Where Do We Stand on Vitamin D?

Heike A. Bischoff-Ferrari, MD, MPH

Overview

Briefly, I'll talk about vitamin D levels. When do we talk about deficiency? What are optimal levels and when do we talk about toxicity? I'll talk about the effects of vitamin D on muscles, on falls, and on fall-related fractures. I'll also talk about the recent trials on vitamin D, issues of compliance, and do we need additional calcium to vitamin D supplementation?

Slide 2. Vitamin D Levels: Deficiency, Adequacy, and Toxicity

Severe vitamin D deficiency is commonly defined as 25-hydroxy D levels below 30, or more per liter, or equivalently below 12ng/mL. Is that a level that we are still facing in daily clinical practice? Yes, we know that today about 50% of hip fracture patients admitted from home with an acute hip fracture will have levels below that, even when they are coming from home. This level is even encountered in 75% of individuals with acute hip fractures coming from nursing homes or assisted living situations. The optimal 25-hydroxyvitamin D (25-OHD) levels are suggested to be 75 nmol/L, and I will show you some of the data supporting this, and suggest this level was a
recommendation of a recent expert panel published in *Osteoporosis International* last year. The first author is Bess Dawson-Hughes. And, just to give you an idea how many individuals today will reach this optimal 25-hydroxy D level, this will be reached in about 5% of hip fracture patients and we know that only 30% of ambulatory older individuals in the US population will reach such a level today. This is based on NHANES data, and last year, a worldwide survey was presented at ASBMR on women with osteoporosis; 64% of these women did not reach the 75nmol/L. So, this is important to know. We are still encountering counting everyday vitamin D deficiency, and there is a lot of work to do to change that. As a first sign of toxicity, only 25-hydroxy D levels of more than 220 nmol/L have been associated with hypercalcemia. Just to give you an idea of the other end of the distribution, individuals who will be outside a lot exposed to the sun, such as farmers and lifeguards, will naturally achieve 25-hydroxy D levels between 135 and 168 nmol/L.

**Effect of Vitamin D on Muscle**

*Slide 3. Vitamin D*

The muscle effect of vitamin D is an exciting area because we know a lot of hip fractures may not be prevented just by improving BMD, so, it’s very nice to have something that would address muscle strength and the risk of falling.

*Slide 4. Skeletal Muscle Is a Target of Vitamin D*
As a first indicator that vitamin D has an effect on muscle, we do have the vitamin D receptor present in muscle tissue, and we know that the vitamin D receptor in muscle tissue does decline with age, suggesting that maybe age-related sarcopenia is related to vitamin D receptor status in muscle tissue.

**Physiologic Explanation**

- 1,25-hydroxyvitamin D, the active vitamin D metabolite, binds to the highly specific nuclear VDR in muscle tissue.
- This may lead to de novo protein synthesis affecting muscle cell growth.
- In one study, 1-alpha-hydroxyvitamin D increased the relative number and size of Type II muscle fibers in elderly women within 3 months.
- VDR (-/-) mice have small and variable muscle fibers, independent of secondary metabolic changes.

---

**Slide 5. Physiologic Explanation**

What is the physiologic mechanism that may stand behind the benefits of vitamin D on muscle? Some tests have been hypothesized that vitamin D, in active form the 1,25-hydroxyvitamin D, goes directly to the highly specific nuclear receptor in muscle tissue and induces de novo protein syntheses, inducing muscle cell growth, and there is one clinical study that investigated this. In this trial, the investigators, Sorensen and colleagues, gave 1-alpha-hydroxy vitamin D to osteoporotic women over 3 months, and the investigators did biopsies at baseline, and at follow-up, and they saw an increase in the number and the size of the fast type II fibers in these women, indicating that protein synthesis may really take place. A nice model indicating that vitamin D may also be important in muscle development is the vitamin D receptor knockout mouse, which has small and variable muscle fibers.

**Slide 6. What Is the Desirable Serum 25-OHD Level for Optimal Lower Extremity Function?**

---

**Slide 6. What Is the Desirable Serum 25-OHD Level for Optimal Lower Extremity Function?**
Function?

What is optimal 25-hydroxy D levels that we want to achieve for lower extremity function and strength? There are nice data coming out of NHANES III. NHANES III measured 2 tests: the 8-foot walk test and the repeated sit-to-stand test. Both of these tests are predictors of future hip fracture risks, so they are interesting to look at. What you see here in the graphs are seconds needed to perform the test plotted against 25-hydroxy D levels. And, you see here the correct equation curve adjusted for several variables that we know are associated with function. What you nicely see here is that individuals coming out of very low levels improve steeply if levels around 60 nmol/L are reached, but there is ongoing improvement thereafter and similarly receive that for the repeated sit-to-stand test. If we look at the place where we would like to be from these curves, it’s clear that we want to at least achieve the 60 nmol/L, but optimally probably between 75 to 100 nmol/L for optimal strength and function.

