Title

Do capacitively coupled electric fields accelerate tibial stress fracture healing? A randomized, controlled trial.

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1 **Abstract** (word count = 248)

2
3 **Background:** Tibial stress fractures increasingly affect athletes and military recruits, with few
4 known effective management options. Electrical stimulation enhances regular fracture healing
5 but the effect on stress fractures has not been definitively tested.

6 **Hypothesis:** Capacitively coupled electric field stimulation (CCEFS) will accelerate tibial stress
7 fracture healing.

8 **Study design:** Double blind, randomized controlled clinical trial.

9 **Methods:** 20 men and 24 women with acute posteromedial tibial stress fracture were referred
10 from local clinicians. Subjects were randomly assigned active or placebo CCEFS to be applied
11 for 15 hours per day until healed, given supplemental calcium and instructed to rest from
12 provocative training. Healing was confirmed when hopping to 10 cm for 30 seconds could be
13 achieved without pain.

14 **Results:** No difference in time to healing was detected between treatment and placebo groups.
15 Females in the treatment group healed more slowly than males ($p = 0.05$). Superior treatment
16 compliance was associated with reduced time to healing ($p = 0.003$). Rest non-compliance was
17 associated with increased time to healing ($p = 0.05$).

18 **Conclusions:** Whole group analysis did not detect an effect of CCEFS on tibial stress fracture
19 healing, however, greater device use and less weight bearing loading enhanced the effectiveness
20 of the active device. More severe stress fractures healed more quickly with CCEFS.

1 **Clinical relevance:** While the use of CCEFS for tibial stress fracture healing may not be
2 efficacious for all, it may be indicated for the more severely injured or elite athlete/recruit whose
3 incentive to return to activity may motivate superior compliance.

4 **Key terms:** STRESS FRACTURE; BONE STRESS INJURY; TREATMENT - NOVEL
5 ENTITIES; ELECTRIC FIELD STIMULATION; FRACTURE STIMULATION

1 **Introduction**

2 Stress fractures are focal structural weaknesses in bone occurring with the repeated
3 application of sub-fracture threshold forces (15). Stress fractures typically result from chronic
4 skeletal overloading occurring over a period of time that is inadequate to allow appropriate bone
5 adaptation. They are increasingly common injuries in athletic and military populations, and
6 thought to affect more female army recruits than male(4, 21).

7 With some exceptions, fractures of this nature heal spontaneously if the injury site is
8 relieved for a time from the aggravating loading. The period of time required for healing to
9 occur with rest, however, can be quite prolonged. The most common site of stress fracture is the
10 tibia(5). A comprehensive review of the literature reveals that an average of 12 $\pm$ 7 weeks rest
11 has been recommended for the resolution of tibial stress fractures. Such a lengthy duration is
12 highly problematic for athletes in critical training or competitive periods, for army recruits
13 engaged in 14-week basic training courses, and for individuals simply attempting to maintain a
14 level of fitness for health benefits.

15 Few treatments to enhance the rate of stress fracture healing have been empirically tested,
16 and of those that have, results have been disappointing or equivocal. For example, the use of a
17 pneumatic leg brace was reported to enhance the rate of healing in a small (n = 18) athlete
18 study(35), but not in a larger (n = 31) controlled study of soldiers with tibial stress fractures(1).

19 Electric fields are known to activate the bone formation process *in vitro*(23).
20 Furthermore, electric and electromagnetic field stimulation has been shown to facilitate the of
21 healing of recalcitrant fractures in humans, *in vivo*(32-34). The rationale for the current study
22 was based on the assumption that, as bone repairs via a similar mechanism regardless of the
23 nature of the fracture, electric field stimulation should similarly promote healing of stress

fractures. Some preliminary evidence exists to support such an hypothesis(3), however, no controlled, randomized trial has previously been conducted to appropriately test the theory.

