

Study Title: Vitamin D3 Supplementation and Stress Fracture Occurrence in High-Risk Collegiate Athletes

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Background/Justification

Although active vitamin D3 (1,25-dihydroxyvitamin D) has numerous functions in the body, one of its more important roles is maintaining serum calcium levels. By regulating osteoclast activity, it modifies bone resorption to keep serum calcium levels within homeostatic ranges. Thus, it is a crucial vitamin for overall bone health. Inactive forms of vitamin D are synthesized in the skin as well as absorbed from the diet, and then converted into the active form when necessary. Studies have shown that populations living in higher latitudes, receiving less sun exposure, and those with poor diets have an increased susceptibility to vitamin D insufficiency or deficiency.^{1,2,3} These low levels may affect bone health, which in turn may lead to skeletal injuries.

One area of particular interest is the effects of vitamin D deficiency on stress fracture occurrences. As bones and muscles undergo stress from training or increased activity, remodeling occurs to adjust for this change and improves the structural integrity of the bone. Normally, a conditioned athlete or an individual with a rapid change in activity with adequate calcium and vitamin D levels will be able to compensate for this added stress. However, a deficiency in vitamin D has been shown to decrease bone repair. When tissue demand from stress outweighs tissue repair, overuse injuries occur. This is the basis behind studying vitamin D supplementation and occurrence of stress fractures.

According to a review by Neal et al., the study of vitamin D levels and stress fracture occurrences is a relatively new topic.¹ The best understood data comes from studies on military recruits, due to their rapid increase in activity and musculoskeletal stress. However, there is much less data regarding the effects of vitamin D levels on stress fracture occurrences in conditioned athletes.¹ Furthermore, since levels of vitamin D have been shown to vary with season and sunlight exposure, this leads to the idea that indoor sports and winter seasons may at a higher risk for stress fractures. One study by Valimaki et al.(need reference number here) showed a significant increase in vitamin D levels in Finnish men over a period of 6 months. First measurements in July listed only 0.9% of their subjects having levels below 20 nM/L, while in the winter the number of subjects in the deficient range increased to 38.9%.⁴ These findings support the idea that vitamin D levels are different at various seasons of the year.

As mentioned, there are several studies on vitamin D levels and/or calcium levels and their relationship with bone health. One study by Lappe et al. examined this relationship in female navy recruits by running a double-blind study, giving vitamin D and calcium supplementation to half of the subjects and a placebo to the other half.⁴ There were 3700 recruits that finished the study, and 309 recruits were diagnosed with at least one stress fracture. From the data, their results concluded that group with supplementation showed a decrease in stress fracture occurrence by roughly 21% compared to the control group.⁵ This significant decrease shows that supplementation of both vitamin D and calcium benefited in maintaining adequate bone health. The study also showed a reversal in bone mineral content. They found that vitamin D and calcium supplementation not only stopped bone mineral loss, but also began increasing total content by 2-3%.

In a 2014 literature review by Dao et al., a total of 9 studies from 238 original listings were found to focus strictly on vitamin D levels and stress fracture occurrences in the military.⁶ Through their analysis, the general consensus was that stress fractures were more prominent in individuals with low vitamin D levels, both at the time of recruitment and at the time of diagnosis. This review also noted a lack of studies and data taken from athletes. One unpublished study of note by Shindle showed that 51% of National Football League athletes were vitamin D insufficient, and 30% were technically deficient.² Tenforde et al. also reviewed literature on calcium and vitamin D supplementation and found that retrospective studies contain mixed results and there are very few prospective studies.⁷ They also noted the lack of data on male athletes, with most research focusing on females roughly between the ages of 18 and 26.

