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# The effect of prophylactic treatment with risedronate on stress fracture incidence among infantry recruits

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**Abstract**

When subjected to strains or strain rates higher than usual, the bone remodels to repair microdamage and to strengthen itself. During the initial resorption phase of remodeling, the bone is transitorily weakened and microdamage can accumulate leading to stress fracture. To determine whether short-term suppression of bone turnover using bisphosphonates can prevent the initial loss of bone during the remodeling response to high bone strain and strain rates and potentially prevent stress fracture, we conducted a randomized, double-blind, placebo-controlled trial of 324 new infantry recruits known to be at high risk for stress fracture. Recruits were given a loading dose of 30 mg of risedronate or placebo daily for 10 doses during the first 2 weeks of basic training and then a once a week maintenance dose for the following 12 weeks. Recruits were monitored by biweekly orthopedic examinations during 15 weeks of basic training for stress fractures. Bone scans for suspected tibial and femoral stress fractures and radiographs for suspected metatarsal stress fractures were used to verify stress fracture occurrence. By the intention-to-treat analysis and per-protocol analysis, there was no statistically significant difference in the tibial, femoral, metatarsal, or total stress fracture incidence between the treatment group and the placebo. We conclude that prophylactic treatment with risedronate in a training population at high risk for stress fracture using a maintenance dosage for the treatment of osteoporosis does not lower stress fracture risk.
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*Keywords:* Stress fracture; Bisphosphonates; Remodeling; Microdamage

## Introduction

Millions of people worldwide participate in regular exercise programs [1]. While enhancing cardiovascular and musculoskeletal fitness, exercise programs often result in acute or overuse injuries, many involving bone.

Like any other structural material when subjected to cyclic overloading, the bone can undergo fatigue failure [2]. In bone, this process is called a stress or fatigue fracture. Infantry recruits, runners, and usually sedentary people who suddenly increase their activity are at risk for stress fracture [3].

Unlike nonbiological materials, bone has the ability to adapt itself to unusual forces that can produce fatigue failure, thereby preventing or delaying the onset of fracture. This ability is greatest in the young and decreases with advancing age [4]. When bone is subjected to higher than usual strains and strain rates that create microdamage, it remodels to repair the damage [5]. The first stage of remodeling involves resorption of bone during which bone is transiently weakened. If the excessive loading continues during this stage before new and stronger bone is deposited and mineralized, then microdamage may accumulate and lead to stress fracture formation [6–10].

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The etiology of stress fractures has been the focus of both ex vivo and in vivo bone strain studies [11–17]. During physical activity, forces placed on bone result in its deformation (strain). In ex vivo laboratory bench testing cortical bone fails in fatigue within $10^3$ to $10^5$ loading cycles when strains are between 5000 and 10,000 με [14]. Strains in the physiologic range of 1000–1500 με in ex vivo studies have been shown to cause fatigue and microdamage, but not to cause complete fracture of cortical bone even after 37 million loading cycles [2]. Human in vivo bone studies have focused on the tibia both because it is the most common site for stress fractures among runners and military recruits [18] and because it is surgically a convenient site for strain gauge application [11]. Even during the most vigorous of physical activities, human tibial strains of sufficient magnitude to cause stress fracture from cyclic loading alone have not been found in vivo [11], yet fracture occurs within a few thousand cycles [9]. In contrast, strain levels sufficiently high to cause fatigue failure of the second metatarsal within 10,000 cycles have been found in human ex vivo [19] and in vivo studies [17].

