# Vitamin D in Orthopedics John J Cannell, MD

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#### Disclosures

- I am paid a salary to be the Executive Director of the Vitamin D Council, a 501(c)(3) non-profit.
- I receive royalties from Purity Products for a vitamin D formula with my name and likeness on it (but I don't have any of it with me).
- I have a book out on athletic performance and vitamin D, entitled Athletes Edge, Faster, Quicker, Stronger with vitamin D (but I don't have any copies with me).



 Anybody remember
 who is pictured here and where he is?

- Bob Beamon at the 1968 Olympics in Mexico City.
  - He jumped 29 ft. 2 1/2 in, bettering the existing world record by almost 2 feet.
  - He did it at latitude 19 degrees N. in the summer, where UVB radiation is very intense, after he had to acclimatize for several weeks (months?) because of the altitude.
  - He did it at altitude 7,350 feet (higher altitudes mean more intense UVB) but he encountered less wind resistance as well.

# Was it because of vitamin D?

- This session, I'm going to talk about vitamin D in orthopedics. Specifically:
  - Fracture healing, including nonunion
  - Chronic pain
  - Vitamin D in surgery and postoperative recovery
  - Sports health and athletic performance

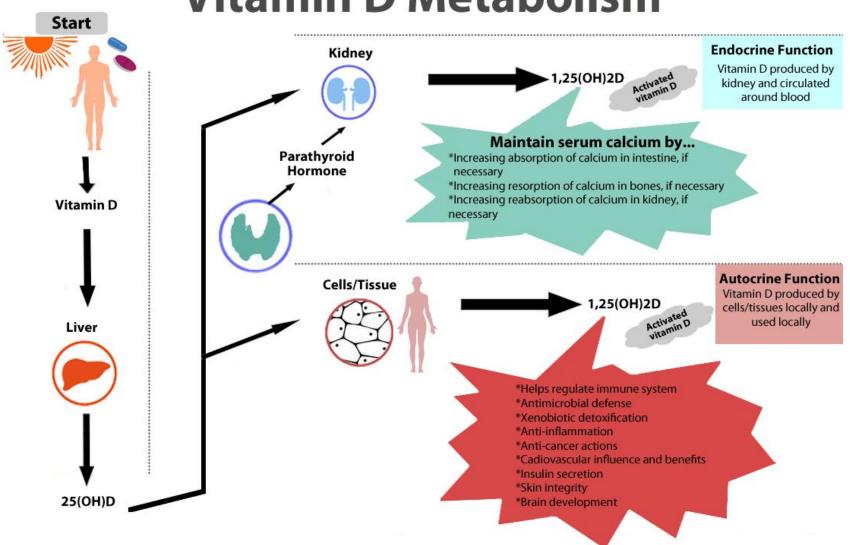
- A look again at vitamin D physiology
  - Nutritionally, humans can get vitamin D from three sources:
    - Endogenous production when skin is exposed to sun
    - Supplements
    - Found in small quantities in food, such as cold water fatty fish (salmon and sardines) and small amounts in fortified foods such as milk

- Metabolism of vitamin D
  - Vitamin D carried to liver by vitamin D binding protein (DBP), whether from skin or gut
  - Once vitamin D reaches the liver, the liver hydroxylates vitamin D into 25(OH)D.
  - 25(OH)D is how we measure vitamin D clinically.
    - 25(OH)D is often just called "vitamin D level"

- Metabolism of vitamin D
  - After the liver produces 25(OH)D, DBP takes this to the kidney and 36 other tissues all around the body.
  - The kidney pumps 1,25(OH)2D, also known as "activated vitamin D" into the blood to maintain serum calcium, the endocrine function.
  - Other 36 tissues produce 1,25(OH)2D locally or intracellulary, the paracrine and autocrine function.

- Function of activated vitamin D
  - Endocrine function
    - Kidney produces activated vitamin D, which circulates in the blood to maintain calcium homeostasis, which is why it's important for bone health.
  - Autocrine and paracrine function
    - 36 other tissues in the body produce activated vitamin D locally, which is why vitamin D is important for a host of bodily functions and diseases.