In testing for bone mineral density, the standard for measurement comes from dual-energy X-ray absorptiometry. DXA is a method used to distinguish between soft tissue and bone, and also provides information about bone structure and mineralization. Many studies have examined the use of quantitative ultrasound as a replacement for DXA in determining the risk of fracture in the elder population.^{8,9,10} Ultrasound imaging is much less invasive, less expensive, and unlike DXA it does not involve the use of ionizing radiation. Among others, one study by Pluijm et al. found that ultrasound results were strong predictors of bone mineral density and risk of bone fracture.⁸ Although ultrasound has not been studied as thoroughly as DXA, results have suggested it is comparable in determination of fracture risk between different study groups.^{8,9,10}

After examining current literature, it is clear that vitamin D plays a crucial role in bone health and can affect the rate of skeletal-related injuries. Studies on military recruits provide promising data, but an important difference to note is musculoskeletal strength in recruits compared to conditioned athletes. Therefore, it is necessary to study the effects of vitamin D supplementation on bone health in athletes in order to help prevent stress fractures and related injuries. Our study would add to the current deficit in this area of research and would allow athletes and teams to adjust diets and training plans accordingly. The principal investigator has observed an increase rate in stress fractures in those athletes who participate in the following sports: basketball, soccer, track/field, and cross country for both male and females athletes. The overall aim is to demonstrate the evidence of stress fracture prevention in order to keep athletes performing at their highest abilities.

Objectives/Research Aims

Objectives

The main objective of this study is to find a correlation between vitamin D deficiency and stress fracture occurrences in athletes who participate in high-risk activities. These high-risk athletes undergo elevated bone turnover, which requires adequate levels of vitamin D in order to support bone health. It is hypothesized that providing supplemental treatment to athletes showing lower than normal serum vitamin D levels will decrease the occurrence of stress fractures. By recording the dates and specific occurrences of fractures, it may be possible to correlate injury rates with seasons, providing more supportive data to pre-existing literature.

This area of research is lacking in the quantity of prospective studies. Previous studies primarily focus on adolescent, elder, or military recruit populations. While literature has shown that vitamin D plays an important role in bone health, there are no previous studies that directly examine vitamin D deficiency and supplemental treatment in conditioned collegiate athlete populations. This study will add to the existing knowledge and will provide a more specific analysis for athletes.

Specific Aims

1. To compare the proportions of student athletes experiencing stress fractures during the 2015-16 academic year with the five previous years.
2. To compare the proportions of 2015-16 academic year student athletes experiencing stress fractures in the vitamin D insufficient or deficient group and the group with vitamin D levels ≥ 30 ng/mL.
3. In 2015-16 athletes, to explore associations between the TRIAD questionnaire risk factors and low baseline vitamin D levels.
4. In 2015-16 athletes, to explore associations between the TRIAD questionnaire risk factors and subsequent stress fractures.

Setting

This study will focus on athletes who are at a higher risk of lower extremity stress fractures. Specifically, this study will be looking at male and female athletes on the track, cross-country, soccer, and basketball teams at the University of South Carolina. During the pre-season physical of each student athlete, serum vitamin D levels will be taken and recorded. There will be a certified nurse to draw the blood samples. This will take place at the University of South Carolina Athletic Department and/or the Palmetto Health Lab at 2 Medical Park. Potentially, every athlete of the given teams will be enrolled in the study unless they choose not to. Only subjects showing concentrations below 30 ng/mL, which is indicative of insufficient or deficient levels, will be provided supplemental treatment of 25-(OH) vitamin D. Every enrolled subject will be monitored for injury throughout the season. Any and all injuries will be positively identified, and any confirmed stress fractures will be recorded. Data from prospective seasons will be compared to an incidence percentage of athletes from previous seasons. Previous athletes did not receive any vitamin D treatment. These will be used as a control to determine if treatment affected the occurrence of stress fractures. All physicals and tests will be performed at the USC Sports Medicine clinic by the sports medicine staff.

Resources Available

Track, cross-country, soccer, and basketball are all considered high-risk sports due to the constantly high loads being placed on the lower extremities. Basketball is also included because

of the extreme stresses involved when jumping. Combining all four sports as a single cohort would provide an adequate number of athletes to form a test group. Each sport's season occurs at different times of the year, and indoor sports like basketball and track may have athletes with less sun exposure. This will allow a comparison of occurrences across different sports, not just between treatment and control groups. Depending on the number of individuals meeting criteria for the study, it may be necessary to extend the timeframe to multiple seasons. The initial phase of the study will include a retrospective analysis of data from deficient athletes in these sports from past seasons that have not received any supplemental treatment. This will be used to find the percentage of stress fracture incidences occurring during those seasons.