The current study objective, therefore, was to examine the effect of capacitively coupled electric field stimulation versus placebo treatment on rate of tibial stress fracture healing in men and women via a double blind, randomized, controlled trial. A capacitively coupled electric field (CCEF) device that operates with signal parameters known to stimulate osteoblasts and designed to optimize patient compliance was selected to deliver the intervention stimulation (OrthoPak[®] Bone Growth Stimulator Systems, EBI, formerly Bioelectron, Inc., Hackensack, NJ; FDA approved for non-union fracture healing, see Figure 1).

Materials and Methods

The study was approved by the US Army Human Subjects Research Review Board, the Stanford University Panel on Human Subjects in Medical Research, the Griffith University Human Research Ethics Committee, and the Australian Defence Human Research Ethics Committee.

Sample size and power

Women and men between the ages of 18 and 50, recently diagnosed with one or more tibial stress fractures, were recruited from a subject pool of referrals from San Francisco Bay area (California, USA) and the Gold Coast region (Queensland, Australia) over a period of seven years. Apriori power calculations (based on a predicted effect size of 3 weeks, $s = 4$, $\alpha \leq 0.05$, and $\beta = 0.80$) indicated a total of 32 subjects (8 in each of 4 groups) would be required to detect between-group healing differences according to both device status and sex. We chose to recruit additional subjects to avoid potential group shortfalls consequent to blind random allocation,

1 aiming for a total of 40 subjects, 20 men and 20 women. Our figures were derived from the
2 consideration that a healing time difference of three weeks would constitute a practically
3 worthwhile effect, based on literature reports of an average time to tibial stress fracture healing
4 of 12 weeks. Ultimately, power to detect differences between treatment and placebo groups
5 based on our final subject numbers and times to healing was 95.7%, and power to detect
6 differences between male and female responses was 100% for the 95% confidence interval. (See
7 Figure 2, CONSORT diagram of subject flow.)

8 Subject selection

9 Eligibility for the study was based on the presence of one or more acute tibial stress
10 fractures, for which no significant treatment, aside from rest, had been prescribed. Only
11 posteromedial mid to distal third and proximal medial tibial stress fractures were investigated.
12 Mid anterior tibial shaft stress fractures were excluded, being of dissimilar etiology to typical
13 tibial stress fractures, and particularly prone to delayed- or non-union(14). Subjects were
14 excluded from the study if they were pregnant, used a pacemaker, had a metabolic bone disease,
15 or took medication known to influence bone healing.

16 Clinical diagnosis

17 Patients diagnosed with tibial stress fractures were referred to study investigators from
18 local sports medicine clinicians. Study personnel then performed a comprehensive injury
19 assessment to standardized evaluation criteria. The diagnosis of stress fracture was determined
20 according to patient history (development of substantial, localized, exercise-related bone pain)
21 and the presence of significant focal tenderness at either of the above described sites that was
22 most pronounced during weight bearing loading. Intensity of signs and symptoms including:
23 tenderness, night pain, pain with percussion, localized bone swelling, spongy texture overlying

the injury, and warmth at the site, were recorded on a scale of 1-3. A “clinical severity score” was calculated by the addition of all sign and symptom scores for a possible total of 21.

Diagnostic imaging

Although eligibility for study enrollment was based exclusively on clinical diagnosis, a comprehensive series of imaging examinations was ordered for each subject to obtain further information regarding injury severity. Plain x-rays have poor diagnostic sensitivity to stress fracture, detectable changes often lagging two to six weeks from onset of symptoms, but were obtained in order to standardize findings and rule out unforeseen pathology. Triple phase technetium bone scans are highly sensitive to bone stress reactions and are historically the most common imaging modality for stress fractures. Increasingly considered a more specific gold standard for stress fracture diagnosis, magnetic resonance images were taken at baseline and follow-up in order to more precisely observe location and degree of local swelling. Although not widely used, computed tomography has also been reported for stress fracture imaging, and thus was included in the radiological protocol for the purposes of comparison.