**Vitamin D Metabolism** 



- Is vitamin D's role in bone health, endocrine or autocrine function?
  - We used to think that it was exclusively endocrine function.
    - Vitamin D via endocrine function helps body absorb adequate calcium
  - However, we now believe it a combination of autocrine and endocrine function.

- What about vitamin D's role in other orthopedic aspects, endocrine or autocrine?
  - The benefits of vitamin D beyond bone health; things like sports health, balance, postoperative recovery, chronic pain, etc...are likely mostly due to its autocrine (inside cells) or paracrine (around cells) functions.
  - Vitamin D is working inside cells or closely around cells locally to exert beneficial effects and it's endocrine functions are probably not involved.

# Fracture Healing

- Does vitamin D help in fracture healing?
  - It is generally assumed that vitamin D's active form, calcitriol, works locally at the site of fracture.
  - Thus, vitamin D may have a role in fracture healing.
  - However, little data exists.

- Does vitamin D help for nonunion fractures?
  - A case report from Johns Hopkins:
    - A morbidly obese 13-year-old African-American boy who presented with sudden worsening of chronic hip pain and was diagnosed with stable, bilateral, grade-III slipped capital femoral epiphysis and severe vitamin D deficiency.
    - He was initially treated with bilateral single-screw percutaneous fixation.

Skelley NW, Papp DF, Lee RJ, Sargent MC. Slipped capital femoral epiphysis with severe vitamin D deficiency. Orthopedics. 2010 Dec 1;33(12):921. Department of Orthopedic Surgery, The Johns Hopkins University, Baltimore, Maryland, USA

- Does vitamin D help for nonunion fractures?
  - Case report continued...
    - However, after continued pain and nonunion, a right valgus subtrochanteric osteotomy was performed in association with correction of his severe vitamin D deficiency.
    - This procedure led to improvement of his hip function and successful resolution of the pain.
    - Approximately 3 months after the second operation and vitamin D supplementation, the patient had signs of union, and his weight bearing progressed without discomfort.

Skelley NW, Papp DF, Lee RJ, Sargent MC. Slipped capital femoral epiphysis with severe vitamin D deficiency. Orthopedics. 2010 Dec 1;33(12):921.

#### Does vitamin D help heal fractures?

- Case report from orthopedists in Turkey:
  - An 82-year-old woman, sustaining an intertrochanteric fracture treated with proximal femoral nail.
  - 14 months later X-rays revealed a femoral neck fracture on the operative side with no history of trauma.
  - Laboratory studies showed no significant abnormalities except for 25 (OH)D of 14 ng/ml. Total hip replacement performed.
  - Vitamin D replacement therapy begun (dose not given). Three months later, she had a "totally satisfactory" clinic result. Her 25 (OH)D level increased to 54 ng/ml. At the last visit, the patient was pain free and active in all her recreational activities.

Kayali C et al. A rare complication after intertrochanteric fracture treated with proximal femoral nail: femoral neck insufficiency fracture. Eur J Orthop Surg Traumatol. 2013 Jan 24.

#### Stress fractures

- RCT: 5201 female Navy recruit volunteers randomized to 2000 mg calcium and 800 IU vitamin D/d or placebo for 8 weeks.
- A total of 309 subjects were diagnosed with a stress fractures with incidence of 5.9% per 8 wk.
- Using intention-to-treat analysis by including all enrolled subjects, the calcium and vitamin D group had a 20% lower incidence of stress fractures than the control group

Lappe J et al. Calcium and vitamin d supplementation decreases incidence of stress fractures in female navy recruits. J Bone Miner Res. 2008 May;23(5):741-9.