The staff directly working on the study will consist of a licensed orthopedic surgeon, a doctor of athletic training and nutrition, a physician in occupational medicine, a research assistant, and a master's student. During each individual sport's season, other athletic trainers, physicians, and coaching staff may offer assistance as well. Every individual engaged with the study will be familiar with the basics of the topic and protocol as a minimum. The physicians will provide most of the expertise and insight when providing care for the athletes. Should any unexpected consequences arise, the staff and athletes will have direct access to both orthopedic and athletic training facilities as well as the linked hospital and clinics. The staff is in constant communication and will have regular meetings in order to stay current on the progress of the study.

Prior Approvals

Each individual sports team member, along with the coaching staff, team physicians, and athletic trainers, will be informed of the study. Approval will be required from the teams listed, as well as from the University of South Carolina Orthopedic Clinic.

Study Design

a) Recruitment Methods

Potential subjects will be screened from men's and women's track and field, soccer, and basketball teams, and women's cross-country. Individual players of each described team will be informed of the study during their pre-season physical. It is hoped that every player on the specified teams will be able to enroll in the study, whether they are vitamin D deficient or not.

Any subject that has consented and meets inclusion/exclusion criteria will be tested for serum vitamin D levels, and those individuals showing deficiency will be provided supplemental treatment in order to raise vitamin D levels to normal ranges. Individuals who do not show deficiency levels will be included in the study, but will not receive any treatment. These subjects will be added to an additional control group. There will be no payment for enrollment in the study.

b) Inclusion/Exclusion Criteria

Each individual who has given consent will have blood work tested. Should serum vitamin D levels be lower than 30 ng/mL, they will be included in the treatment group. Subjects with normal ranges will be included in the prospective control group. Both male and female athletes will be eligible to enroll. Any individual who currently has a stress fracture or is in the stage of recovering from a lower extremity musculoskeletal injury will be excluded from the study. Questionnaires will be provided in order to gather an understanding of diet, exercise regimen, and related lifestyle questions. Specifically, there will be a question regarding current vitamin D or other multivitamin supplement currently being taken, what the dosage is, and how often it is taken. Female athletes will be provided a separate questionnaire in regards to individual dietary habits and menstrual cycle.

c) Local Number of Subjects

The number of subjects in the study will be based on the number of individuals meeting the inclusion/exclusion criteria and provide written consent. They will be drawn from men's basketball, soccer, and track/field, and women's basketball, soccer, track/field, and cross-country. There will be no cutoff to the number of individuals accepted. Tentatively, there will be roughly 200 athletes enrolled in the study.

d) Study-Wide Number of Subjects

The number of subjects in the prospective portion of the study will be the number of qualified enrollees. This number may change, depending on the length of the study. Should it be necessary to extend the timeline, the study will enroll new subjects for the second season, but will still include them in the test group.

e) Study Timelines

Each enrolled subject will be monitored from the time of their pre-season physical to the conclusion of activities for their particular sport. The pre-season physicals will occur in August 2015, prior to the start of the school year. Subjects will be enrolled in the study even if the sports season has not begun. In the event of a study extension, any athlete partaking in a subsequent season will be asked to remain in the study as long as inclusion/exclusion criteria is met. The estimated date of completion is July of 2016, but may be extended if the data is inadequate for completion of the study.

Following the initial examination, all subjects will have serum 25(OH) vitamin D levels tested again in January. Subjects with deficient levels receiving treatment will undergo a follow-up examination 8 weeks from the initial treatment. This will help determine if subjects are responding to the treatment.

f) Study Endpoints

The primary endpoint of this study will be marked as when enough data has been collected to show a correlation between supplemental treatment and stress fracture occurrence, whether it is positive or negative. Tentatively, data collection for the study will stop at the conclusion of the last sports season. It may be necessary to extend the study for an additional school year if there are not enough data points to show a true correlation.

Supplemental treatment of 25(OH) vitamin D3 may have several adverse effects, including hypervitaminosis D and hypercalcemia. Should any subject show symptoms of these issues, they may be removed from the study.

g) Procedures Involved

Prospective: Subjects will be enrolled starting in August 2015, following the pre-season physical. It is possible many subjects, including returning athletes, may have taken summer physicals, and those subjects will be recruited and tested at a date upon return to school. Subjects should be tested prior to the start of individual seasons, although some overlap may occur. A flowchart is attached.