The strain magnitude and cycle number required to produce tibial stress fractures in vivo are apparently much lower than those required to produce fatigue fracture during ex vivo mechanical testing [9]. This apparent discrepancy may be an effect of stressed volumes, whereby larger volumes of material are expected to have worse fatigue properties than the small segments of cortical bone often used in ex vivo mechanical testing [20]. However, others have hypothesized that tibial stress fractures and probably femoral stress fractures occur through the mediation of the bone remodeling response [6–10]. If this is true, then short-term suppression of bone turnover using bisphosphonates could prevent the initial loss of bone during the remodeling response to high bone strains and potentially prevent stress fracture [21]. This pharmacological approach could offer a potential solution to the problem of stress fractures without compromising the high level of training that is essential for the development of an elite athlete or infantry soldier. To test this hypothesis, we performed a randomized, double-blind, placebo-controlled study evaluating the effect of prophylactic treatment with the bisphosphonate risedronate on the incidence of stress fractures among infantry recruits known to be at high risk for stress fracture.

## Materials and methods

New male infantry recruits (473), training on the same base between December 2002 and March 2003, were approached to participate in the study. Three hundred twenty-four recruits, median age 18.8 (range 18–28), signed informed consent that was administered by civilian personnel. The study was approved by the Institutional Review Board of the Israel Defense Forces Medical Corps.

The recruits were surveyed for the presence of known risk factors for stress fracture. Preinduction participation in sports was assessed by an oral questionnaire. Measurements were made of height, weight, tibia length, hip external rotation, and foot arch height. The width of the flat medial tibia surface was measured at the mid-diaphysis by ultrasound (Mysono, 2001, Medison, Seoul, South Korea).

Participants were randomly assigned to receive either risedronate or placebo. A blister pack was made up for each recruit. Each blister pack cell contained two identically shaped pills either of 15 mg of risedronate or placebo. Distribution of the drugs was done by a team of three doctors. Subjects were given either 30 mg of risedronate or placebo daily for 10 days during the first 2 weeks of basic training period before they began any physically demanding training. Doses were taken with water on an empty stomach and observed by the medical team. After the initial 10-day loading dose, subjects received a 30-mg maintenance dose on Monday of each week for the next 12 weeks of the remaining 13-week training period. Recruits who were not present on the base any given Monday did not receive that week's dose. If a subject took less than 80% of his weekly maintenance doses (missed more than two doses) during the training period, he was not considered to be fully medicated. All subjects in the study were clinically followed for the duration of the study.

After the initial loading with 10 doses, a survey of possible adverse reactions to the medication was completed. For this purpose, the study's Health Safety Committee temporarily opened the treatment codes. During the course of basic training, recruits were reviewed by the orthopedic team every 2 weeks for the presence of subjective and objective signs of lower extremity stress fracture. Recruits with a suspicion of stress fracture from their orthopedic stress fracture examination [22] were given 2 weeks of relative rest. If their symptoms persisted, they were further evaluated according to the Israeli Defense Forces Stress Fracture Protocol [23]. Subjects with suspected metatarsal stress fractures were sent for X-rays and those with suspected tibial, femoral, femoral condyle, or navicular fracture were sent for bone scan. Metatarsal X-rays that showed either a fracture line or fracture callus were considered to be diagnostic of stress fracture. Bone scans were read from a 1–4 stress fracture scale by a blinded observer [24]. A discrete focal area of increased activity was considered to represent a stress fracture. At the end of basic training, all subjects had a final orthopedic examination and all blister packs were collected.

Statistical analysis was performed using the Statistical Analysis System (SAS, Cary, NC). Comparability of the study arms at baseline was assessed for possible risk factors related to stress fracture using the $t$ test for the continuous variables and the chi-square test for participation in running or ball sports, which was dichotomous. Data were analyzed in two ways: first with inclusion of all data, whether the

subjects continued their assigned treatment (intention-to-treat analysis), and then separately with inclusion of only those data obtained from subjects who completed their assigned treatment (per-protocol analysis). For the intention-to-treat analysis and the per-protocol analysis, the risedronate-treated group was compared to the placebo-treated group using chi-square in separate 2 × 2 contingency tables indicating frequency of occurrence of all types of stress fractures, tibial stress fractures, femoral stress fractures, and metatarsal stress fractures. Chi-square was also used to test the differences between the groups in the frequency of adverse reactions. Analysis of the relationship between possible risk factors for stress fracture and the occurrence of fracture was done using *t* tests and chi-square.

