Amended (3) Study Proposal

Zurich Disability Prevention Trial

Monthly vitamin D to improve vitamin D status and maintain function in pre-frail older individuals living at home (KEK – 39/09)

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Version 6, Place/Date: Zurich, 24.10.2011  Prof. Dr.med. H.A. Bischoff-Ferrari, DrPH
STRUCTURED PROPOSAL

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Time line

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## SYNOPSIS

| Sponsor | Prof. Heike A. Bischoff-Ferrari, MD, DrPH  
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8091 Zurich  
Switzerland |
<table>
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<tbody>
<tr>
<td>Title</td>
<td>Zurich Disability Prevention Trial (KEK – 39/09)</td>
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</table>
| Short Description | Monthly vitamin D to improve vitamin D status and maintain function in pre-frail older individuals living at home  
3 arms – parallel group design:  
(1) **Active I (n=70):** monthly dose of 60'000 IU vitamin D3  
(2) **Active II (n=70):** monthly dose of 24'000 IU vitamin D3 plus monthly dose of 300 mcg of 25(OH)D.  
(3) **Control (n=70):** monthly dose of 24'000 IU vitamin D3 |
| Setting | Ambulatory, community-dwelling adults age 70 years and older with a history of a fall in the previous 12 months (pre-frail population) |
| Study Design | • 12 month, double-blinded randomized controlled trial (month 0-12)  
• 6 month open follow-up (month 13-18) – switch to daily vitamin D  
• **Post-trial cohort: after 18 month of follow-up, all participants will participate in the life-long Zurich Fall Cohort** |
| Endpoints | Primary endpoints  
1. We test the effectiveness of monthly high-dose vitamin D₃ supplementation (active groups I and II) compared to monthly standard vitamin D₃ supplementation in lowering the risk of functional decline (proportion of individuals with functional decline based on binary repeated measure assessment across 4 lower extremity tests)  
2. Improving 25-hydroxyvitamin D levels in late winter (season of lowest expected 25(OH)D level) and late summer (season of highest expected 25(OH)D level) – Percent of individuals reaching desirable 25-hydroxyvitamin D levels of at least 75 nmol/l in late winter and in late summer.  
Secondary endpoints  
We test the effectiveness of monthly high-dose vitamin D₃ supplementation (active groups I and II) compared to monthly standard vitamin D₃ supplementation in  
• improving dual task performance (cognition)  
• improving muscle strength  
• reducing muscle pain  
• improving blood pressure  
• reducing the rate of falling  
• improving bone density  
• improving muscle mass, reducing the risk of sarcopenia  
• lowering health care utilization (rate of hospital admission /cost / improving quality of life)  
• decreasing bone resorption  
• decreasing upper and lower respiratory infections (any infection, infections that
<p>| lead to inpatient care |  |</p>
<table>
<thead>
<tr>
<th>Measurements</th>
<th>Primary endpoints</th>
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<tbody>
<tr>
<td></td>
<td>• proportion of individuals with functional decline based on binary repeated measure assessment across 4 lower extremity tests (Knee extensor and flexor strength, Timed-up and go test, Repeated sit-to-stand test)</td>
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<tr>
<td></td>
<td>• 25-hydroxyvitamin D level</td>
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<tr>
<td>Secondary endpoints</td>
<td>(1) Safety at baseline, 2 weeks, 6 months, 12 months</td>
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<tr>
<td></td>
<td>• Serum calcium adjusted for albumin</td>
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<td>• Serum creatinine</td>
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<td>• Urinary calcium/creatinine ratio</td>
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<td>(2) Measures for secondary endpoints</td>
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<tr>
<td></td>
<td>• Balance/Gait while walking combined with a cognitive task</td>
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<td>• Short Physical Performance Test Battery</td>
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<td>• McGill pain map</td>
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<td></td>
<td>• Blood pressure</td>
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<td></td>
<td>• Falls: diary, monthly phone calls, and a hotline</td>
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<tr>
<td></td>
<td>• grip strength</td>
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<td></td>
<td>• Bone density and muscle mass (body composition)</td>
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<td></td>
<td>• Health care utilization: in collaboration with insurance companies for outpatient and inpatient health care costs. EuroQol. Rate of hospital admission (fall-related injury, infections, other). By monthly phone calls</td>
</tr>
<tr>
<td></td>
<td>• Serum N-telopeptides and other markers of bone remodeling</td>
</tr>
<tr>
<td></td>
<td>• Upper and lower respiratory tract infections, any infections, infections that lead to inpatient care: monthly phone calls</td>
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</table>

| Number of Participants | 210 (70 in each of the 3 treatment groups; 2 active groups and 1 control) |