Severity of injury was graded on a scale of 0-4 for each method of imaging. A “radiological severity score” was calculated by the addition of imaging scores for each modality for a possible total out of 16. The total radiological severity score was stratified into four injury grades (grade 1 = 1-3, grade 2 = 4-6, grade 3 = 7-9 and grade 4 = >10) to approximate the stress fracture grading systems recently reported in the literature(2, 18-20, 36). The low-end range of the stratification was emphasized to account for the low sensitivity of plain films and CT, and the consequent likely small contribution of those scores to the overall radiological severity score.

All images were blinded and graded independently by musculoskeletal radiologists on separate occasions in order to evaluate inter-reader reliability. A complete description of the radiological analysis will be reported elsewhere.

Subject characteristics

A comprehensive record of relevant physical and behavioral characteristics was collected (age, height, weight, medical history, training patterns, orthopaedic abnormality, menstrual status, etc). Each subject completed a National Cancer Institute Health Habits Food Frequency Questionnaire (Block Dietary Systems, San Francisco, CA) to determine average daily calcium consumption in milligrams. Subjects were provided with calcium supplements (*TUMS 500 Chewable*, 500 mg calcium carbonate, SmithKline Beecham) and instructed to consume one supplement per day to ensure adequate calcium availability during the course of the intervention. All subjects were examined by dual energy x-ray absorptiometry (XR-36 Quickscan densitometer, software version 2.5.3a, Norland Medical Systems, Inc., USA) to determine bone mineral density at the whole body, proximal femur, lumbar spine and forearm. A bone mass score was derived for each subject by calculating the average z score from all regions. Broadband ultrasound attenuation (BUA) of the non-dominant calcaneus was employed to record an additional index of bone quality (QUS-2 Ultrasound Densitometer, Quidel Corporation, CA, USA).

Treatment

Active and inactive (placebo) electric field stimulators (OrthoPak[®] Bone Growth Stimulator Systems, EBI, Hackensack, NJ), were provided coded and blinded to investigators by the manufacturers. The active device was a small, portable, capacitively coupled electric field

(CCEF) stimulator that applied a sinusoidal wave of 3 - 6 V at 60 kHz and 5 - 10 mA via two adhesive, water-based gel electrodes (Figure 1).

Once diagnosed, and baseline data collection was complete, each subject was immediately assigned a device with replacement 9 Volt batteries and electrodes, and the intervention initiated. The CCEF device manufacturer recommends that patients use the device constantly, unless engaged in water activities. Our subjects were instructed to use the device for 15 – 20 hours per day to maximise usage but minimize variability between subjects that was likely to occur as a consequence of a somewhat burdensome protocol. We instructed subjects to replace the battery every morning, and to keep the device alarm switched on. The alarm would sound if electrode contact was lost from the skin or battery power was low, an event signalling that the electric field had been interrupted. Electrode contact could be recovered by moistening the electrodes or replacing them. A daily treatment record log was provided for subjects to record actual hours of use and any side effects or exercise activity they undertook. Devices were issued according to sequential serial number, as device status had been randomized in this order. Active and inactive devices looked and ostensibly functioned in the same manner, and all subjects were treated identically.

All subjects received standard stress fracture rehabilitation advice in order to avoid treatment withholding from the placebo group. Regular rehabilitation primarily consisted of rest from any painful activity. In-saddle stationary cycling and pool running were acceptable training alternatives to repetitive weight bearing training. Crutches were available for subjects unable to perform activities of daily living without pain, but this was never the case. Subjects were issued with acetaminophen to be used as needed (Tylenol Extra Strength Gelcaps, 500 mg, McNeil Consumer Products, Fort Washington, PA, USA), and asked to avoid non-steroidal anti-

1 inflammatories (NSAIDS). No subject reported use of any form of pain medication during the
2 course of the study.

3 Subject monitoring

4 Participants were contacted by phone or email every second day for a progress report and
5 asked to re-rate any existing signs and symptoms from 1 – 3. Running was not attempted until
6 subjects were pain free with walking, and hopping was not attempted until subjects were pain
7 free with running (50 meters).