## Results

Of the 324 subjects in the study, 165 were randomized into the risedronate group and 159 into the placebo group (Fig. 1). There was no statistically significant difference in the mean values of possible risk factors for stress fracture between subjects randomized into the two treatment groups, except for femoral length that was minimally higher in the placebo group (Table 1).

At the end of the third week of basic training, 283 out of 324 subjects in the study filled out a survey of the presence of symptoms that might be related to drug treatment (Table 2). There was no statistical difference in the incidence of specific or total symptoms between the treatment groups. One subject from the risedronate group, after

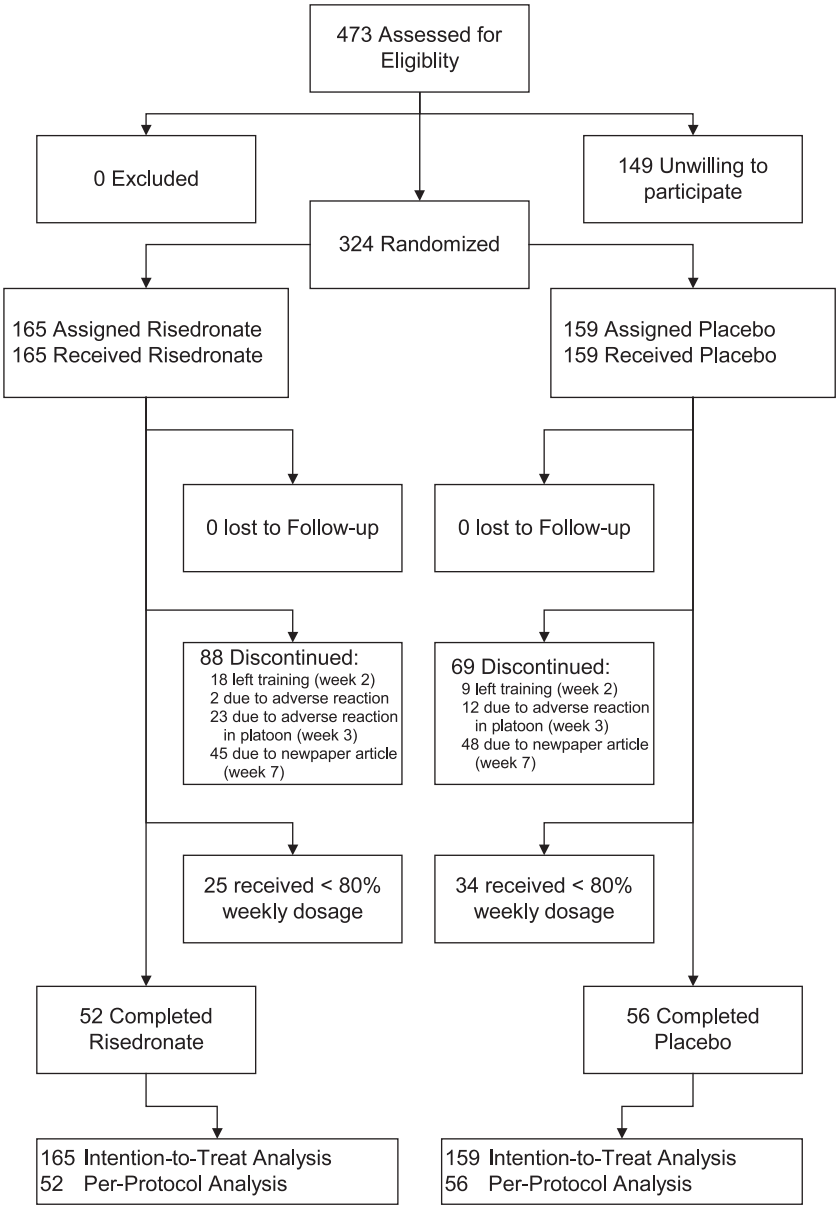


Fig. 1. Patient flow diagram.

