

Simulated effects of marathon training on bone density, remodeling, and microdamage accumulation of the femur

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Abstract

Stress fractures are mechanically induced injuries resulting from fatigue damage to bone due to repetitive loading and are common injuries occurring in runners. In this study, we used computer simulations of marathon training programs to examine the effects of endurance running on femoral density, remodeling, and microdamage accumulation. Simulated remodeling activity increased in the femoral neck and proximal cortex and predicted microdamage increased in all regions examined after 16 weeks for each program. Daily running for three years produced more microdamage than the advanced training schedule over the same time period. Areas of high remodeling and damage corresponded to clinically observed locations of femoral stress fractures, indicating that the simulation may be useful in designing training programs to reduce fracture risk.

Keywords: Stress fracture; Fatigue; Damage; Bone remodeling; Computer simulation

1. Introduction

Stress fractures are mechanically induced injuries to bone resulting from repetitive loading. They are one of the more common injuries arising from endurance training and account for up to 20% of reported musculoskeletal pathologies in athletes [1–3]. The lower extremities are the most common sites for stress fractures and the specific bones affected depend on an individual's activity. More than 90% of diagnosed stress fractures occur in the tibia, metatarsals, tarsals, femur, and fibula [1,4,5]. The incidence of these injuries peaks in young athletes between 18 and 25 years of age and studies indicate approximately 70% of all reported stress fractures occur in runners [1,5–7]. The incidence of fracture has been shown to increase with greater weekly running mileage and many individuals show symptoms immediately following an increase in their duration of training [8–10].

It is believed that the etiology of stress fractures involves increased fatigue microdamage and excessive bone remodeling [11–14]. Although there has been no evidence of changes in serum and urinary bone turnover markers for athletes with stress fractures [15–17], Mori et al. [14] demonstrated histological evidence of local microdamage accumulation and bone remodeling at the site of a stress fracture. In their study, Mori et al. [14] found increased woven bone formation and a highly porous cortex, indicating excessive remodeling activity, in a bone biopsy from the site of a stress fracture. Stained sections of the biopsy revealed elevated levels of microdamage in association with resorption cavities from bone remodeling at the site. In addition, overexpression of interleukin-6 and basic fibroblast growth factor, two cytokines associated with bone resorption, as well as bone formation indicators osteocalcin and bone morphogenetic protein 2, were found at the stress fracture site.

Because of the nature of stress fractures, it is important to understand the relationships between loading, fatigue microdamage accumulation, and remodeling within bones

subjected to cyclic loads. In the present study, we employed a computer simulation to examine the effects of a specific endurance running program, namely a marathon training schedule, on femoral density, remodeling, and microdamage formation and removal. The simulation combined a finite element model of the femur with a previously developed bone remodeling algorithm that accounted for the biological response of bone cells to the mechanical environment of bone [18,19]. Here, we examined the influence of 16 week beginning, intermediate, and advanced marathon training programs on microdamage accumulation and remodeling in the femur. It was expected that the simulation would show variations in regional remodeling activity and microdamage accumulation, and therefore fracture risk, as one progressed from the beginning to the advanced training schedules. In addition, we then explored the cumulative effects in these parameters for the advanced training program over a three year period compared to a simple alternate training schedule in which the simulation modeled a running program where the daily training mileage remained constant throughout the duration of the schedule. For these simulations, the effects on remodeling and microdamage accumulation of varying the daily and weekly running mileage over an extended period of time were studied.

2. Methods

The simulation utilized for this study consisted of a previously developed mechanistic bone remodeling algorithm [19] integrated with a two-dimensional finite element model of the femur. The algorithm was based on the assumption that remodeling by basic multicellular units (BMUs), which are teams of osteoclasts and osteoblasts that resorb and form bone, respectively, is influenced by the local mechanical environment to remove accumulated fatigue microdamage [13,20] and to remove bone that is insufficiently loaded [21]. The local mechanical stimulus for remodeling was assumed to be proportional to the strain range (s) from n different daily activities and the number of cycles per day (R_L) that activity was performed:

$$\Phi = \sum_{i=1}^n s_i^q R_{Li}, \quad (1)$$

where the exponent q was set to 4 [22] and the strain quantity, s , was assumed to be the principal strain component with the largest magnitude.