Potential enrollees will be provided a simple questionnaire regarding dietary habits. This will help the researchers understand individuals' nutritional intake, more specifically vitamin D sources. They will also be provided an informative page on vitamin D function and treatment for deficiencies. During the physical, each subject will have blood drawn and baseline serum 25(OH) vitamin D3 will be recorded. Supplemental vitamin D3 treatment will be given in 50,000 IU dosages once a week for 8 weeks following the initial examination. The prescription will be: Vitamin D3 50,000 IU oral capsule take 1 pill per week for 8 weeks. Subjects receiving supplemental treatment will then have vitamin D3 levels checked again at 8 weeks to ensure serum levels have risen. These values will be recorded. Should serum levels of vitamin D3 remain below the target value of 30 ng/mL, these subjects will be treated again following the same protocol as the primary treatment to ensure the levels rise. The subjects will then be followed throughout the course of the season, including all training activities, practices, and games.

Both deficient and normal subjects will be re-tested in January upon return from winter break. Subjects showing serum 25(OH) vitamin D3 levels below normal will be given supplemental treatment of 50,000 IU dosages once a week for 8 weeks. These subjects may have new or recurring deficiencies. Serum levels will be checked again following the end of treatment to ensure levels have risen. Any subject that was within normal ranges in the fall sports season that drops to deficient ranges will be treated with the same dosage as the primary treatment. Should their serum vitamin D3 levels fail to rise after 8 weeks, a secondary treatment will be administered following the same protocol as the primary treatment.

Throughout the seasons, any subject complaining of pain or injury to the lower extremity will undergo examination by the physician in order to positively diagnosis the injury. Each positively identified stress fracture will be recorded for that subject, and the appropriate treatment and rehabilitation will ensue. The lower extremity will be defined as any portion of the femur, tibia, fibula, and bones of the foot and ankle. Should an injury occur that does not

directly relate to a stress fracture or the lower extremity, the subject will remain in the study. However, these subjects will be included in a separate analysis.

Other than normal activities required for each sport, the main risk to each subject primarily involves taking blood samples. Although sampling is routine, there will still be risks of bleeding, bruising, dizziness, and possible infections. Allowing only trained individuals to take blood samples will minimize these risks. Any injury that occurs during a sports event or training activity will be handled accordingly by one of the physicians or athletic trainers on site. All injuries, regardless of nature, will be recorded per subject.

Blood samples will be tested for 25(OH) vitamin D levels using the order (Vitamin D 25-OH, Calcifediol Request). The data will be kept for each subject, day of recording, and level on an Excel spreadsheet. Any stress fracture reported will be listed on the same spreadsheet, along with the date of occurrence and severity, per subject.

Each team's athletic training staff will administer one vitamin D capsule to each team member once a week before a scheduled meeting or practice. This will help ensure every athlete takes the proper dosage, no dosages are skipped, and every week is accounted for. Athletes may still have decreased levels after the first course, and a second round of 8-week treatment will be administered. Should the second round of treatment fail to elevate vitamin D levels, the January test will confirm and treatment will continue. As many students leave to visit family during break, it will be rather difficult to monitor every athlete's levels during this timeframe.

Retrospective: The retrospective portion of the study will involve review of athletes of the same sports teams and inclusion/exclusion criteria from seasons up to four years ago. Review of previous athlete information will be drawn from electronic records kept by the athletic training staff, both electronic and hand-written records kept by the orthopedic staff, and any lab records retained at Palmetto Health. The information that will be obtained will include athlete demographics, their respective sports, stress fracture occurrences, and vitamin D levels if this was noted. The time period for the retrospective chart review will be from January 2010 through August 2015. The rate of stress fracture occurrence will be compared to the prospective treatment phase. It is important to note that individuals in the retrospective analysis will not have personal information reported, as the main purpose is to determine a baseline stress fracture rate.