Table 1
Comparison of mean values ± SD of possible risk factors for stress fracture according to randomized treatment groups

| Variable | Risedronate ($N$ = 165) | Placebo ($N$ = 159) | $P$ value |
|---|---|---|---|
| Age (years) | 19.1 ± 1.2 | 19.0 ± 0.9 | 0.41* |
| Height (cm) | 177.8 ± 6.5 | 178.5 ± 7.4 | 0.34* |
| Weight (kg) | 70.8 ± 10.6 | 70.8 ± 11.4 | 0.98* |
| External hip rotation (degree) | 54.0 ± 10.7 | 52.8 ± 10.5 | 0.30* |
| Tibia length (cm) | 61.8 ± 4.4 | 62.2 ± 4.5 | 0.43* |
| Femur length (cm) | 89.2 ± 6.2 | 90.7 ± 6.0 | 0.03* |
| Medial tibia width (mm) | 28.0 ± 2.4 | 28.3 ± 2.7 | 0.20* |
| Arch height (mm) | 16.1 ± 5.6 | 15.7 ± 5.8 | 0.56* |
| Run or ball sports participation (%) | 26.1 | 32.7 | 0.2** |

* $t$ test.
** Chi-square.

completing the loading dose, had persistent abdominal pain and his medication was stopped. His symptoms only partially responded to a regimen of magnesium and aluminum hydroxide. He was gastroscoped and a diffuse gastritis was found. A biopsy specimen was *Helicobactor pylori* positive. The subject was treated by triple therapy, responded, and completed his basic training. A second subject from the same platoon and from the risedronate group experienced polyarthralgia after completing the loading dose. His drug treatment was stopped. The subject was referred to a rheumatologist and a work-up was normal. The subject's two brothers both suffered from Crohn's Disease. Within 2 1/2 weeks of their onset, the subject's symptoms resolved and he was able to complete basic training. As a probable direct consequence of these two cases, 35 recruits in the same platoon as these soldiers chose to stop their participation in the study.

During the 6th week of basic training, an article pertaining to the research study appeared in a national newspaper stating that there had been adverse effects from the drug treatment. During the following week, no drugs were given out and all of the subjects were shown the results of the survey of drug side effects to refute these claims. As a result of the newspaper article, 93 subjects chose to discontinue participating in the study. An additional 27 subjects left

Table 2
Survey of possible adverse reactions among recruits after the third week of basic training

| Symptoms | Risedronate ($N$ = 140) | Placebo ($N$ = 143) | $P$ value |
|---|---|---|---|
| Heart burn | 16 (11.4%) | 27 (18.9%) | N.S. |
| Abdominal pain | 16 (11.4%) | 16 (11.2) | N.S. |
| Nausea | 14 (10.0%) | 9 (6.3%) | N.S. |
| Vomiting | 4 (2.9%) | 5 (3.5%) | N.S. |
| Headache | 29 (20.7%) | 21 (14.9%) | N.S. |
| Weakness | 32 (22.9%) | 26 (18.2%) | N.S. |
| Diarrhea | 13 (9.3%) | 12 (8.4%) | N.S. |
| Total recruits with symptoms | 60 (42.9%) | 68 (47.5%) | N.S. |

Table 3A
The relationship between external rotation of the hip ≥65° and femoral stress fracture incidence

| Femoral stress fracture | External rotation of the hip | | |
|---|---|---|---|
| | ≤65° | ≥65° | Total |
| No | 271 (90.3%) | 18 (75%) | 289 |
| Yes | 29 (9.6%) | 6 (25%) | 35 |
| Total | 300 (92.67%) | 24 (7.4%) | 324 |

Chi-square = 5.42.
$P$ value = 0.02.
Odds ratio (95% Confidence Interval): 3.18 (1.18–8.23).

basic training within the first 2 weeks of the study. Not all subjects were present on the training base at the time the drugs were distributed each week, usually because of health or training reasons.