The Longitudinal Aging Study: Amsterdam

- Dutch men and women (n=1,351) age ≥65, confirmed these findings
- A physical performance score (chair stands, walking test, and tandem stand) improved for most from very low levels of serum, 25-OHD up to 50nmol/L, and less pronounced, but continuously, beyond 50 nmol/L

Slide 7. The Longitudinal Aging Study: Amsterdam

Very consistent data have been presented from the LASA study by Paul Lips’ group where Dutch men and women were investigated, and their physical performance core was related to 25-hydroxy D status. Again, the steepest improvement was seen up to 50 nmol/L and after that, less pronounced but continuously, there was ongoing improvement in function.
Slide 8. Evidence for Muscle Effect From RCTs Treated With Cholecalciferol Plus Calcium

So, what kind of trial data do we have that investigated the effect of vitamin D on muscle strength and function? That is a trial from Germany by Michael Pfeiffer and colleagues who tested vitamin D in a dose of 800 units combined with 1,200 mg of calcium compared to calcium alone, and the group showed that within 2 months, body sway improved by 9%. We tested the same regimen in a trial of institutionalized elderly women and saw a significant 5% to 11% improvement in muscle skeletal function over 3 months in these women.

Effect of Vitamin D on Falls

Slide 9. Forest Plot Meta-analysis: Effect of Vitamin D on Falls
This is a meta-analysis of trials that, at the time, looked at vitamin D falls as an outcome. This was published in 2004 and there are new data since then, and I will show some of the new data after that. But, a very important point that I want to make with this Forest Plot here is that you see here, all of the trials and the effect sizes. Here are the trials that gave 800 units of vitamin D, and here is the one trial with 400 units of vitamin D. And, you see here that those 2 trials showed benefit, whereas the 400 units of vitamin D were not enough to reduce the risk of falling. Overall, the pooled result showed a 22% significant reduction in the autofalling using any form of vitamin D. The subgroup analysis for 800 units of vitamin D showed a 35% reduction provided 800 units of vitamin D were given.

**Slide 10.** Short-term Effect of Vitamin D and Calcium on the Rate of Falling in Institutionalized Elderly Women

This is one of the short-term trials just to point out again that regimen combining 800 units of D with calcium compared to calcium alone. I want to point out here that this is a short-term benefit that can be achieved and this is important for especially the older population or very elderly population. So, the trial within 12 weeks showed a 49% reduction in the rate of falling.
Slide 11. Long-term Effect of Vitamin D and Calcium on the Rate of Falling in Ambulatory Older Persons

What about the long term results? This time, picking a healthy ambulatory population in Boston, these are the results from the Boston STOP IT trial with 246 women and 199 men who were followed over 3 years. They received 700 units of vitamin D plus 500 mg of calcium and the comparison was to placebo. The starting levels were much higher than in the trial that I showed before with 67 nmol/L at baseline. Even then, the women showed a 46% reduction in the autofalling with treatment over 3 years. If we looked at a subgroup of inactive women, fall reduction was even more pronounced by 65%. In the trial, the effect was neutral in men.

Slide 12. Australian Trial

These data come from an Australian trial by John Wark and colleagues. This was a randomized trial over 2 years and here frail individuals from 60 assisted-living situations and 89 nursing homes were collected across Australia, and the mean age was 83. With vitamin D supplementation of initially 10,000 units of D2 and then 1000 units daily compared to placebo, the author saw a significant 27% reduction in the rate of falling. These are data that were presented last year at the ASBMR, and put together in one trial the question: What is the optimal dose that we want to give in order to achieve fall prevention?
Slide 13. Age-adjusted Relative Rate of Falls by Vitamin D Supplement Group During the 5-Month Trial for 124 Nursing Home Residents

This was a trial also blinded over 5 months in frail older individuals at the Hebrew Rehab Center receiving different doses of D: 200 units, 400 units, 600 units, and 800 units. Compared to the lower doses, the 800 units led to a 72% reduction in the rate of falling, again supporting the idea that we have to give at least 800 units of D to achieve fall prevention.

