Investigation of Determinants of Atypical Femoral Fractures Using Multiscale Computational Modeling

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Abstract— **Atypical femoral fractures (AFF) are predominantly transverse stress fractures from the lateral aspect of the subtrochanteric and diaphyseal region for which long-term bisphosphonate treatment have been suggested an important determinants. However, the physiological loading environment triggering AFFs in typical femoral regions remain largely unexplored. The aim of this study was to test the hypothesis that typical AFFs onset location is associated with high daily cyclic tensile strains. The study was based on body- and organ-level models from a single donor (female, 81- years- old) and motion data recorded from a body-matched volunteer (female, 25 years-old). Models were the donor's lower-limb musculoskeletal model validated against published measurements of the hip reaction force and the finite-element model of the donor's right femur validated against measurements of cortical strains. Motion data including skin marker trajectories and ground reaction forces were recorded from the volunteer during walking, which is the most frequent daily activity. The muscle and hip forces were calculated using the musculoskeletal model and applied to the finite-element model to calculate the cortical tensile and compressive strains in two extreme sections of the femoral diaphysis. The anterior, medial, posterior and lateral femoral aspects were assumed at 0°, 90°, 180°, and 270° respectively. In the sub-trochanteric section the peak tensile strain during stance was 1300-2287 με constantly located laterally (270°-300°) and the peak compressive strain was 1433-2730 με constantly located medially (90°). In the distal diaphysis the peak tensile strain varied from 1714 με to 4171 με located antero-laterally at 300°-330° and the peak compressive strain varied from 1813 με to 4674 με located postero-medially (90°-150°). We conclude that high cyclic tensile strains determine the typical AFFs onset location whereas more research is necessary to understand how different activities and the individual anatomy affect the femur's physiological tensile loads.**

Keywords— **Atypical femoral fracture, finite-element models, bone strains, walking, musculoskeletal simulation.**

I. Introduction

Atypical femoral fractures (AFFs) are responsible for permanent functional disabilities and related complications lead approximately one-fourth of patients to die within two years [1]. AFFs are low-energy stress fractures of the femoral shaft initiating on the lateral femoral aspect and often resulting in a complete, mostly transverse, fracture. AFFs have been associated with long term bisphosphonate treatments, which are increasingly used to treat catabolic bone diseases in patients with low bone mass. Therefore, the incidence of AFFs is expected to increase in the near future stimulating great interest in a better understanding of the AFFs pathogenesis. To date, however, several studies have focused on the effects of bisphosphonate treatments on the bone mechanical properties whereas a limited number of investigations have looked into the physiological loading environment triggering AFFs.

AFFs resemble stress femoral shaft fractures and pseudofractures, often preceded by prodromal pain, callus formation, absence or low trauma, are not comminuted, and mainly transverse [1]. Long-term bisphosphonate treatments have been shown to alter the bone mechanical properties in different and at times contrasting ways, either promoting or reducing the collagen matrix toughness; increasing bone mineralization, i.e., narrowing the bone mineralization density distribution (BMDD); causing a bone strength increase and, at the same time, facilitating microdamage accumulation [1]. Overall, bisphosphonate treatments increase bone fragility creating more favorable conditions for AFFs. Less understood is the mechanical environment where AFFs initiate with current studies mainly based on simple geometrical considerations. Saita et al. (2012) [2] showed that the AFFs location is correlated (R^2=0.64, p=0.008) with the misalignment between the femoral and the tibial axes while Sasaki et al. (2012) [3] showed that Japanese patients who developed AFFs had a more pronounced curvature of the femoral diaphysis than the age- and gender-matched controls. Both scenarios are consistent with high tensile strains in the lateral cortex but reports of femoral shaft strains during daily activities are scarce.

In-vivo bone strains can be estimated by coupling musculoskeletal models for estimating muscle and joint forces [4] and finite-element models of the bone elasticity [5]. Obtaining all the model parameters, however, is complex and often achieved using data from heterogeneous sources somehow rising concerns about the model reliability. Few years ago, the EU-funded project Living Human Digital

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Library (LHDL, IST-2004-026932) made publicly available a complete and consistent data collection from a healthy female donor [6], which includes among others the full body dissection and clinical computed tomography (CT), the full-body magnetic resonance images, the experimental measurements of femoral strains under multiaxial loads, and the motion data recorded on a body match volunteer during the execution of common daily activities. These data were used [4] to generate and validate models of the lower-limb musculoskeletal system and the finite-element model of the right femur, resulting in a tool that can be used for studying the bone strains in the femoral shaft during daily activities.