The damage that accumulated within bone regions was governed by two feedback mechanisms in the algorithm [19]. With the mechanical stimulus in the form of Eq. (1), it was reasonable to assume that damage formed in the bone matrix at a rate equal to a constant multiplied by Φ [18]. Damage formation in the simulation was offset by BMU remodeling-based damage removal. The rate at which damage was removed from the bone matrix was assumed to be proportional to the amount of damage pres-

ent, the density of BMUs in the region, and the rate at which BMUs resorb bone. To spatially associate microdamage with removal by BMUs, a removal specificity factor equal to 5 was included in the formulation [18]. The amount of damage added or removed per day was then found by the difference between damage formed and damage removed by BMUs.

In addition to the removal of damage, BMUs were also activated within bone regions that were insufficiently loaded. From the work by Lanyon, Rubin, and colleagues, it was estimated that a mechanical stimulus of $\Phi_0 = 1.88 \times 10^{-10}$ cycles per day was needed to maintain bone mass [19,23–25]. In the simulation, bone regions for which Φ was less than Φ_0 were considered to be insufficiently loaded and evoked a remodeling response.

Bone resorption and formation rates for BMUs were estimated from an average osteonal cement line diameter of 0.190 mm [26], and remodeling periods of 24 days for resorption and 64 days for formation [19]. Daily BMU activation frequency was calculated from accumulated damage, the amount of insufficient loading (as determined by $\Phi - \Phi_0$ for values of $\Phi < \Phi_0$), and the surface area available for remodeling using previously defined dose–response relationships [19]. Active resorbing and forming BMUs were calculated by integrating daily activation frequency over the respective resorption or formation periods. Porosity changes within the bone region were determined from the net amount of bone removed or added by each resorbing or forming BMU, respectively. The modulus distribution for the finite element model was calculated from the density using a previous relationship determined from empirical data for both cortical and trabecular bone [19] and assuming that density is linearly related to porosity (density = 2 g/cm³ for a porosity of 0, density = 0 g/cm³ for a porosity of 1).

To simulate the effects of marathon training, the remodeling algorithm was integrated into a two-dimensional finite element model of a femur (Fig. 1, Patran 8.5, MSC, Santa Ana, CA), which was created by digitizing a radiograph of a representative femur. The model consisted of 4216 4-node quadrilateral elements and was constrained distally to prevent vertical and lateral motion. The material properties were assumed to be linear elastic and isotropic, with Poisson’s ratio for bone kept constant at 0.3 throughout the simulation. The elements were assigned a thickness of 37 mm and a bony side plate of graded thickness between 2 mm and 10 mm was included in the model to account for the three-dimensional nature of the femur and the cortical bone which resides out of the plane of the analysis [27]. The material properties of the side plate of cortical bone (elastic modulus of 17.8 GPa and Poisson’s ratio of 0.3) remained constant during the simulation.

The daily loading history was simulated by three load cases consisting of joint reaction and abductor muscle forces similar to those proposed by Carter et al. [28] for normal activity (Fig. 1). For the load conditions, single-leg stance was applied for 4500 cycles per day (cpd) and