By univariate analysis of all subjects in the study for possible risk factors for stress fracture, recruits who sustained tibial fractures had shorter tibias than those who did not ($P$ = 0.03, $t$ test). Recruits who sustained femoral stress fractures had higher external rotations of their hip than those who did not ($P$ = 0.02, chi-square test) (Table 3A). Regular sports participation in ball and running sports for at least 1 year before army induction (Table 3B) lowered the incidence of stress fracture ($P$ = 0.02, chi-square test). Femoral length was not found to be related to either tibial or femoral stress fracture.

Using intention-to-treat analysis, no statistically significant difference in the incidence of tibial, femoral, metatarsal, or total stress fractures was found between treatment groups (Table 4). There was no difference between the treatment groups with respect to stress fracture severity as judged by the bone scintigraphic uptake or the time of onset of the stress fractures as judged by the time of appearance of pain.

Using a per-protocol analysis comparing subjects who completed basic training and received full dosage of risedronate with those who received full placebo dosage, no statistically significant difference in the incidence of tibial, femoral, metatarsal, or total stress fractures was found between treatment groups (Table 5).

## Discussion

The results of the intention-to-treat analysis show that prophylactic treatment with risedronate did not lower the

Table 3B
The relationship between regular sports participation in ball and running sports at least 1 year before army induction and stress fracture incidence

| Stress fracture | Participation in ball and running sports | | |
|---|---|---|---|
| | No | Yes | Total |
| No | 192 (83.8%) | 89 (93.7%) | 281 |
| Yes | 37 (16.2%) | 6 (6.3%) | 43 |
| Total | 229 (70.7%) | 95 (29.3%) | 324 |

Chi-square = 5.65.
$P$ value = 0.02.
Odds ratio (95% Confidence Interval): 0.35 (0.14–0.86).

Table 4
Stress fracture incidence according to intention-to-treat analysis

| Stress fracture type | Risedronate ($N = 165$) (%) | Placebo ($N = 159$) (%) | Odds ratio (95% Confidence Interval) | $P$ value |
|---|---|---|---|---|
| All stress fractures | 14.5 | 13.2 | 1.1 (0.6–2.1) | 0.7 |
| Tibia | 9.1 | 5.7 | 1.7 (0.7–3.9) | 0.2 |
| Femur | 6.7 | 6.3 | 1.1 (0.4–2.6) | 0.9 |
| Metatarsus | 4.8 | 2.5 | 2.0 (0.6–6.7) | 0.3 |

incidence, the time of onset, or the severity of stress fractures among infantry recruits. The 14% overall incidence of stress fractures found in the study was within the range of that expected for nonelite infantry recruits in the Israeli Army [18].

Compliance in this study was defined as subjects who took at least 80% of their weekly doses. When a per-protocol analysis was performed using this criterion, no statistically significant difference in tibial, femoral, or total stress fractures incidence was found between treatment groups. It is the practice in clinical trials to draw definite conclusions when the per-protocol and intention-to-treat analyses are in reasonable agreement.

The hypothesis of this study was that short-term suppression of bone turnover using bisphosphonates could prevent the initial loss of bone during the remodeling response to high bone strains and potentially prevent stress fracture. Risedronate inhibits bone resorption [25,26]. Risedronate, like other bisphosphonates, inhibits the mevalonate pathway in osteoclasts, enhancing osteoclast apoptosis [27,28] and suppressing bone resorption [25,26]. Risedronate was chosen for use in this study because there is evidence to suggest that its half-life is shorter than that of alendronate [29,30], thereby allowing for more rapid withdrawal of the drug if adverse effects should occur. In a study of postmenopausal women, it was found that after an initial loading dose of 30 mg of risedronate/day for 2 weeks, the three principal markers of bone resorption were markedly decreased from baseline. Following discontinuation of the drug, there was a gradual return toward baseline, which was nearly complete at 12 weeks [31].

In this study, markers of bone resorption were not measured. It was estimated on the basis of prior studies, that a 2-week loading dose of 30 mg risedronate/day would reduce bone remodeling by 75–80% and that the 30-mg once-a-week dose would maintain that level [29,31–35]. For the purposes of this study, subjects who missed two or fewer doses of risedronate during the study were considered to have approximately reached this level of suppression.