#### Stress fractures

- Nested case controlled:
  - 600 female Navy recruits undergoing basic training who were subsequently diagnosed with stress fracture of the tibia or fibula compared to 600 matched controls.
  - There was approximately half the risk of stress fracture in the top (mean 50 ng/ml) compared with the bottom quintile (mean 14 ng/ml) of serum 25(OH)D concentration (odds ratio = 0.51, p ≤ 0.01).
  - Monotonic inverse dose-response gradient between serum 25(OH)D and risk of stress fracture.

Burgi AA et al. High serum 25-hydroxyvitamin D is associated with a low incidence of stress fractures. J Bone Miner Res. 2011 Oct;26(10):2371-7.

- Does vitamin D help for nonunion fractures?
  - In an in vitro study....
    - Researchers took human mesenchymal stem cells from fracture sites and demonstrated that Vitamin D and vitamin K synergistically promoted differentiation towards osteoblasts.

Gigante A et al. Vitamin K and D association stimulates in vitro osteoblast differentiation of fracture site derived human mesenchymal stem cells. J Biol Regul Homeost Agents. 2008 Jan-Mar;22(1):35-44.

- Does vitamin D help for nonunion fractures?
  - In vitro study continued...The authors state:

"Our results indicate for the first time that vitamin D3 and K in association is able to modulate in vitro the differentiation towards osteoblastic phenotype of human mesenchymal stem cells derived from fracture sites, thus offering clinicians a promising and low-cost strategy for reparative osteogenesis."

Gigante A et al. Vitamin K and D association stimulates in vitro osteoblast differentiation of fracture site derived human mesenchymal stem cells. J Biol Regul Homeost Agents. 2008 Jan-Mar;22(1):35-44.

#### My advice:

- 5,000 10,000 IU/day (NOAEL) may help fracture healing.
- We know patients are deficient in it, so important to treat it anyway.
   Also why not have nonunion patients take a product that has:
  - · calcium (dairy)
  - vitamin K2 (Natto, fermented cheese and organ meat)
  - boron (dried fruit)
  - magnesium (tree nuts and vegetables)
  - silicon (whole grains and beer)
  - "Bone Restore with Vitamin K2" (no relationship) has everything except enough D3
- Many Americans are deficient in the above four nutrients.

(case controlled cohort) Feskanich D et al. Vitamin K intake and hip fractures in women a prospective study. Am J Clin Nutr. 1999;69:74–9. (review) Nielsen F. Studies on the relationship between boron and magnesium which possibly affects the formation and maintenance of bones. Magnes Trace Elem. 1990;9(2):61–9.

(RCT) Stendig-Lindberg G, Tepper R, Leichter I. Trabecular bone density in a two year controlled trial of peroral magnesium in osteoporosis. Magnes Res. 1993;6(2 Case controlled Framingham):155–63. Jugdaohsingh R. et al. Dietary silicon intake is positively associated with bone mineral density in men and premenopausal women of the Framingham Offspring cohort. J Bone Miner Res. 2004 Feb;19(2):297-307..

#### Avoid vitamin A

- Risk of osteoporosis was ~8 times higher in women with the highest retinol levels, as compared with women with the lowest retinol levels.
- 15 nutrition experts, including Professor Walter Willett at Harvard, explicitly warned of widespread vitamin A toxicity in the USA.
- I do not recommend a lot of vitamins or minerals. Avoid extra vitamin A.
- Mata-Granados JM et al. Vitamin D insufficiency together with high serum levels of vitamin A increases the risk for osteoporosis in postmenopausal women. Arch Osteoporos, 2013
- Cannell JJ, Vieth R, Willett W, Zasloff M, Hathcock JN, White JH, Tanumihardjo SA, Larson-Meyer DE, Bischoff-Ferrari HA, Lamberg-Allardt CJ, Lappe JM, Norman AW, Zittermann A, Whiting SJ, Grant WB, Hollis BW, Giovannucci E. Cod liver oil, vitamin A toxicity, frequent respiratory infections, and the vitamin D deficiency epidemic. Ann Otol Rhinol Laryngol. 2008 Nov;117(11):864-70. Review.