8 When a complete absence of pain during hopping on the affected limb for 30 seconds to a
9 height of 10 centimetres off the ground was reported and confirmed by investigator examination,
10 the subject was considered healed and the intervention ceased. Participants immediately
11 received a follow-up MRI examination and returned their device and completed treatment log to
12 investigators. Device use was tested using the manufacturer-provided Physician Test Meter
13 which detected days of use in 24 hour periods. A functional measure of healing was deliberately
14 chosen as the outcome measure, rather than appearance on follow-up imaging, in order to
15 standardize the dependent variable to a practical benchmark and reflect usual practice for stress
16 fracture management in the clinical setting. No standardized system of classification to confirm
17 stress fracture healing on MRI was available at the study inception.

18 Statistical analysis

19 Device effect was evaluated via two-way ANOVA to determine if differences existed in
20 time to healing between active and placebo treated subjects, and between men and women. As
21 time to healing from start of treatment was positively skewed, we also performed a natural log
22 (LN) transformation of the data and re-ran the ANOVA with LN time to heal from start of
23 treatment as the dependent variable. In order to account for variation between subjects in

1 duration of injury before study enrollment, the analysis was run for both the time between date of
2 injury and healing, and the time between initiation of intervention and healing. A further
3 analysis was run to examine actual treatment time (time the device was worn) according to the
4 Physician Test Meter. The latter varied from number of days to healing as subjects were
5 instructed to use the device for only 15 hours per day.

6 To determine if severity of injury affected time to healing, a number of severity indices
7 were also compared with outcome measures. Two-way ANOVA was used to compare time to
8 healing using device status and clinical severity score as factors. Time to healing was also
9 compared via two-way ANOVA using device status and radiological severity score as factors.
10 Finally, time to healing according to tibial stress fracture injury grade (1-4) was compared via
11 one-way ANOVA for the whole group and using a split file analysis for device status.

12 The effect of subject compliance with investigator instructions on treatment time was
13 similarly examined via two-way ANOVA. One model examined actual hours of device use
14 (from the Physician Test Meter) per number of real treatment days, i.e. treatment compliance,
15 versus device status. Device use compliance was examined more closely by way of a t-test
16 comparison of subjects who complied >70% with those who complied <70% using Physician
17 Test Monitor hours to healing as the dependent variable. Further, a split file (according to device
18 status) correlation analysis of days to healing from start of treatment versus device use
19 compliance was performed. A second compliance model used a rating assigned to level of
20 weight bearing activity during the intervention (derived from number and intensity of exercise
21 bouts recorded in the subject log), that is, rest compliance, versus device status.

22 Correlation analyses were performed to observe the nature of specific relationships
23 between time to healing and variables such as injury severity or delay to treatment start.

Results

A total of 50 tibial stress fracture treatments were initiated, of which 44 (20 male and 24 female) were completed. Twenty-three of the randomly allocated devices were active (9 to men, 14 to women), and 21 were placebo (11 to men, 10 to women). Subjects excluded from the final analyses included four misdiagnoses (one anterior tibial stress fracture, one hemangioma, two cases of complex regional pain syndrome Type I), two subjects released for failure to initiate the protocol, and one extreme outlier (see Figure 2).

All statistical analyses satisfied Levene's test for homogeneity of variance for between group comparisons.

Subject characteristics are summarized in Table 1. Subjects were primarily involved in running and running-related activities (Table 2). Treatment versus placebo group comparisons revealed no subject characteristic differences with the exception of percent fat (active > placebo, $p = 0.02$) and percent lean mass (active < placebo, $p = 0.03$). Within sex, there were no differences between treatment and placebo groups with the same body composition exceptions. Women allocated an active device had significantly greater percent body fat ($p = 0.02$) and less lean mass ($p = 0.03$) than women issued a placebo device. Between sex group comparisons revealed predictable differences in height, weight, BMI, percent fat, percent lean mass and BUA, men being significantly taller and heavier with lower percent fat than women. Men consumed more calcium than women (1391.7 ± 689.1 vs 958.1 ± 359.9 mg, $p = 0.02$).