Analysis of the historic group will follow similar protocol as the recruitment of new subjects. Information from previous subjects will include including gender, age and sports team information. Additional information obtained will include stress fracture occurrence(s) and location, and vitamin D levels (if recorded).

h) Data and Specimen Banking

Data for each enrolled subject will consist of name, age, gender, ethnicity, and sports team. Any personal or private information collected will only be used during data analysis. This may contain information regarding menstruation, dietary habits, and previous pregnancies. Names and private information of subjects will not be released outside of personnel directly attached to the study, and they will not be included in the final study publication. Serum 25(OH) vitamin D levels for each subject will be recorded at the initial examination and 8 weeks following the beginning of treatment. Every injury diagnosis will be recorded per individual. There will be no blood sample banking after vitamin D levels are determined.

i) Statistical Analysis

Sample Size Justification

A power analysis was performed using PASS 2008 software on the research aim to compare the proportion of athletes that experience a stress fracture in those with normal vitamin D levels (either normal at baseline or treated by supplementation) compared to four previous years when this approach was not used. You can see that if the proportion of athletes experiencing stress fracture in the control group is 10%, then if the true reduction in the treated group was to 4% or less, we would have greater than 80% chance (power) in this study to achieve statistical significance in a test of the two proportions.

Two Independent Proportions (Null Case) Power Analysis

Numeric Results of Tests Based on the Difference: P1 - P2

H0: P1-P2=0. H1: P1-P2=D1<>0. Test Statistic: Z test with pooled variance

Power	Sample	Sample	Prop H1	Prop	Diff if H0	Diff if H1	Target Alpha
	Size Grp 1	Size Grp 2	Grp 1 or Trtmnt	Grp 2 or Control			
	N1	N2	P1	P2	D0	D1	
0.9946	200	800	0.0200	0.1000	0.0000	-0.0800	0.0500
0.9509	200	800	0.0300	0.1000	0.0000	-0.0700	0.0500
0.8220	200	800	0.0400	0.1000	0.0000	-0.0600	0.0500
0.6188	200	800	0.0500	0.1000	0.0000	-0.0500	0.0500
0.4048	200	800	0.0600	0.1000	0.0000	-0.0400	0.0500
0.2337	200	800	0.0700	0.1000	0.0000	-0.0300	0.0500
0.1224	200	800	0.0800	0.1000	0.0000	-0.0200	0.0500

Statistical Analyses

1. To compare the proportions of student athletes experiencing stress fractures during the 2015-15 academic year with the four previous years.

A large sample test of the difference in two independent proportions will be carried out, along with computation of 95% confidence interval on the difference between the two proportions. An exploratory logistic regression model will be built with stress fracture as the outcome, group (2015-16 versus the previous four years) as the major predictor variable and type of sport and gender as covariates.

2. To compare the proportions of 2015-16 academic year student athletes experiencing stress fractures in the vitamin D insufficient or deficient group and the group with vitamin D levels ≥ 30 ng/mL.

A large sample test of the difference in two independent proportions will be carried out, along with computation of 95% confidence interval on the difference between the two proportions. An exploratory logistic regression model will be built with stress fracture as the outcome, group (baseline vitamin D deficient versus normal baseline vitamin D level) as the major predictor variable and type of sport and gender as covariates.

3. In 2015-16 athletes, to explore associations between the TRIAD questionnaire risk factors and low baseline vitamin D levels.

Exploratory descriptive and inferential statistics will be carried out, including the building of linear and logistic regression models, looking for an association between the questionnaire items and baseline vitamin D levels (continuous and dichotomized).

4. In 2015-16 athletes, to explore associations between the TRIAD questionnaire risk factors and subsequent stress fractures.

Exploratory descriptive and inferential statistics will be carried out, including the building of logistic regression models, looking for an association between the questionnaire items and the subsequent occurrence of a stress fracture.

j) Data Management

Data collected will include preliminary vitamin D3 serum levels, vitamin D3 serum levels in January, and vitamin D3 levels eight weeks post-supplementation. Additionally, should a stress fracture or other injury occur, the following information will be recorded: name of subject, team, date of injury, activity to cause injury, and location of injury. Each data point will be recorded on a spreadsheet and saved for final analysis. Each individual working on this study will be to date with all required CITI and HIPAA training. Only individuals directly involved with the study will have access to records for the subjects.

k) Confidentiality

Blood samples used for testing vitamin D3 levels will only be kept temporarily. Once each subject has been tested, serum levels will be recorded and samples will be disposed of following laboratory safe handling procedures. The data collected for each subject will be recorded. Any follow-up vitamin D3 tests will follow the same order. Only individuals directly working on the study will have access to the data collected. Personnel collecting blood samples for the vitamin D3 test will temporarily have access to the results for the specific subject being tested.