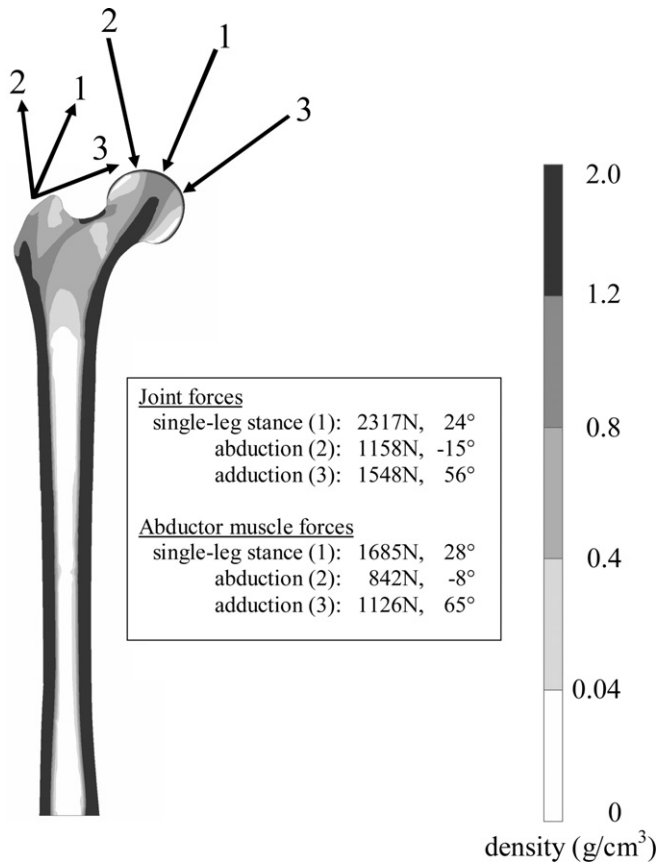


Fig. 1. Simulated femoral density for the steady state condition of the baseline simulation, which served as the initial condition for each of the training programs. Also shown are the loading conditions used in the simulation. Joint and abductor muscle forces were distributed over 11 nodes on the head of the femur and 25 nodes on the greater trochanter, respectively.

abduction and adduction were each applied for 750cpd. The marathon training schedules were simulated by adding a fourth loading condition consisting of a joint contact force of 4160 N (or 5.2 times body weight [29] of an 800 N individual) and a corresponding increase in the abductor muscle force to 3025 N. Each training program was 16 weeks long and concluded with a 26 mile marathon. Individuals in the beginning training program ran for 0–20 miles per day (16–39 miles per week) for a total of 387 miles including the marathon in week 16. The intermediate program consisted of 0–20 miles per day (23–50 miles per week) for a total of 590 miles. Runners in the advance training schedule completed 0–22 miles per day (29–55 miles per week) and 672 total miles including the marathon. The beginning program included 3 rest days per week during which no running was scheduled while the intermediate and advanced programs included 2 rest days per week for each of the 16 weeks. Daily running mileage was converted to cycles per day by assuming an average of 85 cycles per minute [30] at a pace of 7.5 min per mile.

The bone remodeling algorithm was incorporated into the finite element model, which provided the strain distri-

bution for the simulation, and the analysis was performed using Abaqus 6.3 (HKS, Pawtucket, RI). Starting the model with homogenous material properties [19] determined using a porosity of 4.43% to represent equilibrium between Haversian canals of osteons removed and added by BMU-based remodeling [18], the simulation was run for 1200 days under normal daily loading until the density and remodeling parameters achieved a steady state (baseline) condition. This baseline condition served as the starting point for each of the 16 week training programs. Density, remodeling activation, and microdamage were quantified from element averages in four regions of the femur (head, cortical regions of the neck, proximal cortex, and trochanter) for the baseline simulation and after 16 weeks for the training schedules.

To examine the effects of the advanced training schedule over an extended period of time, the 16 week schedule, including the marathon, and a subsequent three week layoff was repeated over a three year period. During this period, two marathons were run the first year and three marathons were run the second and third years. Bone remodeling, density, and microdamage results in the four regions of the femur for this simulation were then compared with an alternative schedule that consisted of a running program in which the individual runs the same mileage (approximately 5.8 miles) each day. This daily running schedule also consisted of a 16 week program that culminated in a marathon. The total miles run over the 16 weeks were 672 miles, the same amount as the advance training schedule. To compare this program to the advanced schedule over an extended period, the daily running schedule and a subsequent three week layoff was also repeated over the three year period.

3. Results

Density results for the baseline model (Fig. 1) were similar to regional densities observed clinically [31–33], and the density distribution was consistent with many features observed in femoral morphology: a Ward’s triangle region, trabecular bone of varying density in the head and trochanter, and dense cortical bone in the diaphysis and calcar region of the neck. Following 16 weeks of training, density results in the regions examined varied slightly from the corresponding baseline values (<2%) for each of the three training schedules of the study.

BMU remodeling activity predicted by the simulation increased above baseline values in the cortical regions of the neck (57–98%) and proximal cortex (43–82%) after 16 weeks of the beginning, intermediate, and advanced programs (Fig. 2). In addition, higher levels of remodeling activation in both of these cortical regions were observed in the model after 16 weeks of running for the more advanced schedules. Decreases in BMU activation frequency compared to the baseline results were predicted in the trabecular regions of the femoral head and trochanter after 16 weeks for all three training programs.