Slide 14. Severe Vitamin D Deficiency is a Risk Factor for Repeated Falls

These are recent data, again, from LASA, the group of Paul Lips and colleagues. He was interested in whether low vitamin D levels were predictive of the risk of repeated falls, and he looked at falling 2 times or more or 3 times or more and saw that low levels predicted a 5-fold increased risk of falling 2 times and similarly 3 times. However, this effect was mostly seen in the less than 75-year-olds and was less pronounced in those older than 75.
In summary, what are important points when we look at muscle strength and vitamin D? If we give vitamin D in any form, we should expect a 20% reduction in the risk of falling. If we give 700 to 800 units of vitamin D based on the recent meta-analysis and more recent data than that, we could expect a 35% and up to 65% reduction in the autofalling, and this benefit will take place over the short term and also over longer terms. The dose of vitamin D to prevent falling should be at least 700 to 800 units. If we look at lower-extremity function, it seems to be important to achieve at least 40 nmol/L, but ideally 75 to 100 nmol/L would be most advantageous.

**Meta-analysis of Vitamin D and Fall-related Fractures**

What about vitamin D and fall-related fractures? I want to look at optimal 25-hydroxy D levels for BMD. Again, these are data from the National Health and Nutrition survey.
On the left side, the data for younger adults 20 to 49, and on the right side, the older adults. You see here BMD plotted against 25-hydroxy D levels again adjusted for several important covariants. You see here the regression curves for white individuals, Mexican Americans, and black individuals. The unshaded area marks the reference range of the DiaSorin assay being 22 to 94 nmol/L. For young Caucasian individuals, there is an ongoing increase in BMD even beyond the reference range, indicating that we really may benefit in bringing younger individuals to higher 25-hydroxy D levels for achieving early-on higher BMD. A similar, less pronounced association was seen for the Mexican Americans, less pronounced for African Americans. We have to point out though that very few African Americans reached higher levels of 25-hydroxy D in NHANES. When we look at the older adults, the picture seems very homogenous against suggesting that 25-hydroxy D levels throughout the reference range are beneficial or the higher the better in terms of BMD. When we think about where we want to be for optimal BMD, it’s at the upper end -- at least 75 to 100 nmol/L based on these data.

Effect of Oral Vitamin D on Fractures

Methods for Meta-analysis

- 5 high-quality, primary prevention RCTs for hip fracture (n=9,294) and 7 high-quality primary prevention RCTs for nonvertebral fracture risk (n=9,820)
- All trials used oral cholecalciferol
- There was heterogeneity among studies for both hip fracture and nonvertebral fracture prevention
  - Heterogeneity disappeared
    - After pooling RCTs separately with low-dose vitamin D (400 IU/day) and higher dose vitamin D (700 to 800 IU/day)

Slide 17. Methods for Meta-analysis

And in terms of fracture risk, there are data from a recent meta-analysis published in 2005. In the meta-analysis, there were 5 high-quality trials included for the primary prevention of hip fractures of about 9,000 individuals and 7 high-quality primary prevention trials for any non-vertebral fractures -- those were about 10,000 individuals. All of the trials gave all cholecalciferol or D3, and when we initially pooled all of the
trials, there was heterogeneity. One of the predefined possible factors introducing heterogeneity was dose of vitamin D. Indeed, if you then separately pooled the low-dose trials, 400 units of vitamin D, and the high-dose trials, 700 to 800 units of vitamin D, we had homogeneity.

Slide 18. Results

At the high dose, 700 to 800 units of vitamin D, the relative risk for hip fracture was reduced by 26% and that was significant in any non vertebral fracture by 23%. On the other hand, there was no significant benefit for the 400 units of vitamin D.

Slide 19. Fracture Efficacy by Achieved 25-OHD Levels

Again, we were asking what are optimal 25-hydroxy D levels when we want to achieve fracture efficacy with vitamin D? And, what you see here is the plot for the meta regression analysis. You see here plotted the relative risks achieved in the single trials that went into the meta-analysis, and you see here that they are plotted against the achieved 25-hydroxy D levels in the treatment groups of the trials. Here in yellow, you see the 400 units of vitamin D trials; the orange dots are the 800 units of vitamin D.
levels. You see here that fracture efficacy significantly improves with higher 25-hydroxy D levels achieved in the treatment groups. These higher levels were really only achieved with the 800 units of vitamin D. The 400 units of vitamin D trials usually bring you around to 60 nmol/L. With the 800 units of vitamin D, you have the hope that you bring the mean up to 75 nmol/L. And, this association was significant for both fracture sides hip and any non vertebral fracture.