Athletes have proven to be difficult to use for the study of stress fractures because their training is too varied and individualistic. The Israeli infantry recruit is ideal for the study of stress fractures because of the uniformity of training, controlled environment, and a high incidence of fracture [36]. It is also a good physiological model for studying the effect of demanding physical training on young bone [37,38]. Using these recruits, stress fracture epidemiology has been studied and risk factors identified [1,18,37–41]. Numerous preventative measures have been utilized in the Israeli army to try to lower the incidence of stress fracture, but the problem remains inherent to the demanding training [42].

Previously identified risk factors for stress fractures in Israeli infantry recruits were present in the current study [1]. Recruits who participated in regular ball and running sports for at least 1 year before military induction had a lower incidence of stress fractures than those without this background [41]. This reflects the bone's adaptive ability to strengthen itself when exposed to higher or new patterns of strain. Recruits with longer tibias were at lower risk for tibial stress fracture than those with shorter tibias. This reflects the fact that one of the essential parameters of bone strength is its geometric size and longer tibias are associated with wider tibias. It has been shown that narrow tibial bone width in the medial–lateral axis as measured by radiographs is related to increased tibial and femoral stress fracture risk [39], but this parameter was not measured in this study. Instead, a new bone dimension readily measurable by ultrasound, the anteroposterior width of the flat medial tibial surface, was assessed. This measurement is in a different anatomical axis and was not found to be related to stress fracture risk. In this study, high hip external rotation increased the risk for femoral stress fracture [1]. The reason for this association is not known.

This study is unique in that the effect of a bisphosphonate on normal young bone was evaluated. Bisphosphonates are usually used to lower bone turnover in conditions in which bone turnover is higher than normal. In this study, the bone turnover of the recruits can be assumed to have been normal at the beginning of training. With the onset of vigorous training and bone's subsequent adaptive response, bone turnover should have increased. Although suppression of this response was the goal according to the hypothesis of the study, it may have been suppressed too much or for too long a time or resulted in reduced formation of bone [43].

This study is compromised because the drop out rate was high, with only one-third of the subjects completing the

Table 5
Stress fracture incidence according to partial and full treatment groupings of recruits who completed basic training

| Stress fractures | Full risedronate ($N = 52$) (%) | Partial risedronate ($N = 95$) (%) | Full placebo ($N = 56$) (%) | Partial placebo ($N = 94$) (%) |
|---|---|---|---|---|
| All sites | 19.2 N.S.* | 14.7 | 14.3 | 13.8 |
| Femur | 9.6 N.S.* | 6.3 | 5.4 | 7.4 |
| Tibia | 15.4 N.S.* | 7.4 | 7.1 | 5.3 |
| Metatarsal | 5.8 N.S.* | 5.3 | 5.4 | 1.1 |

*Chi-square, comparing full risedronate vs. full placebo.

protocol. Two uncontrollable events occurred in this study that greatly contributed to the drop out and affected statistical power. Eight percent of the recruits in the intention-to-treat analysis left training at the beginning of the study and therefore were not at risk for stress fracture.

In spite of the high dropout rate, two definite conclusions may be made from this study. (1) Risedronate, when given to a young male population, has no more side effects than placebo treatment. (2) No benefit in terms of reduced stress fracture rate with prophylactic risedronate was exhibited in this study. Because there were no measurements of remodeling in this study, the reason for the lack of benefit is not known. It may be that remodeling to repair microdamage created by overloading is not the process that drives the pathogenesis for stress fractures. Another possibility is that remodeling may have been suppressed too much by risedronate, providing an alternative basis for stress fracture in the treatment group.