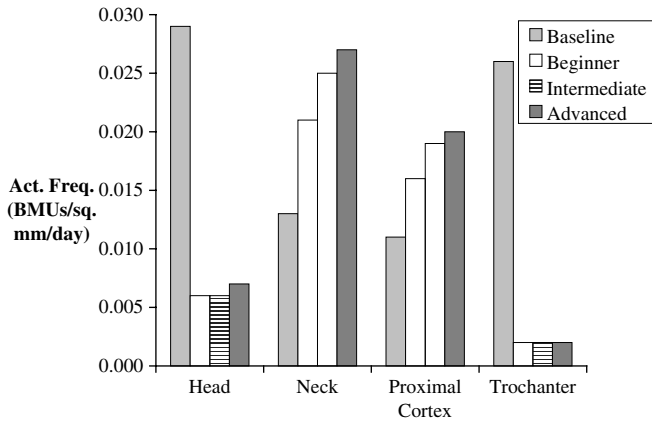


Fig. 2. BMU activation frequency of the femur as predicted by the model after 16 weeks of training for the beginning, intermediate, and advanced programs compared to the baseline condition in the femoral head, cortical regions of the neck, proximal cortex, and greater trochanter.

The model also predicted increases in microdamage of 13–20% in the cortical regions of the inferior and superior neck and 13–21% in the proximal cortex for the three training schedules after 16 weeks compared to baseline results (Fig. 3). As was seen with the remodeling activation results, predicted damage increased in these regions as the number of miles increased in the running program. While the amounts of microdamage were shown to be much lower in the trabecular regions of the head and trochanter of the baseline model compared to cortical areas, increases in damage in these regions of 32–45% (head) and 39–56% (trochanter) were predicted after 16 weeks for the three training programs examined.

When simulating the cumulative effects of the advanced training program and a daily running schedule as they were repeated over a three year period, density in the cortical regions decreased slightly compared to baseline values

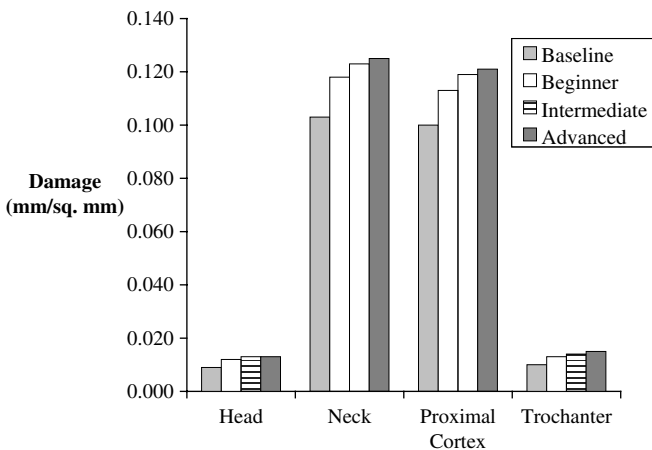


Fig. 3. Predicted bone microdamage in the femur after 16 weeks for the beginning, intermediate, and advanced running programs compared to the baseline condition. Microdamage, expressed as damage length per bone area, was evaluated in trabecular bone regions of the femoral head and greater trochanter and cortical bone regions of the neck and proximal cortex.

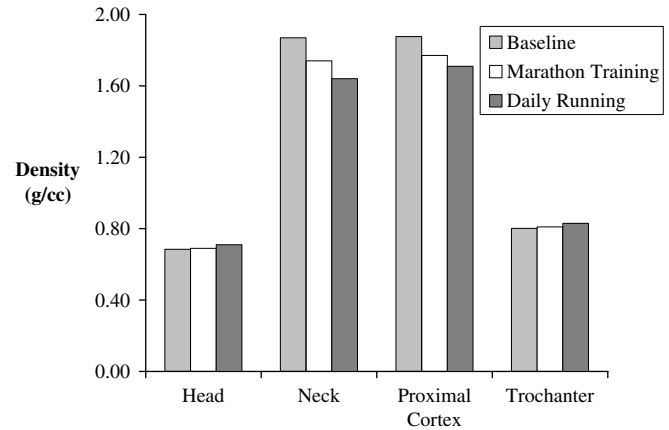


Fig. 4. Femoral density after three years of the simulation for the advanced marathon training schedule and a daily running schedule with equivalent mileage compared to the initial steady state (baseline) condition. Density values are shown for the femoral head, cortical regions of the neck, proximal cortex, and greater trochanter.