**Clinical Trials**

**Recent Large Trials**

US Women’s Health Initiative (WHI) trial:
- 400 IU vitamin D plus 1,000 mg calcium per day with a mean baseline vitamin D intake of 300 IU per day did not reduce fracture risk in calcium-replete, postmenopausal women (HR=0.88, 95% CI, 0.72 to 1.06)
  - Consistent with the 2005 meta-analysis (Rockett Ferrer, JAMA)
  - Compliance was 55%
    - Baseline 25-OH D levels between 42 and 46 nmol/L
    - 28% increase according to authors with the given 400 IU vitamin D = 59 nmol/L
  - If women who ceased to adhere to the study medication were excluded
    - Hip fracture risk was reduced by 29% (HR=0.71, 95% CI, 0.52 to 0.97)

There are 2 trials not included in this meta-analysis because they were published more recently. You all know the Women’s Health Initiative (WHI) trial. Here, a large number of women were given 400 units of vitamin D plus 1,000 mg of calcium and allowed to go on with their baseline supplements. The mean intake in addition to treatment was 360 units of vitamin D per day. However, compliance was 59% and when the authors looked at those women who adhered to the study medication, the hip fracture risk was actually reduced by 29% and it was significant. Baseline levels in WHI were 42 to 46 nmol/L, and when you look closely into the papers, the authors state that in this treatment, there was an increase by 28%. So, the achieved 25-hydroxy D levels were probably around 59 nmol/L.
Another large trial from the UK Record. You heard all about that trial probably as well and that was a double-blind, randomized, control, secondary-prevention trial. All individuals had a minimal trauma fracture and the authors compared 800 units of vitamin D with or without calcium to placebo. Participants were recruited from 21 hospitals and the age was 70 and older. Eighty-five percent were women. The total number was over 5,000, and there was no significant benefit in terms of fracture prevention. However, compliance was 60% at 12 months and 47% at 24 months.

When we look at the achieved 25-hydroxy D levels, individuals started at 38 nmol/L and achieved 62 nmol/L. This change in 25-hydroxy D levels would be similar to what one would expect with 400 units of vitamin D, which indicates that compliance was an issue in the trial. How do we make sense of the results of WHI and Record? One way
to look at it is, again, we go back to the NATA regression analysis and we plot into the picture the result of WHI and Record and when we look at the achieved 25-hydroxy D levels and the associated relative risk, the fit is perfect. Here and also for Records, where we achieved 62 nmol/L, this was a non-significant risk reduction for any non-vertebral fracture. So, it is crucial where we go and where we get in terms of 25-hydroxy D levels when we are aiming for fracture reduction.

Slide 23. Hip Fracture Efficacy by Actual Vitamin D Intake: Study Medication Plus Baseline Intake in the Treatment Group Under Consideration of Compliance

This is another trial where I tried to bring in the aspects of compliance, which is, of course, a very important topic. In that plot you see fracture efficacy of the different trials that you heard of before by estimated vitamin D intake and the estimate is based on the trial intake in the different trials plus baseline intake. That was important in WHI because the women, in addition, took 360 units of vitamin D at mean times percent compliance. You see that fracture efficacy improves with higher estimated vitamin D intake. So, fracture efficacy here becomes significant if we get at least 600 units of vitamin D and improves thereafter. So, this summarizes the results of the more recent trial with the older trials.

Vitamin D Plus Calcium
Does Vitamin D Need Calcium for Fracture Efficacy?

**Slide 24. Does Vitamin D Need Calcium for Fracture Efficacy?**

Do we need calcium in addition to vitamin D? I think it is pretty much established that calcium is a good thing when we want to achieve fracture prevention, and we all know that older individuals are not only vitamin D deficient but also calcium deficient. They usually have very low intakes, but there is 1 study that I want to point out by Trivedi and colleagues in the UK. She did an elegant intervention with 100,000 units of vitamin D every 4 months and achieved good compliance; of course, and this is equivalent to a dose of 820 units/day, and this is also a large trial of 2,600 community-dwelling individuals. The relative risk of nonvertebral fractures comparing vitamin D to placebo was significant with 0.67. I also want to point out that with this level and the better compliance that was achieved in Record, the investigators found the achieved 25-hydroxy D level in the treatment proved to be 74 nmol/L. Although calcium was not given in addition to vitamin D in this trial, the investigators measured daily calcium intake, and it was 740 mg/day. So, this could mean this is the minimal dose of calcium that we need if we have compliance to 800 units of vitamin D per day.