# Chronic Pain

- Can vitamin D help with chronic pain?
  - Studies continually demonstrate that vitamin D can alleviate chronic pain and improve general well-being.
  - What kind of chronic pain? Studies have demonstrated vitamin D's efficacy for alleviating pain with a variety of different etiologies.

- RCT: Researchers out of Italy wanted to know if vitamin D could reduce CRP in 60 women given a bisphosphonate (zoledronic Acid).
  - They administered a onetime dose of 300,000 IU of vitamin D or placebo and then the patients were clinically evaluated for pain and CRP after 7 days.
  - Vitamin D indeed reduced musculoskeletal pain (P < 0.05).</li>
  - The CRP was about .25 on day one in both groups but by day seven
     CRP was .58 in the vitamin D group compared to 2.74 in the placebo group, a five-fold difference (P < 0.005) .</li>

Catalano A, Morabito N, Atteritano M, Basile G, Cucinotta D, Lasco A. Vitamin D reduces musculoskeletal pain after infusion of zoledronic Acid for postmenopausal osteoporosis. Calcif Tissue Int, 2012.

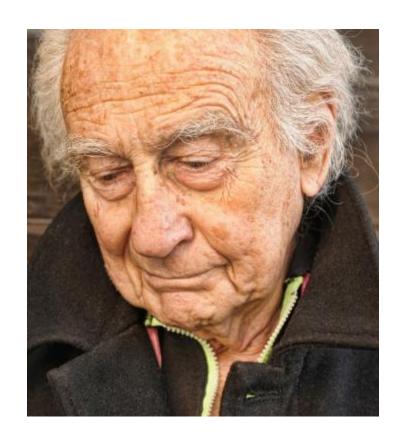
- RCT pilot: Researchers wanted to see if vitamin D could ease pain symptoms in patients with sickle cell disease.
  - They administered 4,000 to 100,000 IU of vitamin D once per week or placebo.
  - They found patients who received vitamin D experienced less "pain days" and improved general well-being.

Osunkwo I et al. High dose vitamin D therapy for chronic pain in children and adolescents with sickle cell disease: results of a randomized double blind pilot study. Br J Haematol, 2012.

- RCT: Researchers wanted to know if vitamin
   D could improve symptoms of general
   muscle pain for 84 non-Western immigrants
   living in the Netherlands.
  - They administered a onetime oral dose of 150,000 IU or placebo at baseline and 6 weeks.
  - After 12 weeks, the vitamin D group showed better improvement in ability to walk stairs (21.0% vs 8.4%, P=.008) and reported less pain (35% vs 19%, P=.04).

Schreuder F, Bernsen RMD, van der Wouden JC. Vitamin D supplementation for nonspecific musculoskeletal pain in non-western immigrants: A randomized controlled trial. Annals of Family Medicine. November 2012.

- How does vitamin D reduce pain?
  - Researchers don't know
  - Possibly due to changes in neuronal functioning
  - Possibly because it reduces inflammation
  - Possibly because it improves muscle strength



# Surgery and Postoperative Recovery

- It is thought that the body uses (metabolically clears) tremendous amounts of vitamin D when healing from orthopedic surgery.
  - Prospective study of patients undergoing knee arthroplasty.
    - Measured vitamin D levels before and after.
    - 5 days after surgery, vitamin D levels decreased by 40%.

Reid D, et al. The relation between acute changes in the systemic inflammatory response and plasma 25-hydroxyvitamin D concentrations after elective knee arthroplasty. Am J Clin Nutr. 2011 May; 93(5): 1006-11.

- Prospective cohort study: Patients' vitamin D levels measured two-weeks prior undergoing ACL surgery.
  - -Those with vitamin D levels over 30 ng/ml recovered their muscle strength after ACL surgery much better than those with levels under 30 ng/ml.

Barker T, Martins TB, Hill HR, Kjeldsberg CR, Trawick RH, Weaver LK, Traber MG. Low Vitamin D Impairs Strength Recovery After Anterior Cruciate Ligament Surgery. Journal of Evidence-Based Complementary & Alternative Medicine. July, 2011.