A summary of injury severity ratings and compliance scores is presented in Table 3. There were no differences in severity of injury between treatment and placebo groups, whether assessed clinically or radiologically. There were no detectable differences in treatment

1 compliance (number of hours per day of device use) between treatment and placebo groups, nor
2 in degree of compliance with the instruction to rest from weight bearing activities during
3 treatment. Similarly, no between-sex differences existed in any compliance or injury severity
4 variable.

5 A summary of healing data is present in Table 4. There was no main effect of device
6 status on time to healing from the start of treatment (treatment group - 29 days; placebo group -
7 25.9 days), however, overall women healed more slowly (31 days) than men (23 days) ($p =$
8 0.05). Analysis of the log transformed data revealed an interaction effect, such that the sex
9 difference was only evident in the treatment group (Figure 3).

10 In the analyses of (i) treatment compliance (actual hours of device use per number of real
11 treatment days), and (ii) rest compliance (amount of weight bearing activity during treatment)
12 two main effects were revealed. Increased hours of device use per day was associated with
13 greater reduction in time to healing in the treatment group than the placebo group ($F = 57.533$, p
14 $= 0.003$). The split file correlation analysis similarly indicated a significant inverse relationship
15 between time to healing and device use compliance for subjects allocated an active device ($r = -$
16 3.55 , $p = 0.05$), but no relationship for placebo allocated subjects ($r = -.009$, $p = 0.972$). Subjects
17 who complied more than 70% (used the OrthoPak[®] for >12.25 hours/day) healed significantly
18 faster than those who complied less than 70% ($t = 2.739$, $p = 0.009$, 95% CI 2.07, 13.797).
19 Greater engagement in weight bearing activities during treatment (rest non-compliance)
20 increased the time to healing from the start of treatment for subjects using the active device in
21 comparison with placebo users ($F = 2.583$, $p = 0.05$).

22 Although no main effects of clinical or radiological injury severity on time to healing,
23 could be detected, a direct comparison of time to healing according to radiological injury grade

(1-4, described above) revealed significant between-group differences ($F=4.79$; $p = 0.007$). When a split file analysis was run according to device status, time to healing differed between subjects of different injury grades only if they were allocated a placebo device ($F = 11.08$; $p = 0.001$). That is, there were no differences between healing times of subjects with bone scan severity grades of >2 versus #2 in the treatment group ($23.5 \nabla 16.3$ vs $31.2 \nabla 22.0$ days, respectively). However, there was a significant difference in healing time for the same comparison of subjects allocated a placebo device ($48.0 \nabla 36.8$ vs $24.4 \nabla 8.7$ days, $p=0.01$). These figures indicate that grades 3 and 4 tibial stress fractures treated with an active device healed 24.5 days faster than those allocated a placebo device. It is important to note that these analyses are not sufficiently powered to make definitive conclusions owing to the small number of subjects classified >2 in bone scan severity grade.

Correlation analyses revealed no significant relationships between time to healing and variables such as injury severity or delay to treatment start. One exception was a split file analysis for device status that reconfirmed a significant positive relationship between radiological injury severity and time to healing from date of injury for subjects issued placebo devices (Pearson's $r = 0.456$, $p = 0.03$). Appearance of follow-up MRI did not consistently reflect clinical healing. The use of CCEFS bore no relationship to the appearance of post-treatment MRI.

Discussion

Our goal was to examine the effect of capacitively coupled electric field stimulation on rate of stress fracture healing with a level of study design rigor not previously reported. We

1 standardized stress fracture site and included both male and female subjects in a double blind,
2 randomized, controlled trial.

3 Primary between-group comparisons detected no differences in rate of healing between
4 treatment and placebo groups, but indicated that men healed an average of eight days faster than
5 women from the initiation of treatment. The sex difference was small (2.4 days) in the placebo
6 group, but significant in the treatment group wherein men healed an average of 13.2 days faster
7 than the women, suggesting a sex-CCEF interaction effect existed. The observation that women
8 but not men in the treatment group had greater percent body fat and less lean mass than the
9 placebo group coincides with the sex-specific treatment effect. It is unclear how body
10 composition might modify the effect of CCEF stimulation on stress fracture healing, as factors
11 influencing and influenced by fat and lean mass were not measured. The observation of the
12 significantly greater daily calcium consumption (433.6 mg) of male subjects versus female may
13 be of relevance to the sex-specific treatment response.