The aim of the present study was to investigate the physiological bone loading conditions during a common daily activity in those regions where AFFs typically occur. Cortical tensile and compressive strains in the femoral shaft were calculated during walking using the validated musculoskeletal and the finite-element models and compared with the femoral regions where AFFs typically occur.

II. Material and methods

The donor's model (female, 81 years old) was obtained by coupling a musculoskeletal model for the calculation of muscle and joint forces and a finite-element model of the right femur. The donor's data necessary for generating the models are available for download at www.physiomespace.com as well as the motion data collected from a body-matched volunteer (female, 25 years old) during walking. The muscles and the hip force were calculated using the musculoskeletal model. Bone tensile and compressive strains were calculated using the femur finite-element model (Fig. 1).

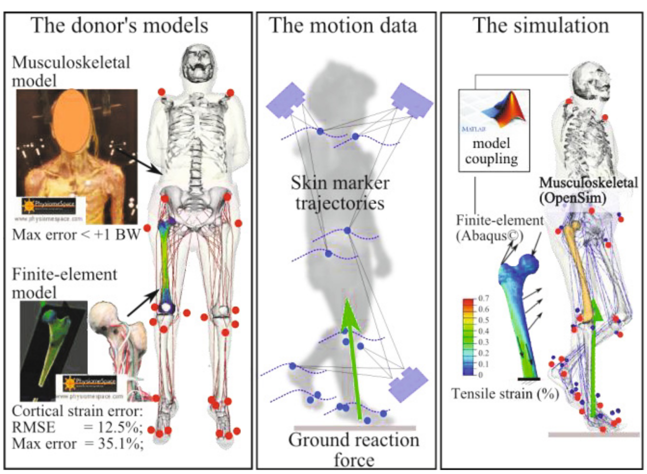

Fig. 1 The modeling process: From the left, the donor's musculoskeletal and finite-element models, the motion data, and a simulated walking frame.

A. Physical activities

Public motion data were collected from a volunteer anatomically similar to the donor in terms of body weight, height, pelvic width, tight and shank length (Table 1). The body height and weight were taken using a commercial meter and scale while the intra-segmental lengths were measured by an expert anatomist. Three measures for each parameter were taken and averaged.

Table 1 The volunteer's and the donor's anatomies

Parameter	Volunteer	Donor
High (cm)	165	167
Weight (kg)	57	63
Pelvis width (cm)	241	24.4
Femoral length (cm)	44.4	45.2
Shank length (cm)	39.4	42.9

A selected walking trial was used for the study. Motion data consist of skin markers trajectories recorded accordingly with the protocol proposed by Leardini et al. (2007). Motion data were collected using an eight-camera motion system (Vicon Motion Capture, Oxford UK) at a sampling rate of 100 Hz. The ground reaction force (GRF) at both feet was recorded at a sampling rate of 2000 Hz (Kistler Instrument AG, Switzerland). Recorded GRF patterns were consistent with published patterns although 0.2 bodyweights (BW) higher during late stance [4,7] (Fig. 2).

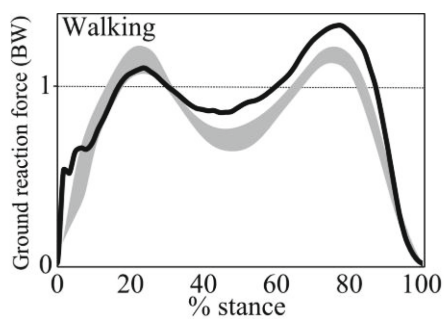

Fig. 2 The measured (solid black line) ground reaction forces (GRF) expressed in body-weights (BW) and the published patterns [4,7].