- Can vitamin D help in the ICU, with mortality and morbidity?
  - Multicenter prospective observational study:
    - 2399 ICU patients followed for 30 days.
    - In those with vitamin D deficiency (<15 ng/ml), odds ratio for mortality was 1.69 (p < .0001).
    - Odds ratio blood culture positivity 1.64 (p = .03).

- Can vitamin D help in the ICU, with mortality and morbidity?
  - Prospective observational study of 1,325 patients.
    - 25-hydroxyvitamin D was categorized as deficiency in 25-hydroxyvitamin D (≤ 15 ng/mL), insufficiency (16-29 ng/mL), and sufficiency (≥ 30 ng/mL).
    - The odds ratio for mortality was 1.94 (p = .01) for lowest vs highest groups.

- Can vitamin D help in the ICU, with mortality and morbidity?
  - Prospective cohort of 196 ICU patients:
    - 25(OH)D status was not significantly associated with 28-day all-cause mortality.
    - However, higher levels of 25(OH)D were associated with a shorter time-to-alive ICU discharge (HR, 2.11).
    - Deficient patients showed a trend toward a higher infection rate (OR=3.20, P = .11).

- Can vitamin D help in the ICU, with mortality and morbidity?
  - Prospective observational:
    - 130 consecutive ICU patients requiring mechanical ventilation.
    - The average survival time was 15 days for vitamin D deficient patients (< 20 ng/ml) compared with 24 days among those with "normal" (>20 ng/ml) vitamin D levels.

Arnson Y et al. Vitamin D deficiency is associated with poor outcomes and increased mortality in severely ill patients. QJM. 2012 Jul;105(7):633-9.

- Can vitamin D help in the ICU, with mortality and morbidity?
  - Prospective observational study: vitamin D status on 258 consecutive patients admitted to a surgical intensive care unit
    - Severe vitamin D deficiency was categorized as less than 13 ng/mL; moderate deficiency was categorized as 14 to 26 ng/mL; mild deficiency was categorized as 27 to 39 ng/mL; and normal levels were categorized as greater than 40 ng/mL.
    - The mean length of stay: severe vitamin D-deficient group was 13.33 ± 19.5 days versus 5.17 ± 6.5 days (P = .002).
    - The mean treatment costs were \$51,413 for the severe vitamin D-deficient group, \$28,123 for the moderate group, and \$20,414 for the mild vitamin D-deficient group (P = .027).
    - Mortality rate for the severe vitamin D-deficient group was 17 versus 11 in the moderate group (P = .125). No deaths in mild or normal categories.

Matthews LR et al. Worsening severity of vitamin D deficiency is associated with increased length of stay, surgical intensive care unit cost, and mortality rate in surgical intensive care unit patients. Am J Surg. 2012 Jul;204(1):37-43.

- Why not give 50,000 IU/day of D3 for 5 days to ICU patients?
- No one can get toxic on that dose.
- Vitamin D3, 50,000 IU capsules now available to your pharmacy through McKesson.
- Give 50,000 IU of D2 (Drisdol) if you can't find the D3.

## Athletic Performance



- How can vitamin D help in sports?
  - Help improve muscle strength
  - Help improve balance
  - Help improve neuromuscular system
  - ? Reduce incidence of injury
  - New England Patriots and ? New York Giants.
  - Cannell JJ. Athletes Edge: Faster, Quicker, Stronger with Vitamin D. 2011, Here and Now Books, USA.
  - Cannell JJ, Hollis BW, Sorenson MB, Taft TN, Anderson JJ. Athletic performance and vitamin D. Med Sci Sports Exerc. 2009 May;41(5):1102-10.

- The affects of sunlight/vitamin D go back as far as the 1930s.
  - In 1945, two Americans measured the cardiovascular fitness and muscular endurance of 11 male Illinois subjects undergoing training in an indoor physical education class, comparing them to 10 matched controls.
  - Both groups underwent similar physical training.
  - Treatment consisted of ultraviolet irradiation, given in the nude, up to two minutes per session, three times per week, for ten weeks in the late fall and winter.