<table>
<thead>
<tr>
<th>Time Line</th>
<th>Recruitment December 2009 – March 2010</th>
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<tr>
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<td>First screening: December 2010</td>
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<td>Baseline: January – May 2010</td>
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<td>End of double-blind trial period: May 2011</td>
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<td></td>
<td>End of open follow-up: November 2011</td>
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<td>Start of life-long cohort: July 2011</td>
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<td>Treatment duration with study medication: 12 months with the investigational product followed by a 6 months open follow-up with Vi-De 3° for all participants</td>
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</tbody>
</table>

| Inclusion Criteria | • Age 70+ |
|                   | • Fall in the last 12 months before screening (with or without a fracture) |
|                   | • Living at home (community-dwelling) |
|                   | • Men or women |
|                   | • Mobile with or without walking aid – have to be able to use public transportation to attend the clinical visits at the trial centre |
|                   | • Score of at least 27 at the screening Folstein Mini Mental test |
|                   | • Patient understands the study procedures, alternative treatments available and risks involved with the study, and voluntarily agrees to participate by giving a written informed consent. |
|                   | • Patient meets the entry minimal requirements based on routine clinical laboratory safety screening tests and the Folstein mini mental status (score 27+ required) performed at the Screening Visit . |
|                   | • Patient is willing to perform all study tests, attend all required office visits, and provide blood and urine samples. |
### Exclusion Criteria

- Serum calcium adjusted for albumin of > 2.6 mmol/l
- Pathologic fracture in the last year (except for fractures due to osteoporosis)
- Chemo therapy / Radiation due to cancer in the last year
- Treatment which has an effect on calcium metabolism (e.g. PTH, calcitonin, chronic cortisone intake > 5mg/day in the last 12 months (except for inhalation and sporadic infiltration))
- Oral vitamin D intake of more than 800 IU per day
- Unwilling to stop calcium supplementation and vitamin D supplementation during the trial (maximal calcium supplement intake 250mg/d; maximal additional vitamin D supplementation 200 IU/day, if medically indicated or the patient withdraws his declared intention to stop vitamin D supplementation during the study)
- Severe visual or hearing impairment
- Unwilling or unable to take study medication
- Diseases with a risk of recurrent falling (e.g. Parkinson’s disease/syndrome, Hemiplegia after stroke, symptomatic stenosis of the spinal canal, polyneuropathy, epilepsy, recurring vertigo, recurring syncope)
- BMI ≥ 40
- Estimated creatinine clearance < 15 ml/min (estimated Creatinine Clearance Cockroft and Gault)
- Malabsorption syndrome (celiac diseases, inflammatory bowl disease)
- Diseases that may enhance serum calcium: sarkoidosis, lymphoma, primary hyperparathyroidism
- Kidney stone in the last 10 years
- Abnormal indices of calcium metabolism, uncontrolled hypocalcemia.
- Patient heavily consumes alcohol containing products defined as greater than (> 3 drinks (beer, wine, or distilled spirits) of alcoholic beverages per day.
- Patient is unlikely to adhere to the study procedures, to keep appointments, or is planning to relocate during the study.
- Patients who are planning a stay in a “sunny” location (e.g. winter sun resort) for more than two months per year
- Medication which has an effect on 25-hydroxyvitamin D level (e.g. certain anticonvulsants (e.g. Phenobarbital, Carbamazepin, Phenytoin))
- M. Paget (Ostitis deformans)
- Inflammatory arthritis (e.g. rheumatoid arthritis, reiter syndrome, psoriasis arthritis)
- Participation in a study in the last 6 month, except for studies without drug-application, or any influence of the study—medication can be excluded