**Does Vitamin D Need Calcium for Fracture Efficacy? (cont’d)**

  - RCTs with combined vitamin D plus calcium supplementation reduced hip fracture risk significantly
    - RR=0.82, 95% CI 0.71 to 0.94
  - While vitamin D only trials did not
    - RR=1.10, 95% CI 0.89 to 1.35
  - Authors did not analyze nonvertebral fractures
Slide 25. Does Vitamin D Need Calcium for Fracture Efficacy? (cont’d)

This is a meta-analysis by Stephen Boonen and colleagues, and I’m allowed to show this data because he already presented at the IOS in Toronto. They pooled RCTs that gave vitamin D plus calcium supplementation compared to vitamin D alone, and they found that only in the trials with calcium was there a significant reduction in the risk of hip fractures, and this meta-analysis now includes WHI and Record. Vitamin D-only trials did not achieve this benefit. Nonvertebral fractures were not addressed in the meta-analysis.

Summary

- 700-800 IU vitamin D per day is efficient
  - In reducing falls by 35% to 65% in institutionalized and ambulatory women
  - In reducing first hip fractures by 26% and any first nonvertebral fractures by 23% in compliant older individuals
- 400 IU vitamin D is not enough for fall or fracture prevention
- Compliance is important
- For fall and fracture prevention, serum levels of 75 nmol/L should be achieved for optimal health outcomes
- Hip fracture prevention may be enhanced by additional calcium supplementation

Slide 26. Summary

In summary, 700 to 800 units/day are efficient in reducing falls by 35% to 65% in both institutionalized and ambulatory older individuals. The same dose of vitamin D will reduce hip fractures by 26% and first nonvertebral fractures by 23% in compliant older individuals. There were 400 units of vitamin D, which is not enough for both fall and fracture prevention. Compliance is very important. For fall and fracture prevention, ideally 25-hydroxy D levels of 75 nmol/L should be achieved. For hip fracture prevention, the efficacy may be enhanced by additional calcium supplementation based on the most recent data from Stephen Boonen.

Question and Answer Session

Sol Epstein, MD, FRCP, FACP; Tony Keaveny, PhD; Sydney L. Bonnick, MD, FACP; Heike A. Bischoff-Ferrari, MD, MPH

Q: Is there any data on the efficacy of ibandronate versus alendronate on cortical
Sol Epstein: There are no head-to-head trials at present looking specifically at cortical bone, so the answer is no.

Q: Does alendronate have similar effect on cortical thickness as teriparatide and OPG?

Sol Epstein: This is very difficult to look at because it depends on the study population and depends on the technology that was used and the bone biopsies. Then, the question is what is more important, changes in cortical bone or stronger trabecular bone? I think that both are important, but if you had to assign an importance in terms of the type of fracture and the morbidity and mortality associated with the fracture, you would have to say certainly in the short term you would be worried about hip fracture and cortical bone because of the mortality and the morbidity.

Q: Has it been shown that femoral strength is dependent on the orientation of a fall on the greater trochanter? Did we consider this? Should the minimum strength be used to calculate the fracture index?

Tony Keaveny: We used in our calculations pretty bad case falls and we’re looking at a worse case scenario. One could alter the angle of the bone and calculate a range of strengths from them. We have done that a little bit, but on large populations. My sense is that they would be quite correlated and that probably wouldn’t give you any extra predictive power. But, it’s possible there could be some individuals that are particularly sensitive to that. Unlikely, but possible.

Sol Epstein: I’m just going to take the chairman’s prerogative because there’s something that fascinates me in what Tony said about patients in terms of if they fall below the phi or double phi, that no matter what you did to them, you may have very little chance of changing the outcome.

Q: So, the next question is if you’re going to conduct a clinical trial and you are going to use a pharmacologic agent, should you screen every patient in terms of their risk by your method instead of doing a BMD? Could you then guarantee a great success rate?