14 Close scrutiny of the data suggests that an effect of electric field stimulation on stress
15 fracture healing did exist. For example, increased hours of device use per day reduced time to
16 healing in the treatment group but not the placebo group. The fact that the more severe tibial
17 stress fractures treated with an active device healed substantially faster (24.5 days) than similar
18 grade fractures treated with placebo, is additionally suggestive of a treatment effect. In order to
19 prospectively test the hypothesis that tibial stress fracture injury grade influences the efficacy of
20 CCEFS, future investigations must recruit adequate numbers of each stress fracture grade (1-4)
21 in order to maximize statistical power for cross grade comparisons.

22 Electrical stimulation has been used sporadically by clinicians for over a century (28)
23 (26). More recently electric and electromagnetic fields have been shown to effect responses

1 from bone cells in culture (7, 8, 16, 23, 31). Clinical effects such as the stimulation of bone
2 graft, spine fusion, osteotomy and non-union healing(9, 10, 12, 22, 27, 33), and the prevention of
3 disuse osteopenia(6, 30), have also been reported.

4 To date, only one study has investigated the effects of electric field stimulation on stress
5 fractures(3). Of twenty-five stress fractures treated with CCEFS (3.0 - 6.3 V, 60 kHz) for an
6 average time of 7.4 weeks (navicular - 8.6 weeks), 88% healed, 8% improved and 4% did not
7 heal. As the average time between stress fracture symptom onset and beginning treatment was
8 21 weeks (navicular - approximately 32 weeks), time to healing with the addition of electric field
9 stimulation appeared to be a substantial improvement (13 and 24 weeks) on healing without
10 stimulation. While the results were encouraging, the study controlled for neither a placebo
11 effect, nor stress fracture type or prior healing.

12 Although all create potentially effective electric fields in tissue, CCEFS has distinct
13 advantages over direct current (DC) or pulsed electromagnetic field (PEMF) stimulation of bone.
14 DC stimulation (24 hour stimulation) is an invasive approach, necessitating surgery. PEMF
15 (recommended 3-10 hours per day) generates an electromagnetic field from a rigid, unwieldy
16 coil, using a heavy power supply requiring daily recharging. A CCEF device, by contrast, is
17 small and light weight (4 oz); using a 9 Volt battery and small, flexible, gel electrodes. CCEFS
18 has been shown to stimulate significantly more DNA production from bone cells than
19 PEMF(13). The difference in effect is likely due to different mechanisms of action, PEMF being
20 reliant on activation of finite intracellular stores of calcium while CCEFS can utilize the infinite
21 amount of calcium available in the extracellular space(13).

22 Current opinion is that mechanical loads on the skeleton are transduced to bone cells by
23 strain-induced fluid flow within the bone tissue. Membrane shear stress, a tangential force

1 generated by fluid flow, is known to stimulate the reorganization of the cytoskeleton and
2 increase expression of cyclooxygenase-2 following inositol-triphosphate-mediated intracellular
3 calcium release(17, 29), with a similar increase in activated calmodulin that is observed with
4 CCEFS(11, 13). Streaming potentials, detectable from the surface of loaded bone, are
5 measurable evidence of fluid flow across bone cortices. It is conceivable that electric field
6 stimulation of bone achieves its effect by way of fluid flow electroosmosis, an electrokinetic
7 relative of streaming potentials. That is, flow of the electrolytic bone fluid may arise as a
8 consequence of the application of an electric field to bone. That low intensity pulsed ultrasound
9 stimulation (LIPUS) appears to accelerate the healing of frank fractures and complex tibial
10 fractures (24, 25) suggests an ability of sound waves to also perturb bone fluid. We
11 hypothesised that the passive application of an electric field to bone would force fluid to flow
12 through the interstitial spaces and channels, stimulate osteogenesis and, ultimately, stress
13 fracture healing. It is possible that both electrochemical and mechanical mechanisms are
14 involved in the transduction of the osteogenic signal. It is unknown if LIPUS stimulates stress
15 fracture healing. The short treatment time of 20 minutes per day suggests it may be an appealing
16 possible alternative to CCEFS.