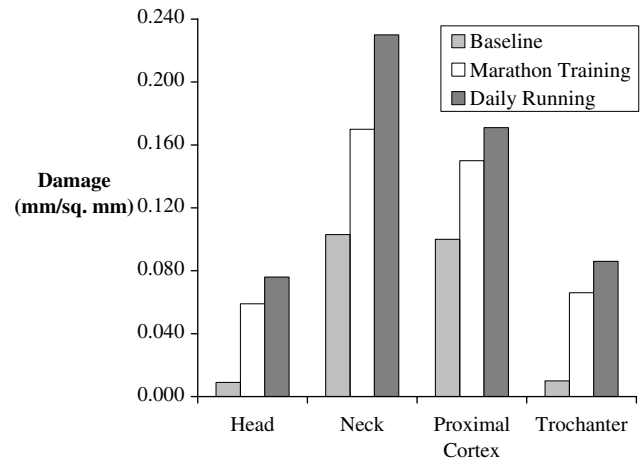


Fig. 5. Simulation prediction of microdamage in the femur, expressed as length of damage per area of bone, after three years of training for the advanced marathon schedule and a daily running program compared to the initial steady state (baseline) condition. Microdamage values are shown for the femoral head, cortical regions of the neck, proximal cortex, and greater trochanter.

(Fig. 4). Density in the cortical bone of the neck was predicted to decrease by 7% for the advanced schedule and by 12% for daily running, while density in the proximal cortex decreased in the model by 7% and 9% for the two programs, respectively. Microdamage also increased after the three year period for the advanced and daily running schedules compared to the baseline values (Fig. 5). In each of the four regions examined, damage values were predicted to be higher for the daily running schedule compared to the advanced marathon training program by 14 (proximal cortex) to 35% (cortical regions of the neck).

4. Discussion

Stress fractures are an important clinical problem for individuals involved in repetitive physical activity, includ-

ing athletes and military personnel. In addition to the time required to diagnose the injury, an average of 10–13 weeks of training is lost by athletes for treatment and recovery from fractures [1,10]. Because stress fractures are believed to involve the response of bone cells to a mechanical fatigue process, it is important to understand the relationships between the loading, microdamage accumulation, and the biological response of bone. Here, we integrated a bone remodeling algorithm with a finite element model of the femur to examine the effects of marathon training schedules on density, bone remodeling, and microdamage accretion. Predicted simulation results indicated increases in cortical remodeling activity and the accumulation of microdamage for beginning, intermediate, and advanced marathon training programs compared to baseline values.

It is believed that stress fracture development is facilitated by excessive local remodeling. While it has been shown that human bone fatigues when subjected to cyclic loading at physiological strain levels [34–37], estimates suggest that it would take significantly longer for stress fractures to develop *in vivo* than what is observed clinically, indicating other factors (e.g. occasional high strains, high strain rates, muscle fatigue, or bone remodeling) play a role in the development of stress fractures. Several investigators have hypothesized that stress fractures result from a positive feedback mechanism between microdamage accumulation in bone as it is fatigue loaded and the remodeling response to remove the damaged bone that involves a transient increase in resorption cavities and porosity [18,35,36,38–41]. Increased porosity in bone would lead to elevated stresses as cyclic loading continued, resulting in further accumulation of microdamage and increased risk of fatigue failure. The simulation presented in this study incorporated this positive feedback mechanism between damage and remodeling. In the model, microdamage was assumed to be one stimulus for remodeling. As the amount of damage present by fatigue loading increased, remodeling and, therefore, the amount of remodeling space or porosity also increased. Since the modulus was governed solely by bone porosity, increases in porosity led to modulus decreases, resulting in increased strain and damage formation in the model as fatigue loading continued. In addition, increased remodeling led to the resorption of damaged bone in the simulation and, therefore, a reduction in accumulated bone microdamage. The balance between damage formed by fatigue loading and damaged removed by bone resorption determined the total microdamage present and the locations predicted to be at risk for stress fractures in the simulation.