### Visits

<table>
<thead>
<tr>
<th>Visit</th>
<th>Details</th>
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<tbody>
<tr>
<td>Visit 1 (= Screening)</td>
<td>Day $T_0 - X$ (X ≤ 3 months)</td>
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<tr>
<td>Visit 2 (= Baseline)</td>
<td>Day 0 (≈ January 2010)</td>
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<tr>
<td>Visit 3 (= Safety check)</td>
<td>Day $T_0 + 14$ days + 0/- 7 days</td>
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<tr>
<td>Visit 4</td>
<td>Day $T_0 + 6$ months + 14/- 7 days</td>
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<tr>
<td>Visit 5</td>
<td>Day $T_0 + 12$ months + 14/- 7 days</td>
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<tr>
<td>Visit 6</td>
<td>Day $T_0 + 18$ months +/- 14 days</td>
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</table>

### Methods /statistics

For detailed method description see study protocol

### Investigational supplements

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<thead>
<tr>
<th>Investigational supplement</th>
<th>Vitamin $D_3$</th>
<th>and</th>
<th>$25(OH)D$</th>
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<tr>
<td>Commercial name:</td>
<td>N/A</td>
<td>and</td>
<td>N/A</td>
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<tr>
<td>provided by:</td>
<td>Dr. Wild &amp; Co AG, Basel</td>
<td>and</td>
<td>DSM Nutritional Products Ltd, Kaiseraugst</td>
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<td>Producers:</td>
<td>MIPHARM</td>
<td>and</td>
<td>DSM Nutritional Products Ltd, Kaiseraugst</td>
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<td>Application schema of investigational supplements</td>
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<tr>
<td><strong>Active group I</strong></td>
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<td><strong>Active group II</strong></td>
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<td>Investigational supplement: Vitamin D₃</td>
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<td>Dose: 24000 IU</td>
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<td>Application: capsule</td>
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<td>Frequency: monthly</td>
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<td>Treatment duration: 12 months</td>
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<td>AND</td>
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<tr>
<td>Investigational supplement: 25(OH)D</td>
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<td>Frequency: monthly</td>
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<td>Treatment duration: 12 months</td>
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<tr>
<td><strong>Control group</strong></td>
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<td>Frequency: monthly</td>
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<td>Treatment duration: 12 months</td>
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BACKGROUND

Vitamin D is now emerging as perhaps the single most important public health strategy of fall and fracture prevention among older individuals. However, recent data indicates that sufficient dosing and adherence is pivotal to its efficacy on fall and fracture prevention. Furthermore, there is increasing evidence that higher 25-hydroxyvitamin D levels between 75 to 100 nmol/l may not only be warranted for anti-fracture efficacy of vitamin D, but also be protective against a number of adverse health outcomes, including declining physical function, cancer, cardiovascular health, periodontal disease, and mortality[1, 2]. Vitamin D supplementation is an inexpensive and safe intervention that could significantly reduce the burden of morbidity and mortality in older persons.

Older individuals are particularly susceptible to vitamin D insufficiency as a result of reductions in mobility, time spent outdoors, sun exposure (contributed to by increased skin coverage), and impaired skin response to UVB radiation[3]. At the same time, the residual lifetime risk of fracture has been estimated to be 44-65% for women and 25-42% for men age 60 years or older [4, 5]. Falling is the primary risk factor of fractures among older individuals[6] and an independent predictor of functional decline[7]. 30% of community-dwelling individuals fall each year when they are 65 years of age and 50% when they are 80. 9% of falls need medical care, and 40% of all nursing home admissions are due to a fall[8].

Vitamin D supplementation of at least 700-1000 IU vitamin D per day among older persons could reduce hip fractures by 18%[9], non-vertebral fractures by up to 33%[9] and falls by up to 26%[10].

Notably, anti-fracture and anti-fall efficacy of vitamin D is absent with a low dose of vitamin D or low adherence to an adequate dose of vitamin D[9, 10]. Low adherence has been identified as a major concern with daily vitamin D supplementation. In fact, recent studies show that adherence to the daily vitamin D regimen may be less than 50% and even worse if combined with calcium supplements[11].