B. The musculoskeletal model

The donor's lower-limb musculoskeletal model was used to calculate the muscle and joint reaction forces acting on the right femur using an open-source musculoskeletal modeling environment [8]. The body was modeled as a 13-segment, 15 degree-of-freedom articulated system, actuated by 84 muscle-tendon units. The skeletal anatomy was extracted from the donor's full-body CT scan. Inertial properties of each segment were derived from the CT images assuming homogeneous density properties for both the hard

(1.42 g/cm^3) and soft (1.03 g/cm^3) tissues. Peak isometric muscle forces were calculated using physiological cross-sectional areas and a specific muscle tension of 1 MPa. The muscle model was registered on the donor's anatomy using a semi-automated procedure. The muscle fibre lengths and tendon slack lengths were uniformly scaled to ensure that muscle optimal lengths occurred at the same joint angles reported by Delp et al. [9]. All other muscle parameters were based on data by Delp et al. [9].

The skin motion markers identified on the volunteer were identified on the donor's skin from the CT scan.

The model kinematics was calculated by minimizing the sum of the squared distances between the volunteer's and the model's motion markers. The net joint moments were calculated through inverse dynamics by inputting to the model the calculated kinematic and the measured ground reaction forces. A static optimization problem was solved to decompose the net joint moments amongst the muscles by minimizing the weighted squared sum of muscle activations. The joint forces were calculated by solving for the static equilibrium at each body segment. The calculated model kinematics, joint moments and muscle forces during walking were in agreement with published patterns [4].

C. The finite-element model

A finite-element model of the right femur was created from the CT images of the donor available online [6]. The bone geometry was segmented from the CT scan using medical image processing software (Amira©, Visage Imaging GmbH, USA). Bone tissue was modeled using 10-node tetrahedral elements of approximately 2mm in size. Bone apparent density was calculated from the CT images by calibrating the image grey levels [5]. The bone mineral content in the relevant region (femoral neck, Ward's triangle, trochanteric and inter-trochanteric region) was calculated and compared to the BMD distribution of the 25 years old population. The donor's T-score was -2.5, placing the femur on the upper bound of the osteoporotic range. The Young's modulus distribution was calculated from the bone apparent density distribution using the relationship found by Morgan et al. [10]. The mesh element's isotropic Young's modulus value was calculated by integrating the voxel-based Young modulus over the elements volume using Bonemat© (Super Computing Solutions, Italy). The model was kinematically constrained at the femoral epicondyles. The Root Mean Square Error of calculated cortical bone strains was 12% and the maximum error was 35%.

Muscle forces and the hip joint reaction force from the musculoskeletal model were applied as boundary conditions of the finite-element model using an in-house Matlab (The MathWorks, USA) routine. Simulations were performed in Abaqus© (Dassault Systemes, USA) for fifteen intermediate frames uniformly distributed during the walking stance.

III. Results

The antero-lateral aspect of the femur was loaded mainly in tension throughout the walking stance (Fig. 3) in correspondence with the typical AFFs onset location reported by Shane at al. [1].

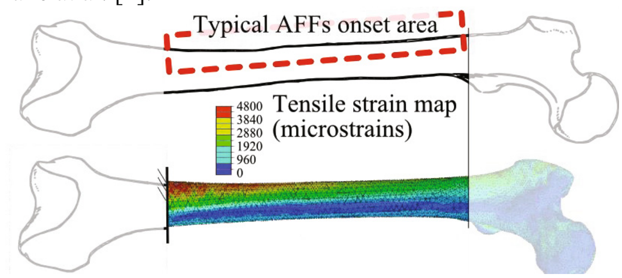

Fig. 3 The comparison between the tensile strain map calculated during late stance (bottom) and the typical AFFs onset location [1] (top).

The strain intensity and orientation varied considerably between the different phases of the walking stance (Fig. 4).

In the sub-trochanteric section, the peak tensile strain was oriented laterally throughout the walking stance at 270°-300°. The peak tensile strain intensity reached 1300 με shortly after heel strike and 2287 με during propulsion shortly before toe off. The peak compressive strain reached 1433 με and 2730 με in correspondence of the first and the second tensile strain peaks respectively, and was oriented medially at 90° during the whole walking stance.