Allen RM and Cureton TK. Effect of ultraviolet radiation on physical fitness. Arch Phys Med Rehab, 1945

#### Study continued...

- After ten weeks, the treatment group had a 19% standard score gain in cardiovascular fitness compare to a 2% improvement in the control students.
- As an aside, the un-irradiated control group reported twice as many viral respiratory infections as the treatment group.

- Similar UV exposure experiments continued
  - In 1952, the German sports medicine researcher,
     Spellerberg, reported on the effects of wholesale irradiation of athletes studying and training at the Sports College of Cologne including many elite athletes with a "central sun lamp."
  - The College routinely irradiated athletes in their bathing suits, on both sides of their bodies, for up to ten minutes, twice a week, for 6 weeks.

- Sports College of Cologne continued...
  - They found "convincing effects" on athletic performance and a "50% reduction" in chronic sports injuries.
  - Results were particularly impressive for swimmers, soccer, handball, hockey, and tennis players, as well as for boxers and most track and field athletes.
  - He reported that irradiation leading to burns, further irradiation of athletes having achieved peak performance, and irradiation within 24 hours of competition, all impaired athletic performance.

Spellerberg AE. Increase of athletic effectiveness by systematic ultraviolet irradiation. Strahlentherapie, 1952

- More recent studies that meet today's quality criteria show same benefit in vitamin D
  - RCT in 2012: 23 participants placed on fitness/muscle resistance program.
  - Half took 4,000 IU/day of vitamin D, half took placebo.
  - Peak power increased significantly in the vitamin D group compared to placebo after 4 weeks.

Carrilo AE et al. Impact of vitamin D supplementation during a resistance training intervention on body composition, muscle function, and glucose tolerance in overweight and obese adults. Clinical Nutrition, 2012.

- RCT out of Liverpool, United Kingdom:
  - Professional soccer players randomized over 8 weeks to take either 5,000 IU of vitamin D or placebo.
  - The authors report:
  - 5,000 IU per day of vitamin D3 for 8 weeks was associated with significant increases in:
  - vertical jump height (P = 0.008)
  - 10 meter sprint times (P = 0.008)
  - a trend for improved bench press and squat repetitions

Close GL et al. Assessment of vitamin D concentration in non-supplemented professional athletes and healthy adults during the winter months in the UK: implications for skeletal muscle function. J Sports Sci. 2012 Oct 22.

- Physical performance in young people
  - RCT: Forty healthy volunteers with hypovitaminosis D were randomized to either (60,000 IU D3/week for 8 weeks followed by 60,000 IU/month for 4 months) and calcium or placebos for 6 months.
  - The supplemented group significantly improved in handgrip strength and six minute walking distance over the placebo group.

Gupta R et al. Effect of cholecalciferol and calcium supplementation on muscle strength and energy metabolism in vitamin D-deficient Asian Indians: a randomized, controlled trial. Clin Endocrinol (Oxf). 2010 Oct;73(4):445-51.

#### Inflammatory cytokines

- Cross sectional:
  - 28 young adults were separated into vitamin D insufficient (<32 ng/mL) or vitamin D sufficient (>32 ng/mL) groups.
  - pro-inflammatory cytokines [interleukin (IL)-2, IL-1 $\beta$ , tumor necrosis factor- $\alpha$ , and interferon- $\gamma$ ] were significantly (all p < 0.05) higher in vitamin D insufficient adults.
  - Peak quadriceps power outputs correlated with 25(OH)D in vitamin D insufficient (p < 0.05) but not in vitamin D sufficient adults (p = 0.36).

Barker T et al. Circulating pro-inflammatory cytokines are elevated and peak power output correlates with 25-hydroxyvitamin D in vitamin D insufficient adults. Eur J Appl Physiol. 2013 Jan 6.