In order to assure optimal vitamin D status needed for anti-fall and anti-fracture benefits of vitamin D, an intermittent monthly oral intake of vitamin D may improve adherence among older individuals and simplify application of vitamin D supplementation in nursing homes. Thus, intermittent dosing may be a significant public health improvement and facilitate optimal care of older individuals in nursing homes.

Ideally, the dosing of a monthly oral treatment with vitamin D would be high enough to bring most individual into the desirable range of at least 75 nmol/l throughout the year. 2000 IU per day or equivalently, 60'000 IU once a month, have been suggested as the target dose that may reach this goal safely among the majority of adults[12]. Given the long half-life
of vitamin D3 (> 1.5 months), longer treatment intervals are possible, and the monthly interval may be most promising ensuring a stable 25-hydroxyvitamin D serum concentration.

According to several studies and a recent pharmacokinetic study performed by our group, the most efficient vitamin D metabolite to enhance 25-hydroxyvitamin D serum concentrations may be 25(OH)D given orally. In the same pharmacokinetic study, 25(OH)D was safe, and a more pronounced benefit on muscle strength and blood pressure was suggested compared to the same dose of vitamin D3 (Attachment 1 and 2).
OVERVIEW
Aims - Hypotheses - Study Design - Setting- Assessments

We propose a double-blind, randomized controlled trial to test the effectiveness of:

(1) **Active I (n=70):** monthly high-dose vitamin D₃ supplement dose (60'000 IU/month, equivalent to 2000 IU daily),
(2) **Active II (n=70):** or a monthly standard vitamin D₃ supplement dose combined with 25(OH)D (24'000 IU/month, equivalent to 800 IU daily PLUS 300 mcg 25(OH)D, equivalent to 10 mcg per day)
(3) **Control (n=70):** compared to a standard vitamin D₃ supplement dose (24'000 IU/month, equivalent to 800 IU daily)

All individuals will be advised to consume calcium from natural food sources in a daily dose of 600-800 mgs a day, including milk products. Maximal intake of supplemental calcium is restricted to 250 mg per day.

**PRIMARY ENDPOINT**
(1) **lowering the risk of functional decline,**
(2) **Improving 25-hydroxyvitamin D levels** in late winter (season of lowest expected 25(OH)D level) and late summer (season of highest expected 25(OH)D level) – Percent of individuals reaching desirable 25-hydroxyvitamin D levels in late winter and in late summer.

**SECONDARY ENDPOINTS**
We test the effectiveness of monthly high-dose vitamin D₃ supplementation (active groups I and II) compared to monthly standard vitamin D₃ supplementation in

(3) **improving dual task performance,**
(4) **improving muscle strength**
(5) **reducing muscle pain,**
(6) **improving blood pressure,**
(7) **reducing the rate of falling**
(8) **improving bone density**
(9) **improving muscle mass, reducing the risk of sarcopenia**
(10) **lowering health care utilization / improving quality of life**
(11) **decreasing bone resorption**
(12) **decreasing upper and lower respiratory infections**

**SAFETY:**
Serum calcium adjusted for albumin, serum creatinine, urinary calcium/creatinine ratio at 2 weeks, 6 months, and 12 months follow-up in all participants.
SETTING
210 ambulatory, community-dwelling adults age 70 years and older with a history of a fall in the previous 12 months (pre-frail population).
HYPOTHESES:

**Primary 1:** Our primary hypothesis I is that there will be a higher proportion of individuals with functional decline (binary repeated measure assessment across 4 lower extremity tests) in the control group compared to both active groups.

**Primary 2:** Our primary hypothesis II is that both active groups are superior to the control group in enhancing serum 25-hydroxyvitamin D levels in both late summer and late winter. In a secondary analysis, we will also test whether the combination group (active group II) is superior to the high-dose vitamin D3 supplement dose (active group I) in enhancing serum 25-hydroxyvitamin D levels in both late summer and late winter.

**Secondary:** Our secondary hypothesis are that both active groups are superior to the control group in improving dual task performance, reducing muscle pain, improving blood pressure, reducing the rate of falling, improving bone density, improving muscle mass, and reducing the risk of sarcopenia. Finally, we hypothesize that both active groups contribute to lower health care utilization, less bone resorption, and lesser upper and lower respiratory tract infections compared to the control group.