17 The lack of generalized effect of the CCEF device to accelerate healing in our cohort may
18 have arisen from an intrinsic threshold rate of stress fracture healing below which extrinsic
19 stimuli failed to promote further affect. It is noteworthy that previous reports of the time
20 required for tibial stress fracture healing of 12 ± 7 weeks (84 days) grossly exceed the average
21 time taken for our study subjects to heal (roughly 27 days from treatment initiation or 55 days
22 from injury), regardless of device allocation. Apriori power calculations based on finding a
23 between-group difference in healing time of three weeks may have constrained the sensitivity of

our statistical analysis. It is possible that the close monitoring of subjects, the constant encouragement to minimize weight bearing training during treatment, the provision of calcium supplements, and the discouragement from ingesting NSAIDS, optimized rate of healing for all subjects. Under such conditions, subtle differences in healing rates become very difficult to detect, and arguably clinically insignificant. This would likely not be the case for more exceptional fractures (frank, non-unions and pseudarthroses) for which healing times are more prolonged, and significant CCEFS efficacy has been reported. Our findings generate the hypothesis that more severe tibial stress fracture may derive considerable benefit from CCEFS, a premise that remains to be tested with larger subject numbers.

Conclusions

Based on primary between-group comparisons, we cannot conclude that treatment with CCEFS accelerated tibial stress fracture healing in our sample. There is compelling evidence, however, that CCEFS accelerated healing in the more severe cases, and that greater compliance and reduced weight bearing activity during healing promoted efficacy.

Our analysis likely reflects the real-life efficacy of CCEFS on the healing of relatively minor tibial stress fractures of the average individual. It is possible, however, that the higher stakes associated with healing for elite or more severely injured athletes or recruits may inspire superior treatment compliance, and justify the use of CCEFS when even minor reductions in days to healing could mean the difference between an ability or inability to compete in a once-in-a-lifetime event.

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Table 1. Means $\forall$ SD of characteristics of stress fracture subjects treated with active and placebo electric field stimulation

Characteristic	Male (n = 19)		Female (n = 24)	
	Active (n = 8)	Placebo (n = 11)	Active (n = 14)	Placebo (n = 10)
Age (yrs)	28.33 $\forall$ 7.68	26.09 $\forall$ 7.99	27.79 $\forall$ 7.93	23.90 $\forall$ 6.23
Height (cm)	178.17 $\forall$ 5.43	178.60 $\forall$ 7.24	164.69 $\forall$ 4.90	166.05 $\forall$ 6.95
Weight (kg)	78.25 $\forall$ 8.35	80.54 $\forall$ 7.53	61.04 $\forall$ 9.61	57.41 $\forall$ 4.68
Body Mass Index (kg/cm ²)	24.65 $\forall$ 2.40	25.26 $\forall$ 2.03	22.56 $\forall$ 3.79	20.83 $\forall$ 1.41
Daily calcium intake (mg)	1543.30 $\forall$ 759.30 ^c	1432.10 $\forall$ 811.20 ^c	1013.2 $\forall$ 437.60	881.0 $\forall$ 207.6
Percent fat	18.40 $\forall$ 5.69	15.71 $\forall$ 6.59	33.76 $\forall$ 7.49	25.10 $\forall$ 5.06 ^a
Percent lean mass	78.26 $\forall$ 5.30	80.51 $\forall$ 6.23	62.65 $\forall$ 7.20	70.37 $\forall$ 5.01 ^b
BUA (dB/MHz)	102.63 $\forall$ 14.06	114.16 $\forall$ 21.21	91.95 $\forall$ 16.29	93.75 $\forall$ 15.84
BMD composite (z score average)	0.73 $\forall$ 1.20	0.88 $\forall$ 1.00	0.55 $\forall$ 1.2	-0.26 $\forall$ 0.60

a Female Active > Placebo, p = 0.02, b Female Active < Placebo, p = 0.03, c Men > Women, p = 0.02. BUA - broadband ultrasound attenuation, BMD - bone mineral density

Table 2. Primary sport/activity of tibial stress fracture subjects according to sex.