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## References

[1] Giladi M, Milgrom C, Simkin A, Danon YL. Stress fractures. Identifiable risk factors. Am J Sports Med 1991;19:647–52.
[2] Schaffler MB, Radin EL, Burr DB. Long-term fatigue behavior of compact bone at low strain magnitude and rate. Bone 1990;10:321–6.
[3] Devas M. Stress fractures. Edinburgh: Churchill Livingstone; 1973.
[4] Forwood MR, Burr DB. Physical activity and bone mass: exercises in futility? Bone Miner 1993;21:89–112.
[5] Mori S, Li J, Kawaguchi Y. The histological appearance of stress fractures. In: Burr DB, Milgrom C, editors. Musculoskeletal fatigue and stress fractures. Boca Raton: CRC Press; 2001. p. 151–9.
[6] Martin RB. A mathematical model for fatigue damage repair and stress fracture in osteonal bone. J Orthop Res 1995;13:309–16.
[7] Martin RB. The role of bone remodeling in preventing or promoting stress fractures. In: Burr DB, Milgrom C, editors. Musculoskeletal fatigue and stress fractures. Boca Raton: CRC Press; 2001. p. 183–201.
[8] Burr DB, Forwood MR, Fyhrie DP, Martin RB, Schaffler MB, Turner CH. Bone microdamage and skeletal fragility in osteoporotic and stress fractures. J Bone Miner Res 1997;12:6–15.
[9] Burr DB. Bone, exercise, and stress fractures. Exerc Sport Sci Rev 1997;25:171–94.
[10] Schaffler MB. Bone fatigue and remodelling in the development of stress fractures. In: Burr DB, Milgrom C, editors. Musculoskeletal fatigue and stress fractures. Boca Raton: CRC Press; 2001. p. 161–82.
[11] Burr DB, Milgrom C, Fyhrie D, Forwood M, Nyska M, Finestone A, et al. In vivo measurement of human tibial strains during vigorous activity. Bone 1996;18:405–10.
[12] Burr DB, Milgrom C, Boyd RD, Higgins WL, Robin G, Radin EL. Experimental stress fractures of the tibia. Biology and mechanical aetiology in rabbits. J Bone Jt Surg 1990;70B:370–5.
[13] Carter DR, Hayes WC. Fatigue life of compact bone-1. Effects of stress amplitude, temperature and density. J Biomech 1976;9:27–34.
[14] Carter DR, Caler WE, Spengler DM, Frankel VH. Fatigue behavior of adult cortical bone. The influence of mean strain and strain rate. Acta Orthop Scand 1981;52:481–90.
[15] Lanyon LE, Hampson GJ, Goodship AE, Shan JS. Bone deformation recorded in vivo from strain gages attached to the human tibial shaft. Acta Orthop Scand 1975;46:256–68.
[16] Milgrom C, Finestone A, Simkin A, et al. In vivo strain measurements to evaluate the tibial bone strengthening potential of exercises. J Bone Jt Surg 2000;82B:591–4.
[17] Milgrom C, Finestone A, Sharkey N, et al. Metatarsal strains are sufficient to cause fatigue fracture during cyclic overloading. Foot Ankle 2002;23:230–5.
[18] Milgrom C, Giladi M, Stein M, et al. Stress fractures in military recruits. A prospective study showing an unusually high incidence. J Bone Jt Surg 1985;67B:732–5.
[19] Donahue SW, Sharkey NA, Modanlou KA, Sequeira LN, Martin RB. Bone strain and microcracks at stress fracture sites in human metatarsals. Bone 2000;27:827–33.
[20] Taylor D, Kuiper JH. The prediction of stress fractures using a stressed volume concept. J Orthop Res 2001;19:919–26.
[21] Burr DB. Pharmaceutical treatments that may prevent or delay the onset of stress fractures. In: Burr DB, Milgrom C, editors. Musculoskeletal fatigue and stress fractures. Boca Raton: CRC Press; 2001. p. 259–70.
[22] Milgrom C, Finestone A, Shlamkovitch N, Eldad A, Saltzman S, Giladi M, et al. The clinical assessment of femoral stress fractures. A comparison of two methods. Mil Med 1993;158:190–2.
[23] Milgrom C, Finestone A, Shlamkovitch N, Giladi M, Lev B, Wiener M, et al. Stress fracture treatment. Orthopaedics (Int Ed) 1995;3:363–7.
[24] Zwas ST, Elkanovitch R, Frank G. Interpretation and classification of bone scintigraphic finds in stress fractures. J Nucl Med 1987;28:452–7.
[25] Eriksen EF, Melsen F, Sod E, Barton I, Chines A. Effects of long-term risedronate on bone quality and bone turnover in women with postmenopausal osteoporosis. Bone 2002;31:620–55.
[26] Reszka AA, Rodan GA. Bisphosphonate mechanism of action. Curr Rheumatol Rep 2003;5:65–74.
[27] Reszka AA, Halasy-Nagy JM, Masarachia PJ, Rodan GA. Bisphosphonates act directly on the osteoclast to induce caspase cleavage of mst1 kinase during apoptosis. A link between inhibition of the mevalonate pathway and regulation of an apoptosis-promoting kinase. J Biol Chem 1999;274:34967–73.
[28] Fisher JE, Rodan GA, Reszka AA. In vivo effects of bisphosphonates on the osteoclast mevalonate pathway. Endocrinology 2000;141:4793–6.
[29] Mitchell DY, Heise MA, Pallone KA, et al. The effect of dosing regimen on the pharmacokinetics of risedronate. Br J Clin Pharmacol 1999;48:536–42.
[30] Dunn CJ, Goa KL. Risedronate—A review of its pharmacological properties and clinical use in resorptive bone disease. Drugs 2002;61:685–712.
[31] Raisz L, Smith JA, Trahiotis M, et al. Short term risedronate treatment in post menopausal women: effects on biochemical markers of bone turnover. Osteoporosis Int 2000;11:615–20.
[32] Brown JP, Hosking DJ, Ste-Marie L, et al. Risedronate, a highly effective, short-term oral treatment for Paget's disease: a dose-response study. Calcif Tissue Int 1999;64:93–9.
[33] Brown JP, Kendler DL, McClung MR, et al. The efficacy and tolerability of risedronate once a week for the treatment of postmenopausal osteoporosis. Calcif Tissue Int 2002;71:103–11.
[34] Delaney MF, Hurwitz S, Shaw J, LeBoff MS. Bone density changes with once weekly risedronate in postmenopausal women. J Clin Densitom 1993;6:45–50.
[35] Gordon MS, Gordon MB. Response of bone mineral density to once-weekly administration of risedronate. Endocr Pract 2002;8:202–7.
[36] Milgrom C. The Israeli elite infantry recruit. A model for understand-