**Safety:** We hypothesize that both high-dose (active groups I and II) and standard dose monthly vitamin D supplementation is safe with respect to hypercalcemia, kidney function, and hypercalcuria.

**ASSESSMENTS**

Dual task performance will be assessed with a GaitRite system that assesses digitally gait patterns while walking combined with a cognitive task (i.e. ability to walk and count). Lower extremity function will be assessed with the timed-up and go test and the repeated sit-to-stand test, and the Short Physical Performance Battery. Pain will be assessed with the McGill pain map, blood pressure will be assessed with a standardized protocol, and falls will be assessed with 3 methods (diary, monthly phone calls, and a hotline). Muscle strength will be assessed as knee extensor and flexor strength, as well as grip strength. Bone density and muscle mass (body composition) will be assessed by DEXA. Several published definitions for Sarcopenia will be tested as well as a composite assessment using both muscle strength (quality) and muscle mass (quantity). – The definition of sarcopenia is being evaluated in a separate project by our group. Health care utilization will be assessed in collaboration with insurance companies for outpatient and inpatient health care costs. In addition, health care utilization will be assessed by monthly phone calls. Bone resorption will be assessed with serum N-telopeptides and other markers of bone remodeling. Rate of upper and lower respiratory tract infections will be assessed by monthly phone calls.
OPEN DAILY SUPPLEMENTATION FOLLOW-UP MONTH 13-18
Finally, after the double-blind 12-month trial phase is finished, all individuals will stop their monthly vitamin D and will switch to daily 800 IU vitamin D3 for 6 months to assess in an open follow-up trial phase:

1. preference of the monthly vitamin D versus daily vitamin D
2. side effects monthly vitamin D versus daily vitamin D
3. adherence to daily vitamin D
4. efficacy in maintaining 25-hydroxyvitamin D and lower parathyroid hormone levels (calcium metabolism) – we compare the August under monthly vitamin D supplementation with the August under daily vitamin D in the same individuals

LONG-TERM FOLLOW-UP: MONTH 19+
After 18 month of follow-up participants will be followed in the life-long Zurich Fall Cohort with 6-monthly telephone assessments of function, adverse events (falls, fractures, hospital admission, nursing home admission), and need of care.
STUDY SCHEMA

There will be a double-blinded phase for 12 months with 5 visits to the study center (1 safety visit at 2 weeks after treatment start). Then the monthly dose will be stopped followed by a 6 month open follow-up with daily vitamin D drops in all participants. The final visit at month 18 will include a follow-up 25-hydroxyvitamin D assessment (30 patients – 10 randomly selected patients from each of the original monthly groups) or a phone call (for those not selected for the final visit). Throughout the course of the trial and the open follow-up, falls will be assessed by a diary and a hotline. In addition, we will place monthly phone calls to assess falls and ensure the monthly and the daily dose has been taken during the double-blinded trial phase and the open follow-up, respectively.

After 18 month of follow-up, all participants will participate in the life-long Zurich Fall Cohort with 6-monthly telephone assessments of function, adverse events (falls, fractures, hospital admission, nursing home admission), and need of care. The cohort extension is not illustrated in the study schema.
STATE OF THE ART

Today, there is a wide gap between evidence-based recommendations for vitamin D and the care patients receive (Attachment 3 and 4). One component of this gap is lack of implementation or low adherence to daily treatment, especially if vitamin D is combined with calcium supplementation. Another component is that alternative supplementation strategies are missing.

This trial has been stimulated by a clinical need to overcome barriers of successful vitamin D supplementation among older individuals (nationally and internationally[13]). The results of the trial will offer the possibility of a change in our prevention strategy with vitamin D from daily to monthly and from daily with calcium supplementation to monthly with natural sources of calcium, preferably milk.

This trial will also test an enhanced supplementation strategy (active group II) with the addition of 25(OH)D to a standard monthly vitamin D3 dose. This could be a step up option in clinical practice for high risk subgroups (Attachment 1 and 2).