l) Provisions to Monitor the Data to Ensure the Safety of Subjects

Subjects in this study are only at minimal risk with regards to treatment and testing. Difficulties may arise during administration of vitamin D supplements and during blood sampling.

m) Withdrawal of Subjects

There are several circumstances that may require the subject to be withdrawn from the study without consent. Any subject that ceases activities and involvement with a given sports team will be withdrawn from the study. Likewise, if a subject develops an injury that is not within the parameters of the study will be withdrawn from the study. These injuries may include, but are not limited to, fractures to bones not defined as lower extremity, severe muscles strains that inhibit their ability to perform, ligament sprains or tears that are not directly related to bone strength in the lower extremity, and any other injury that requires the subject to stop sports related activities. Any subject that becomes pregnant during the study will be removed from the study.

Should it be deemed necessary for a subject to be withdrawn without consent, the subject will be notified and will sign a form acknowledging their release. Any data collected from the subject prior to removal will be kept for partial analysis but will not be included in the final analysis with subjects completing the entire study. Subjects being removed from the study will stop receiving supplemental treatment as part of the study, but may continue if it is beneficial for any injury or health related condition that occurs. Subjects will still be under the supervision of physicians and athletic training staff.

8) Risks to the Subjects

Subjects in the study are being examined for occurrence of stress fractures in the lower extremities. The main purpose of the study is prevention of these injuries, however they are still likely to occur. Stress fractures are the primary injury of note related to this study. Stress fractures show a range of symptoms, from mild discomfort and tenderness to the region, to severe pain and the inability for the subject to function normally. Each injury will be treated individually in order to promote the quickest and safest recovery. Being a sports related study, other injuries and difficulties that may occur outside of the parameters of the study may include torn muscles, tendons, or ligaments, ligament sprains and muscle strains, meniscus tears, bone fractures above the lower extremities, concussions, bruising, dehydration, fainting during training or events, and heat stress. These injuries will be treated by appropriate personnel, but will not be applied towards analysis in the study.

Blood sampling in order to obtain serum 25(OH) vitamin D levels can impact subjects differently. The risks are minimal, but may include slight pain or discomfort, bruising, bleeding, dizziness, becoming light-headed, or fainting. However, blood tests are a normal part of medical treatment and these risks do not put the subject in danger. Supplementation of vitamin D is considered a safe treatment as long as dosages are monitored and adequate. Doses higher than necessary may lead the subject to experience weakness, headaches, dry-mouth, nausea, or other

discomforts. Several possible difficulties may arise from the increased serum calcium levels due to vitamin D. These include heart arrhythmias, kidney problems, and over-active parathyroid function. These problems are very minimal and are unlikely to occur.

9) Potential Benefits to the Subjects

Subjects enrolled in the study will be receiving supplemental treatment for insufficient serum vitamin D levels. Benefits to the subjects may include increased structural integrity of bones, decreased likelihood of musculoskeletal injury, higher athletic performance, and increased overall bone health. It is hoped that supplementation reduces the risk of stress fracture injury, thus allowing the athlete to perform at peak levels. Many stress fractures can lead to surgical intervention, and a reduction in stress fracture rate and/or severity will reduce the need for surgery.

10) Provisions to Protect the Privacy Interests of Subjects

Information obtained from subjects will be secure and only visible to personnel directly involved with the study. Each subject will be informed of who has access to the information and data collected. The release of any data, or publication of final results, will not be linked to any personally identifiable information of a subject. Private information will not be shared with anyone outside of the researchers and will only be used to distinguish between inclusion and exclusion from the study. Subject information will not be shared between subjects in the study.

11) Compensation for Research-Related Injury

The research-related risks to the subjects are minimal. Stress fractures, or other injuries that occur during sports activities, are a risk each subject is aware of when joining the team. These are not included as a research-related risk.

12) Economic Burden to Subjects

Subjects are not responsible for any costs of treatment during the study. Vitamin D tests and treatment will be covered by funds allocated for the purpose of the study. Physicians and athletic training staff will treat injuries that develop during sports-related activities. These injuries may or may not be related to the study.

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