Tony Keaveny: Well of course, I disclosed that I have a company that does this kind of stuff, so pretend I don’t so I can check an answer on this. My sense is that we’ve really just seen these data, so I haven’t had an awful lot of time to sleep on this, but my sense is the optimal power of your study would be if you could preselect people. So, if you could take CT scans at baseline and based on those, select those patients who are within a bandwidth of what we consider to be the fracture threshold. In that case, you could possibly design a smaller clinical trial because there would be more advance for the individuals who are left in the study. So, I think it might be a way to consider designing clinical trials with fewer numbers of participants.

Sol Epstein: Q: So, do you think that for example non-responders, which is a huge issue, may well be because of the fact that the finite element analysis is probably, according to your method, may be needed or perhaps may be showing things which the BMD and the bone markers did not capture?
Tony Keaveny: Okay so, a couple of things there. You said the word non-responders. That's been defined as I understand as perhaps not a positive change in BMD.

Sol Epstein: Right. It’s about 3% depending upon the product. So, if you look at the FACT trial, it’s considered to be a 3% depending upon the site.

Tony Keaveny: Right. So, for example, we’ve seen on the correlation between the finite element calculations and the changes in BMD. There are some cases that show a negative BMD and we see a positive, at least, finite element strength and vice versa. A small number of cases. So, those would be kind of false-positive -- false negatives in terms of non-responders. But, the point that I was trying to show there is that it’s not an issue of not responding. You could respond very well to treatment, but it might not bring you over the fracture threshold. So, somebody who certainly responded very well, but if it were a fracture trial, if they had that fall to the side of their hip, they would still fracture. So, you know, it’s different than non-responders.

Sol Epstein: Heike?

Q: Okay, I have a question. In your meta-analysis on vitamin D and fractures, those who took 400 units of vitamin D had a much lower intake of calcium -- about 400 to 700 mg/day. Do you think this affected the results? That maybe that was a reason for decreased fracture risk that was seen with 400 units of supplementation?

Heike Bischoff-Ferrari: In the meta-analysis, we tried to address the issue of calcium, but indeed, all of the trials but one, the Trivedi trial, used calcium with the 800 to 700 units of vitamin D. For the 400 units of vitamin D, there was one trial, Paul Lips’ trial, where 1,000 mg of calcium per day was recommended. Now, I don’t know how compliance was in regard to that because intakes were not measured. So, I think there are 2 answers to that. I do think calcium is important. Stephen Boonen’s meta-analysis indicates that this is true for hip fractures. On the other hand, I think we have to see the evidence from Trivedi and colleagues where vitamin D alone seemed to work with at least a mean intake of 740 mg of calcium per day. So, in addition, all of the data that we looked at in the meta-regression indicate that really 400 units of vitamin D is not enough to achieve 25-hydroxy D levels that are associated with fracture efficacy.

Sol Epstein: Just let me expand on that. Since that original article was 7 to 8 times the therapeutic dose, in other words pharmacologic doses both of risedronate and alendronate, the bottom line is that despite the microcrack accumulation, this had no impact in terms of the bone quality or the bone strength. This has been repeated even looking at the crystalline structure under the same conditions, and crystalline structure alignment and size were no different. There are some papers here today, in fact, looking microcracks, which again, confirmed that we don’t know the significance of microcracks. They do not have impact in terms of the strength of bone, particularly as therapies are concerned. And, if you look at some of the data that were shown today and have been shown before and if you’ll look at the incidence of microcracks or the density of microcracks, you compare them only to those who had a fracture and those who did not. There is no difference in the microcrack density. So, microcracks, in fact, may not be of pathologic significance as a result of therapy and may be a normal physiologic response either to loads and a means by which old bone is removed and replaced. So, let’s get that quite clear. The clinical relevance of microcracks in terms of the therapeutic doses that are used for the bisphosphonates have not been shown to
impact on overall bone quality or fragility.

Sol Epstein: So, your question is the conversion of 1- alpha if I’m not mistaken? Or is it 25? 1,25. Do you want to answer that, Heike? I’m not quite clear.

Heike Bischoff-Ferrari: I am also not quite clear, but I think it’s difficult to compare that because 1,25-dihydroxy D production depends on the kidneys and so the substrate that you give in terms of D3 -- and the outcome of active hormone -- will depend on kidney function.

Tony Keaveny: I just want to make a comment in case anybody misunderstood. What I was saying about people who may not cross the fracture threshold might be proven not to include in a clinical trial. I am not saying for a second you should not treat them. I am just saying that in a clinical trial with a specific time frame, over the time of that clinical trial, they may not change their fracture status. But certainly, over a longer period of time, they may come down and change their fracture status. So, don’t think for a second that I’m suggesting that if you are too far gone, we forget about you.