We have recently documented that severe vitamin D deficiency is highly prevalent in community-dwelling and institutionalized older individuals admitted to acute care with a hip fracture in Switzerland (Attachment 4[14]). More than 50% of older individuals admitted from home and 75% of older individuals admitted from institutions had severe vitamin D deficiency of less than 30 nmol/l. Less than 5% reached desirable 25-hydroxyvitamin D levels of at least 75 nmol/l and less than 10% had any amount of vitamin D supplementation including low doses from multivitamins[14]. Even during summer months, 25-hydroxyvitamin D levels did not increase into the desirable range for fracture prevention (Attachment 4).

Our Swiss data regarding the high prevalence of vitamin D deficiency among older persons is consistent with the literature world-wide and experts around the world are puzzled why vitamin D as an evidence-based prevention strategy for falls[10] and fractures[9] is insufficiently implemented and guidelines are not followed, despite its low cost and good tolerability.
Today, Vitamin D supplementation options in Switzerland are limited. Most vitamin D supplements available in Switzerland are combined with calcium. In clinical practice, the combined supplements have 2 important limitations, which are low adherence and side effects (a. and b.). In addition, calcium supplementation may not be needed if vitamin D supplementation is sufficient (c.) and natural calcium sources such as milk may be superior to calcium supplements as milk also provides protein needed for bone and muscle health (d.).

(a.) many older individuals with severe vitamin D deficiency need more than 800 IU vitamin D. With the combined vitamin D plus calcium product, the dose of vitamin D could not be doubled, as doubling of the calcium dose to 2000 mg of calcium / day would be too high.

(b.) Many older individuals have gastro-intestinal side effects from calcium supplements, which further reduces their adherence to vitamin D supplementation if combined with calcium.

(c.) Our new meta-analysis on vitamin D and fracture reduction published in Archives of Internal Medicine in March 2009, shows that vitamin D in a sufficiently high dose of at least 700 IU vitamin D reduces the risk of non-vertebral fracture independent of additional calcium supplementation (abstract see as attachment 5). Consistently, a calcium sparing effect of vitamin D has been described in the literature[15, 16]. In one study, individuals with mean 25-hydroxyvitamin D levels of 87 nmol/l had a 65% higher calcium absorption compared to individuals with a mean of 50 nmol/l[16]. Recently, a population-based study from Iceland showed that as long as 25-hydroxyvitamin D levels are above 25 nmol/l, a total calcium intake beyond 800 mg per day does not further improve calcium metabolism[15]. Which we confirmed in a larger population-based study with hip bone density as the endpoint[17].

(d.) In our meta-analysis of calcium alone compared to placebo published in 12-2007 (attachment 6), calcium supplementation alone did have a neutral effect on non-vertebral fractures and increased hip fracture risk significantly by 64%. Mechanistically, commonly used calcium supplements with a carbonate or citrate component have been shown to shift older individuals into phosphate deficiency[18, 19] and induce bone loss[18, 20, 21]. In order to build calcium into bone, a calcium – phosphate product is needed, which may be disturbed by the described calcium supplement induced phosphate malabsorption. This may be especially critical in frail older individuals at risk for both hip fracture and phosphate deficiency due to low protein intake. Milk as a natural calcium source provides phosphate (via protein) and calcium.

The main Swiss product that provides oral vitamin D without calcium are the ViDe3 drops by WILD. However, in clinical practice, the product has limitations as older individuals often have impaired vision and have difficulties dropping an exact amount. Similarly, nursing staff are often unwilling to prepare these drops as it is too time consuming. One product for high-dose intra-muscular application of vitamin D (300’000 IU per
shot) is invasive plus several studies suggested that intra-muscular vitamin D is **poorly absorbed** plus no classically randomized trial showed fracture reduction with high-dose intra-muscular vitamin D[22].
Adherence is important to yield anti-fracture and anti-fall benefits of vitamin D. Adequate vitamin D plays a critical role in the maintenance of musculoskeletal health [22, 23] and its benefit is dose-dependent. Vitamin D in a received dose greater than 400 IU vitamin D3 per day with or without calcium reduced the risk of a hip and any non-vertebral fractures by about 20%, while a received dose of 400 IU per day or less did not contribute to fracture reduction[9] (Attachment 5). This dose-response relationship of vitamin D and fracture reduction was also confirmed by our latest meta-analysis for falls; 18% percent fall reduction was only present in trials that gave at least 700 IU vitamin D per day and no benefit was seen with a lower dose; in press at the British Medical Journal[10].