#### Balance

- Cross sectional:
  - 35 older adults with 25(OH)D levels > 30 ng/ml.
  - They tested their balance on firm surface and a 3inch thick foam pad.
  - Multiple linear regression analysis showed that serum 25(OH)D concentration was inversely associated with balance on the compliant surface (P = .02), but not on a firm surface.
  - Patients with the highest levels, around 55 ng/ml, had better balance than patient with levels around 30 – 35 ng/ml

Annweiler C et al. Higher serum vitamin D concentration is associated with better balance in older adults with supra-optimal vitamin D status. J Am Geriatr Soc. 2013 Jan;61(1):163-5.

#### Effects on Testosterone

- RCT: 40 healthy young adult volunteers with hypovitaminosis D were randomized to 60,000 IU D3/week for 8 weeks followed by 60,000 IU/month for 4 months with calcium or dual placebos for 6 months.
- No significant change between groups but,
- Compared to baseline values, significant increase in total testosterone levels (from 10.7  $\pm$  3.9 nmol/l to 13.4  $\pm$  4.7 nmol/l; p < 0.001),
- Significant increase in bioactive testosterone (from 5.21  $\pm$  1.87 nmol/l to 6.25  $\pm$  2.01 nmol/l; p = 0.001),
- Significant increase in free testosterone levels (from  $0.222 \pm 0.080$  nmol/l to  $0.267 \pm 0.087$  nmol/l; p = 0.001)
- No significant change in any testosterone measure in the placebo group.

Gupta R et al. Effect of cholecalciferol and calcium supplementation on muscle strength and energy metabolism in vitamin D-deficient Asian Indians: a randomized, controlled trial. Clin Endocrinol (Oxf). 2010 Oct;73(4):445-51.

#### Are athletes deficient?

- Most studies [a NFL team (unpublished), see Angeline et al below],
   gymnasts, ballet dancers, soccer players, even long distance runners in Louisiana] report that athletes are deficient in vitamin D.
- NFL players with low 25(OH)D levels have more injuries (unpublished), see Angeline et al below.
- I know that the New England Patriots are now all on 5,000 IU/day because they take my NSF certified product. All drug tested athletes must take an NSF certified product. NSF stands for National Sanitation Foundation not National Sports Federation.
- Manchester United uses sunbeds for their soccer players.

Angeline ME et al. The effects of vitamin D deficiency in athletes. Am J Sports Med. 2013 Feb;41(2):461-4.

Morton JP et al. Seasonal variation in vitamin D status in professional soccer players of the English Premier League. Appl Physiol Nutr Metab. 2012 May 4.

- 1968 Olympics in Mexico City
  - Record number of outdoor, not indoor, world records broken.
  - Germans and Russians, who used sunbeds until the 1980s, no longer dominated, came in 5th and 6th.
  - Does vitamin D or high altitude explain it?



Was Bob
 Beamon flying
 high on
 vitamin D or
 was it the high
 altitude?

### In summary...

- Vitamin D should be used in orthopedic practice. Why?
  - It's safe, not harmful
  - May help the healing of fractures
  - Can help alleviate chronic pain
  - Can help in ICU mortality
  - Improves athletic performance, while reducing risk of injuries

- Vitamin D should be used in orthopedic practice. How?
  - Make sure your patients are sufficient in vitamin
     D.
  - I recommend levels of 50 ng/ml.
  - This can usually be achieved by dosing with 5,000 IU/day of vitamin D3.
  - Do not use D2 (Drisdol) or ergocalciferol, use human vitamin D3 or cholecalciferol.

- Vitamin D should be used in orthopedic practice. How?
  - Knowing that vitamin D metabolically clears post-surgery, vitamin D should be dosed in higher amounts.
  - I advise 50,000 IU/day for 5 days pre and postsurgery for the deficient, which is basically everyone who is not a lifeguard or not on 5,000 IU/day.
  - 50,000 IU vitamin D3 is now available from McKesson. Ask your pharmacists to order it.

# Thank you. Questions? John J Cannell, MD

Executive Director, Vitamin D Council