Questioner: This question is...actually I have a small comment and a question to Dr. Bischoff. Knowing the noncompliance rate in Women’s Health Initiative study and the Trivedi study that shows quite impressive and all of the non-compliance issues that we face, I was wondering why you were not suggesting a higher dose, but less frequently, to make sure the compliance was more? It seems to me that the way of this approach is quite attractive.

Heike Bischoff-Ferrari: Oh yes. And you know, I totally agree. I think that we do need more data on less frequent dosing of vitamin D with higher doses because I think that is really an important issue in improving compliance, and that’s the way to do it according to what we’ve seen with Trivedi. I totally agree.

Questioner: I have a follow-up question. When I looked at some time ago on the PTH levels and people with low vitamin D levels defined as less than 50 ng/mL, only 50% had actually had increased PTH levels. Assuming that the vitamin D has some effect on the muscle, my question to you is that does it have a direct effect on bone cell function, ie, osteoblasts, without going through the calcium absorption and so forth?

Heike Bischoff-Ferrari: The vitamin D?

Questioner: Yes. A direct bone cell effect.

Heike Bischoff-Ferrari: So, you’re saying that because PTH a lot of times is in the normal range while 25-hydroxy vitamin D is lower. How does it work? Well, I think one important point is, and we showed that in a trial...not in a trial but in an observational study that a lot of times PTH levels may be very low in older individuals with low mobility because you will have increased calcium mobilization from the skeleton due to immobility. Then PTH levels come down and we have seen that and others. So, you have to take that into consideration when this occurs.

Questioner: Do you think there is any effect of vitamin D directly on osteoblast
function?

Sol Epstein: He’s asking is there a direct effect of vitamin D or 25 without going through to form 1,25-dihydroxy with the vitamin D receptor, in other words?

Heike Bischoff-Ferrari: So, the 25-hydroxy D -- does it have an effect on osteoblasts as opposed to the active hormone or...

Sol Epstein: Well, he’s asking does vitamin D-2, D-3, does it have a direct effect without going through the transformation to the active metabolizers?

Heike Bischoff-Ferrari: There is some evidence that even 25-hydroxy D does go to the vitamin D receptors in a higher concentration.

Sol Epstein: Can I make a comment before you leave? I don’t know if you are aware of the publication, I think it came from David Hoskin, that the nonresponder in terms of the PTH -- may have an associated magnesium deficiency. He’s also described the so-called “pseudo-resistant” particularly in the elderly to the administration or the lower levels not causing the appropriate or disproportional inappropriate rise in PTH may be much lower than expected for the level of 25. So, that may be another governing factor in terms of why we’ve not seen the proportionate PTH increases particularly below 20, or round about 20, and they may have other issues, particularly a magnesium deficiency.

Questioner: Well, I was making that comment. I don’t want us to get trapped into the notion that all adverse effects of vitamin D on bone, for example, are entirely mediated by either 1,25 in the kidney or the calcium absorption in the intestine. Perhaps there may be direct effect of vitamin D itself on osteoblast cells. That’s what I was trying to get at.

Sol Epstein: Okay

Questioner: Heike, I would like to follow up on your comment concerning low calcium intake and relatively low vitamin D intake, and I missed in your concept the Larsen study from the Leif Mosekilde group where 400 units of vitamin D together with 1,000 mg of calcium have indeed been shown to reduce severe falls as well as fractures. This brings me to the point that when you have a relatively low vitamin D intake, you can overcome this to a certain degree by a high calcium intake.

Heike Bischoff-Ferrari: I know the Dawson trial was not the classically randomized trial. It was more like a pragmatic intervention, but still...

Questioner: It was a large population-based trial.

Heike Bischoff-Ferrari: Yes. I think this is an unanswered question. How much D and how much calcium do we need in terms of fracture prevention? From our meta-analysis, 400 units are not enough, but 800 seem to be sufficient for fracture reduction. The question with calcium is, I think, unsettled.
Questioner: If you just look at the vitamin D intake, you are all right. There’s no doubt. But, I think you have to add or to include the calcium intake in your concept.