Higher intermittent dosing of vitamin D3 (100'000 IU every 4 months) was associated with high adherence in one large trial resulting in a significant increase in 25-hydroxyvitamin D levels, and a 33% reduction of non-vertebral fractures [24]. The equivalent dose given daily (800 IU per day) did not reduce fractures in another large trial, where adherence was less than 50%[11].
SAFETY
SAFETY- Intermittent Vitamin D3 supplementation

The half-life of vitamin D3 is more than 1.5 months, which allows for intermittent dosing of vitamin D[25]. Vitamin D3 doses of 10'000 IU [26, 27] per day or 18'000[28], 50'000 IU[29], and 100'000 IU [30] per month have been found to be safe in several trials of older individuals. One trial in individuals with a mean age of 82 years added a loading dose of 500'000 IU vitamin D3 to a monthly dose of 50'000 IU vitamin D and documented no increase of any individual serum calcium level outside the normal range at 1, 5, and 9 months of treatment[29].

In preparation of this trial, we have studied a series of 33 elderly patients treated with a single oral bolus of 300'000 IU D3 (von Restorff C, Bischoff-Ferrari HA, Theiler R; in press Bone Journal). Serum 25-hydroxyvitamin D concentrations increased at 3 months after oral supplementation in all patients. 50 nmol/l 25-hydroxyvitamin D were reached in 27 out of 29 patients (93%) after 3 months. Desirable levels of 75 nmol/l were reached in 14 of 29 patients at 3 month (48%). Two patients had mild hypercalcemia at 3 month (2.69 nmol/l), which normalized at 6 month. At 6 months, 92% of all patients had 25-hydroxyvitamin D serum concentrations above 50 nmol/l and 35 percent had desirable serum concentrations of 75 nmol/l.

Several other studies suggest that intermittent dosing of 100’000 IU every 3 month in older individuals living in residential care is safe and advantageous for adherence to treatment[24, 31]. One study tested a low monthly dose with 18’000 IU vitamin D3 and achieved mean 25-hydroxyvitamin D levels of 51 nmol/l[28], another with a higher monthly dose of 50’000 IU vitamin D3 achieved mean 25-hydroxyvitamin D levels of 80 nmol/l[29].

Based on a review of the literature, plus our previous work in the field of vitamin D, we feel that the most likely monthly dose that safely brings most older individuals up to the desirable 25-hydroxyvitamin D range of at least 75 nmol/l is 60’000 IU vitamin D once a month (active group I).

Safety measures during the trial:
Potential participants with serum calcium levels of > 2.6 mmol/l at the screening visit are excluded from the trial.
Safety laboratory will be assessed at baseline, 2 weeks, 6 and 12 months including serum calcium adjusted for albumin, serum creatinine, and urinary calcium/creatinine ratio in spot urine.
SAFETY - Intermittent 25(OH)-Vitamin D3 supplementation

Following synthesis in the skin, vitamin D$_3$ is converted in the liver to 25(OH)D in an unregulated reaction [25]. 25(OH)D is recognized to be the storage form of vitamin D and it is used to assess an individual’s vitamin D status. Skeletal (bone density, fracture risk) and non-skeletal endpoints (lower extremity function, cancer risk, risk of hypertension, risk of cardiovascular mortality) are correlated with 25(OH)D status suggesting a benefit of higher 25(OH)D levels[32].

The half-life of 25(OH)D is shorter than that of vitamin D3[33], approximately 10 days to 3 weeks. The increase in 25(OH)D levels is immediate and more pronounced if compared to an equivalent dose of vitamin D3 (attachment 1). Thus, the combination of 25(OH)D supplementation with vitamin D3 supplementation may be of clinical value for intermitted dosing: complementary benefit with an immediate and pronounced increase in 25-hydroxyvitamin D levels by 25(OH)D followed by a slower but sustained increase in 25-hydroxyvitamin D levels with vitamin D3.