Previous studies using a bone remodeling algorithm similar to that incorporated in the current simulation have examined the sensitivity of the model's feedback mechanism between damage accumulation and remodeling. Increasing loads or loading cycles on cortical bone resulted in more BMUs activated to remove the increased amount of damage, but the simulation parameters achieved new equilibrium levels unless loads or the number of loading

cycles were sufficiently high such that remodeling could not keep up with the increased damage accumulation [18,19]. In these cases, microdamage, activation frequency, porosity, and strain increased rapidly; behavior consistent with high bone turnover in clinical observations of stress fractures [38,42]. Completely suppressing remodeling in a trabecular bone model subjected to physiological loading led to uncontrolled damage accumulation without limit [43].

Because of the difficulty in diagnosing stress fractures of the femur, especially those of the femoral shaft due to the high variability in the intensity and location of thigh pain, the incidence of fractures in the femur may be underreported in many studies. Although the tibia is the most frequent site for stress fractures in runners, accounting for up to 50% of all fractures [1,44,45], Johnson et al. [2] reported that the incidence of femoral stress fractures in athletes was 24% using a more sensitive diagnostic test than those previously reported. Following up their early diagnosis with radiographs and technetium-99m methyldiphosphate scintigrams to further evaluate the suspected site, Johnson et al. [2] confirmed their findings, indicating the common frequency that femoral stress fractures occur in athletes of various activities and underscoring the need for proper early diagnosis before further complications can develop.

Several previous studies showed that the most common locations for femoral stress fractures in athletes, in particular runners, were the proximal one-third of the shaft and the compressive cortex of the neck. Lombardo and Benson [46] examined six young runners with stress fractures and found two in the femoral neck and four in the proximal medial diaphysis. In addition, Johnson et al. [2] found that of the eight athletes that presented with femoral stress fractures in their study (out of 34 total stress fractures in a study of 914 athletes), seven were located in the proximal one-third of the medial or posteromedial diaphyseal cortex and one was in the inferior (compressive) cortex of the femoral neck. Also, Clement et al. [10] examined 74 stress fractures of the femur in 71 athletes and found that running was the most common activity that resulted in the injury and that 73% of the cases reported fractures in the femoral shaft (53%, although the location of the fracture along the shaft was not specified in this study) or lesser trochanter (20%) and 11% reported fractures in the femoral neck. In concurrence with these studies, the results presented here also showed high regions of accumulated damage in the calcar region of the neck and in the cortex of the proximal diaphysis (Fig. 6), indicating that the simulation may be a useful tool for predicting sites within bones at risk for stress fractures.

Results from computer simulations of biological mechanisms should be interpreted in accordance with the many limiting assumptions contained within the models. Although the cortical bone out of the plane of the analysis was taken into account, the model was still two-dimensional in nature and contained more simplified geometry and loading conditions than what could be provided with

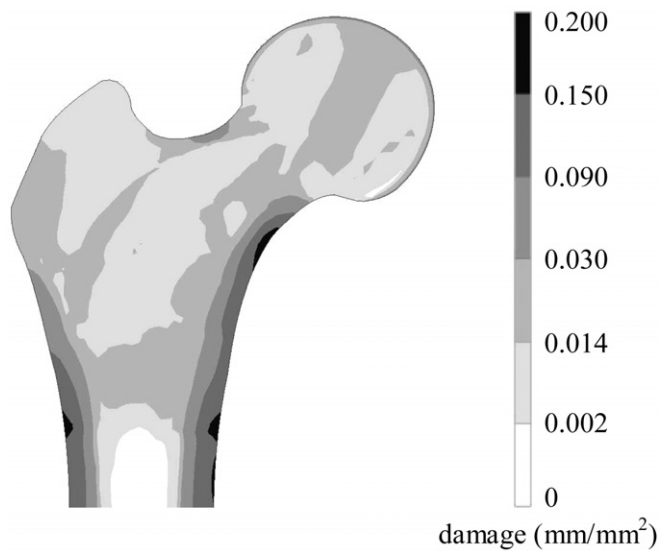


Fig. 6. Predicted microdamage distribution of the femur after 16 weeks of the advanced marathon training program. The calcar region of the neck and the proximal cortex were predicted to have the highest amounts of damage after training. Here, microdamage is expressed as length of damage per area of bone. Simulations of the beginning and intermediate marathon training schedules showed similar damage distributions.