Sol Epstein: May I just take the chairman’s prerogative? I think there was a study showing that in terms of the PTH regulation that it will store vitamin D and not the calcium. So, if you increase your calcium to 1,500 but your vitamin D levels were still suboptimal, the effect on the parathyroid gland was not as robust as for example, until you replace the vitamin D. That is one way of answering the question what is an optimum amount of vitamin D and vitamin D and calcium. But, I think the 2 of you look like the sides are softening, and you may spend the rest of the night debating this. I’m just going to ask Sydney Bonnick, who’s been sitting here, a very pertinent question from a poster which was up yesterday by Ken Faulkner, which I think is extremely sort of germane to what we’ve been discussing. Particularly, you talked about the variability, and I see you went to great lengths to mention which was a Hologic; and, it’s very obvious that you are pointing to something, which was a Hologic and which a Lunar stroke GE. I’m sure you are aware that Ken Faulkner has a poster showing that it’s not good science if you’re doing a trial to look at HSA, particularly in terms of the limitations that you said if you mix and match machines in order to determine some of the parameters. Would you like to comment?

Sydney Bonnick: Yes, Ken’s poster yesterday used the Lunar...the GE Healthcare Lunar. But, using the Prodigy and then the Hologic DXA device, and on both though, using what Ken referred to as the Johns Hopkins approach, which is the methodology developed largely by Tom Beck, to analyze hip structural parameters in a cohort of individuals. And, what he showed is essentially the values that he obtained using the Prodigy and the Johns Hopkins HSA approach versus the Hologic devices and the Johns Hopkins HSA approach were very poorly correlated. The conclusion was, of course, that you really shouldn’t attempt to combine these values within a clinical trial that were coming from these different devices. Now, Dr. Beck would be the first one to tell you that there is absolutely an issue with taking the image data from the Prodigy file format and applying his HSA algorithms. Actually when Dr. Beck was first developing all of this, he was actually using an old clunky Lunar DPA device -- a dual photon device. Then when DXA became available, the algorithms were further developed for and enhanced essentially for Hologic DXA devices, and that is largely where the work has been done. He is able, relatively easily though, to take file formats from Lunar DPX line and apply his HSA algorithms and derive the various structural parameters. But, as any of you who own a Lunar device know, if you went from a DPX series device to a Prodigy, you know that the file formats changed drastically such that, in fact, you could not analyze a conventional DXA scan that was acquired on a DPX device. You couldn’t analyze it on your brand new Prodigy. Alas, I found that out very personally. But, it’s because the file format changed dramatically, and the real problem is with the Prodigy file format specifically, not with Lunar devices generally. It should be said that Dr. Beck asked Lunar for assistance in handling the Prodigy file formats. Understandably and not surprisingly, because there are proprietary issues involved, Lunar could not provide him that assistance, so he’s left to his own devices to try to deal with that issue. I did make a point in the data that I was showing to try to let you know what data were coming from solely Hologic devices using Beck’s methodology, or where there was a combination of devices using Beck’s methodology, or where it was a Lunar device using Lunar’s HSA approach, which is different.

Sol Epstein: I think you made it quite clear to delineate which of the machines. I think your husband has got a message across to the audience here and the question is should older men take 800 IU of vitamin D?
Heike Bischoff-Ferrari: In terms of data for healthy communities trialing older men for the risk of falling, we did see a neutral effect of 800 units, and 700 units of vitamin D in all men. However, when we looked at men’s adherence to treatment and being below the median of physical activity, we could not exclude a benefit. Then in the Trivedi trial, a mean substantial number of men were included, and there seemed to be a similar benefit in fracture prevention in men and in women. So, I would say yes, take it. Also, for other health benefits I have not enough time to show that kind of data, but I think it makes sense to take vitamin D at least when you are 60 and older and probably younger as well.

Questioner: This is for Sydney. I know this data...the positional problems so that it is the New England Journal of Medicine paper measured the radial diameter and so forth and we had some data a number of years ago on a metacarpal measurement, which is subject to much less positional errors. I wonder whether those applications would be slightly better or good or indifferent.

Questioner: I'm asking...I know hip structure analysis is subject to some positioning errors, and I know that the New England Journal of Medicine...David Burrough did the study on the radius and we have some data on a metacarpal. I wonder whether a metacarpal would provide better than the hip would.

Sydney Bonnick: The problem with position with HSA with DEXA really has to do with the fact that values that you obtain are valid for the image plane only and that would not change if we are utilizing a 2-dimensional technique like DEXA regardless of the skeletal side at which we are looking.