ing the biomechanics of stress fractures. J R Coll Surg Edin 1989; 34:18–22.
[37] Margulies JY, Simkin A, Leichter I, et al. Intense physical activity on the bone-mineral content in the lower limb of young adults. J Bone Jt Surg 1986;68A:1090–3.
[38] Leichter I, Simkin A, Margulies JY, et al. Gain in mass density of bone following strenuous physical activity. J Orthop Res 1989; 7:86–90.
[39] Milgrom C, Giladi M, Simkin A, et al. The area moment of inertia of the tibia—A risk factor for stress fractures. J Biomech 1989; 22:1243–8.
[40] Milgrom C, Finestone A, Shlamkovitch N, et al. Youth: a risk factor for stress fracture. J Bone Jt Surg 1994;76A:20–2.
[41] Milgrom C, Simkin A, Eldad A, et al. Using bone's adaptation ability to lower the incidence of stress fractures. Am J Sports Med 2000; 28:245–51.
[42] Finestone A, Giladi M, Elad H, Salmon A, Mendel D, Milgrom C. A randomized clinical trial of the effect of custom biomechanical shoe orthotics on the incidence of stress fractures. Clin Orthop Relat Res 1999;360:182–90.
[43] Khosla S. Parathyroid hormone plus alendronate—A combination that does not add up. N Eng J Med 2003;349:1277–9.