In the distal section, the peak tensile strain was oriented antero-laterally at 300°-330°, reaching 1714 με shortly after heel strike and 4171 με during the propulsion phase, shortly before toe off . The peak compressive strain reached 1813 με and 4674 με in correspondence of the first and the second tensile strain peaks respectively, and was oriented postero-medially at 90°-150°.

IV. Discussion

Atypical femoral fractures (AFFs) are principally transverse stress fractures initiating and progressing from the lateral femoral shaft under physiological loading conditions. The aim of this study was to investigate the femoral shaft strain pattern during walking using validated models from a single donor. Cortical tensile and compressive strains during the walking stance phase were calculated and compared with typical AFFs onset locations reported by Shane et al. [1].

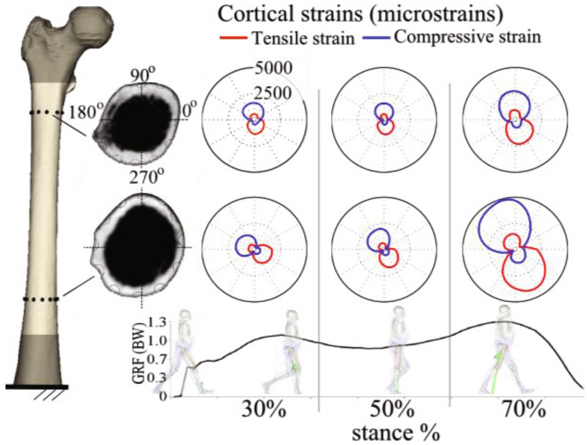

Fig. 4 Cortical strain patterns in a proximal and a distal section of the femoral diaphysis at the 30%, 50%, and 70% of the walking stance.

The antero-lateral aspect of the femoral shaft is subjected to tensile loads throughout the walking stance in correspondence with typical AFFs onset locations. Hence, the combination of tensile loads, to which bone is most susceptible, and increased bone fragility due to long-term bisphosphonate treatments, might constitute a favorable environment for AFFs onset and progression. Tensile strain magnitudes were highly variable over the walking stance (1300-4171 με) suggesting that a reduced walking intensity, i.e. frequency and walking speed, might be effective in reducing the risk for AFFs in subjects most at risk. More work is necessary to understand the relationship between femoral shaft strains, bone quality, the individual anatomy, and the forces driving different physical activities to further elucidate the mechanism/s driving AFFs.

To the authors best knowledge only a single study investigated the femoral strains during walking. Duda et al. [11] reported strain levels up to 2000 με in good agreement with our results obtained for the initial two-third of the walking stance (Fig. 4). The much higher strain levels found in the present study during the propulsion phase are to be likely attributed to the combination of a high ground reaction force recorded on the volunteer (1.33BW) during late stance and the high compliance of the donor's osteoporotic femur (T-score = -2.5).

The most important limitation of the present study is that no direct links have been shown between calculated bone strains and the occurrence of AFFs. However, the systematic and consistent predominance of tensile loading conditions in those bone regions where AFFs typically occur [1] point clearly to tensile loading conditions as important determinant of AFFs. The study was based on a single anatomy while different anatomies, bone qualities, and individual motion patterns may lead to different bone strain levels and consequent risks for AFFs onset and progression. More research is necessary to address these limitations. Last, simulations were obtained by using models from a weak old donor and motion data from a young and active volunteer likely causing an upward shift of calculated bone strains. However, obtaining all the necessary information from a single living subject would have made impossible to obtain the same level of model details and validation obtained using the present approach.

In conclusion, the typical AFFs onset locations are associated with the tensile strain loading pattern during the stance phase of walking. Hence, walking is likely causing most of the AFFs progression in time by inducing high tensile strains in the lateral femur with high daily frequency.

These findings provide insights into understanding the daily femoral loads with particular emphasis in typical AFFs regions and may help drawing lifestyle recommendations to control the risk for AFFs in subjects most at risk. Further work is necessary to investigate the role in femoral strains of different anatomies, bone qualities, individual motion patterns and to better understand how bisphosphonate treatments alter the bone fracture mechanics. Multiscale computational modeling combining musculoskeletal and finite-element models are well suited to investigate the individual femoral mechanics during motion.

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