Sport/Activity	Male (n = 19)	Female (n = 24)
Distance running	10	14
Sprinting	1	4
Aerobics		4
Triathlon	2	1
Team sport (football, netball, ultimate frisbee)	4	
Boxing	2	1

Table 3. Comparison between treatment and placebo group injury severities and compliance scores according to sex (means $\forall$ SD).

	Male (n = 19)			Female (n = 24)		
	Active	Placebo	Total men	Active	Placebo	Total women
Clinical injury severity (pain) score	11.1 $\forall$ 4.8	12.8 $\forall$ 3.0	12 $\forall$ 3.9	13.3 $\forall$ 3.2	13.9 $\forall$ 2.5	13.5 $\forall$ 2.9
Radiological injury severity score	4.9 $\forall$ 1.6	5.5 $\forall$ 2.4	5.2 $\forall$ 2.0	4.3 $\forall$ 1.8	6.1 $\forall$ 2.9	4.9 $\forall$ 2.3
Delay to begin intervention (days)	34 $\forall$ 22.8	18 $\forall$ 16.2	25 $\forall$ 20.6	33 $\forall$ 29.6	27 $\forall$ 19.3	31 $\forall$ 25.3
Device use compliance (Physician Test Meter hours/treatment days)	13.5 $\forall$ 5.8	16.9 $\forall$ 5.2	15.3 $\forall$ 5.6	14 $\forall$ 4.9	15.7 $\forall$ 3.2	14.7 $\forall$ 4.3
Rest compliance (Degree of continued weight bearing activity)	1.1 $\forall$ 0.9	1.2 $\forall$ 0.4	1.1 $\forall$ 0.7	1.0 $\forall$ 0.7	1.3 $\forall$ 0.9	1.1 $\forall$ 0.8

Table 4. Whole group and sex-specific tibial stress fracture healing times according to device status (means $\forall$ SD).

	All subjects (n = 43)		Male (n = 19)			Female (n = 24)		
	Active (n = 22)	Placebo (n = 21)	Active (n = 8)	Placebo (n = 11)	Total men (n = 19)	Active (n = 14)	Placebo (n = 10)	Total women (n = 24)
Time to healing from start of treatment (days)	29.0 $\forall$ 15.8	25.9 $\forall$ 13.5	20.6 $\forall$ 13.9	24.7 $\forall$ 9.0	23 $\forall$ 11.1	33.8 $\forall$ 15.3	27.1 $\forall$ 17.6	31.0 $\forall$ 16.2 ^a
Time to healing from injury date (days)	60.7 $\forall$ 31.5	48.1 $\forall$ 24.3	52 $\forall$ 30.8	42 $\forall$ 23.8	47 $\forall$ 27.0	67 $\forall$ 31.8	55 $\forall$ 24.4	61 $\forall$ 28.9
Actual stimulation time (24 hr periods)	15.2 $\forall$ 9.4	16.2 $\forall$ 7.7	10 $\forall$ 6.2	15 $\forall$ 5.9	13 $\forall$ 6.0	19 $\forall$ 9.7	17 $\forall$ 9.9	18 $\forall$ 9.6 ^b

a Females > males (p = 0.04), b Females > males (p = 0.05)

Figure Legends

1. The capacitively coupled electric field stimulator (OrthoPak[®] Bone Growth Stimulator System, EBI, Hackensack, NJ) in situ for the treatment of mid-to-distal third posteromedial tibial stress fracture

2. CONSORT diagram of tibial stress fracture subject flow

3. Mean natural log time to heal from start of treatment for male and female tibial stress fracture subjects in placebo (0) and treatment (1) groups. A sex difference in time to healing is evident in the treatment ($p < 0.05$) but not placebo group.