocate the highest peak strain, and the actual peak strains in the bone are higher than those that can be measured by strain gauges. A common observation, based on strain-gauge recordings, is that the number of loading cycles causing SFs under field conditions is considerably less than that expected based on laboratory studies (12). This contradiction is understandable by realizing that the actual peak strains in cortical bone are probably higher than those experimentally measured by strain gauges.

The computational model and the in vivo experiments are in accord in regard to the location of the occurrence of a SF in the rat’s tibia. The FE model predicted that the development of a SF, where strains/stresses peaked, would be between the mid-tibia and the proximal third of the tibia for the reference model configuration and all other model variants, excluding the model describing the short shin. In a short shin, which has a shorter unsupported effective length of column, bending loads are milder. Hence, short shins are inherently more protected against SFs. The results from the present computational model and the animal study are supported by previous research that demonstrated, in a rabbit model, using radiographs and scintigraphic images, that SFs tend to initiate approximately at the same location: the proximal end of the tibia (6). SFs in humans can be seen at various locations, but, for distance runners and soldiers, it is typically located in the proximal tibia (9, 32, 36, 38).

Anatomic variants in shin length influenced the strain/stress distributions to a greater extent with respect to all other tested variations. A longer shin resulted in higher and more inhomogeneous tensile strains/stresses. This is in accordance with previous observations showing that a more slender tibia (i.e., ratio of a small tibial cross-sectional area over a large tibial length) is a significant risk factor in the development of SFs (3, 8, 18, 34, 40). In the past, there were efforts to classify human subjects as being at risk for SFs based on the second moment of inertia of the cross section of their tibia, which is attributed to the bending stiffness of long bones (31). The present work is in agreement with this line of research, particularly since the length of the tibia is also a measure of the bending stiffness of the bone. In future human studies, intersubject variations in anatomical structures should be considered as an important parameter to be examined by the model. Given that the present modeling indicates that the bending stiffness of the tibia is the factor having the strongest influence on development of elevated strains and stresses in bone tissue, an analog study looking at contributions of anatomical variants to SFs in humans should focus on parameters influencing bending stiffness. These parameters would be the tibial length, tibial width, cortical thickness, and cortical stiffness, particularly thickness and stiffness at the midshaft region, where the tibia tends to narrow. Much like in the present work, such a study could start with a reference anatomy, representative of the body habitus, age, and sex of the studied population at risk (e.g., male or female military recruits). These parameters can then be changed, one at a time, following which a systematic comparison of the strain/stress magnitudes and distributions can be done across the simulated anatomical variants. In such a study, it is also worthwhile to determine how strain/stress magnitudes and distributions in bone tissue are affected by the presence of initial microcracking (early phase of SFs), given that microcracks in bone tend to cause localized strains/stresses around them (16). This would likely exacerbate the strain/stress conditions in vulnerable anatomies. In terms of the FE simulation technique, introducing a microcrack can be done by creating a gap between bone elements or by sharply decreasing the local stiffness of one or more elements to simulate a forming crack.

This study is limited by the assumptions made in the FE modeling in regard to mechanical properties of tissues and by the relatively small group of animals that was studied. First, some simplified assumptions were made in regard to mechanical properties of tissues. To obtain feasible numerical solutions, we assumed isotropy in tissue mechanical properties and did not consider the dynamics of muscle contraction. Nevertheless, even under these assumptions, the present modeling is the most advanced of its kind in the context of SFs, although anisotropy and muscle contractions are factors that should certainly be looked at in the future. Second, the number of animals that were tested was small, given the chronic nature of the experiments, which imposed that animals would be kept alive with a potentially developing injury over a period of many weeks. This was appreciated and valued by the Institutional Animal Care and Use Committee, which approved only a limited number of animals to be studied. Nevertheless, as this study was aimed at testing the feasibility of validating FE models by an animal study, there was no need at this stage of the research to use a larger group of animals.

In summary, we suggested an approach to use a FE model to extract information in regard to internal bone loads, which cannot be directly obtained from in vivo studies. Supported by the animal study, the present FE model is a valuable tool in the research of SFs.

The approach taken in the present study could be extended in the future for studying various aspects regarding SFs in humans as well. The use of FE modeling based on MRI scans of human subjects who developed SFs, together with information regarding the musculoskeletal loading that the subjects are exposed to, should enable the implementation of the present methodology to study various aspects in the formation of SFs in athletes and military recruits.

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GRANTS

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DISCLOSURES

No conflicts of interest, financial or otherwise, are declared by the author(s).
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