a complete three-dimensional analysis. In spite of these limitations, as well as the idealized material behavior and the lack of a modeling response in the model, the predicted density distribution of the femur still showed many architectural features that are observed clinically: diaphyses around a more porous medullary canal, a calcar region in the neck, varying low density trabecular regions, and Ward's triangle. Another limitation in the model was that the same baseline condition was used for each of the training programs. Thus, the simulation did not take into account the differences in skeletal adaptation based on the prior loading history of advanced runners compared to those who are intermediate or just beginning a training program. A more realistic approach would have been to establish three baseline conditions for each of the training programs based on prior training mileage and cadence; however, starting the simulations from three different initial conditions and using different running paces would have made interpreting variations in remodeling activity and microdamage accumulation between the training schedules difficult since multiple factors would have contributed to the differences. In addition, another assumption in the model was that the relationships between the activation of remodeling, microdamage formation, and the local mechanical environment were estimated from experimental measurements of several previous studies examining cortical bone sites [19]. In this study, we assumed these relationships approximated the behavior in trabecular bone as well as cortical bone. While the baseline simulation produced reasonable remodeling activity and damage accumulation for a representative individual, the form of these relationships is not known nor is it known if the remodeling and

damage results predicted by the simulations for the training programs were reasonable or accurate. More experimental research is needed to further develop the relationships between remodeling, damage, and the mechanical environment of bone.

The model predicted that BMU activation frequency decreased in the trabecular regions of the head and greater trochanter following 16 weeks of marathon training as a result of the additional cyclic loading of the programs causing the mechanical stimulus to approach the equilibrium value Φ_0 in these regions. To our knowledge, the phenomenon of increased loading resulting in reduced trabecular remodeling has not been investigated experimentally. Etherington et al. [47] examined serum bone turnover markers in army recruits before and after 10 weeks of basic training and found decreases in the markers at the conclusion of the program, indicating a fall in bone turnover during training. Several investigators [41,48–50] have found trabecular thickening, coalescence of trabeculae, and increases in bone mineral density in trabecular regions of canines, Thoroughbreds, runners, tennis players, and weightlifters that may result from decreased bone turnover during exercise, but they did not correlate their results to remodeling activity. Future studies examining the effects of cyclic loading on trabecular remodeling is needed to provide further understanding of the bone response in these regions.

Cyclic loading results in the creation of damage which initiates new remodeling BMUs [11–14]. In addition, long bones adapt to cyclic loading by the deposition of new bone on the periosteal and endosteal surfaces (modeling) [24,51–54]. In vivo [24] and mathematical modeling [18] data show that during the modeling process, bone is preferentially added to regions of high stress. In addition to a damage-related remodeling response, an increase in bone size and shape occurs over time, possibly reducing strains and providing further protection for bone from damage. If bone is loaded repeatedly without an opportunity to respond in a sufficient manner, the creation of damage may outweigh the beneficial effects of remodeling and modeling. There is evidence that a graduated approach to training, which incorporates rest periods and a progressive increase in running mileage, may help avoid overuse injuries such as stress fractures [55,56]. Pollock et al. [55] reported that people who trained one to three days compared to five days per week were less likely to become injured. A second study in military recruits [56] showed that inserting a rest period during the third week of an 8 week training program, with no running, jumping or marching taking place, reduced stress fractures by 67%. These findings are supported by the current study which showed that damage and cortical bone activation frequency increased with increasing mileage and training frequency (Figs. 2 and 3), as well as the finding that damage was greatest as a result of a daily running program compared to the advanced marathon training schedule (Fig. 5). While there are several factors (e.g. age, physical fitness, bone characteristics, anatomic factors, or training

equipment [57]) that influence whether an individual will develop a stress fracture, our results suggest that varying daily running mileage, a graduated increase in weekly mileage, and inserted rest periods allow BMU-based remodeling to more efficiently remove damage due to a loading challenge thereby minimizing the risk of stress fracture.

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