In preparation of this trial, we have studied a series of 35 healthy postmenopausal women in a pharmacokinetic trial (data will be presented at the American Society of Bone and Mineral Research Meeting in September 2009; see attachment 1 and 2). In this prospective, double-blind, randomized study with seven parallel groups (age 50 – 74 years, body mass index 18.6 – 30.0 kg/m$^2$), five healthy postmenopausal women per group were supplemented with 20 g 25(OH)D or vitaminD3 daily, with 140 g 25(OH)D or vitaminD3 weekly, or on a single occasion with either 140 g 25(OH)D or vitaminD3 or both. 25-hydroxyvitamin D plasma concentrations were analyzed by a LC-MS/MS method.

Over 16 weeks, mean 25-hydroxyvitamin D levels increased from 30.7 to 162.2 nmol/l in the 25(OH)D group and from 35.5 to 76.2 nmol/l in the vitamin D3 group. The daily dose of 25(OH)D tested in this pharmacokinetic trial was 20mcg per day equivalent to 600 mcg per month. In 15 clinical visits no adverse effects occurred. All serum calcium levels of each participant were in the normal range.

Based on the results of our pharmacokinetic study it is estimated that a combined monthly supplementation of 24'000 IU Vitamin D3 plus 300 mcg of 25(OH)D (active group II) results in a serum 25-hydroxyvitamin D concentration of about 140 nmol/IL in steady-state. A serum 25(OH)D of 150-170 nmol/L is within the observed range for healthy outdoor workers and young adults in summer no hypercalcemia is expected[34].

Safety measures during the trial:
Potential participants with serum calcium levels of > 2.6 mmol/l at the screeing visit are excluded from the trial. Safety laboratory will be assessed at baseline, 2 weeks, 6 and 12 months including serum calcium adjusted for albumin, serum creatinine, and urinary calcium/creatinine ratio in spot urine.

See attachment 9 for investigational product name and formulation.
INNOVATIVE COMPONENTS OF THE PROPOSED TRIAL

Apart from the innovation and improvement the trial will bring to clinical practice with the new monthly vitamin D regimen, we also test important endpoints in this trial comparing the standard dose of 24'000 IU vitamin D3 per month (equivalent to 800 IU per day; control group) to a high-dose of 60'000 IU vitamin D3 per month (equivalent to the safe upper intake of 2000 IU per day; active group I) and to a combined group of 24'000 IU vitamin D3 per month PLUS 300 mcg 25(OH)D per month (active group II) with respect to several important clinical endpoints. All endpoints have been established and discussed with national and international experts in the particular field.

A key target in healthy ageing is the prevention of functional decline. We hypothesize that high-dose monthly supplementation (active group I and II) can prevent functional decline in older individuals with a previous fall compared to monthly standard vitamin D3 dose. Functional endpoints have not been studied with high-dose vitamin D in pre-frail older individuals. We will assess the odds of maintaining or improving function across a 4-test component lower extremity test battery (knee extensor and flexor strength, repeated sit-to-stand, and the timed up and go). In addition the short physical performance battery (SPPB) score will be compared between groups.

**Dual task performance** identifies important deficits that combine function and cognitive abilities in older individuals. This is the first trial to test whether high-dose vitamin D could improve dual task performance in older individuals. One prospective study found that older individuals who stop walking while talking have a high risk of falling[35]. Since then, dual tasking has been explored as an early assessment of impaired function among older individuals[36, 37]. We recruit older individuals with a recent fall in this trial and hypothesize that high-dose monthly vitamin D (active group I and active group II) will improve dual task performance compared to the control group. Vitamin D may be successful in improving dual task performance in older individuals as both skeletal muscle[38] and the brain[39] carry the vitamin D receptor. Also, earlier studies found that higher 25-hydroxyvitamin D status has been associated with better extremity function[1] and improved cognitive function among older individuals[40]. The detailed dual task performance program will be co-developed with Prof. Reto Kressig, who is an international expert in dual task assessment among older individuals and the Head of Geriatrics at the University of Basel.
A further innovative endpoint is the detailed assessment of **musculoskeletal pain**. One clinical sign of vitamin D deficiency is muscle pain. Musculoskeletal pain is highly prevalent in older individuals and a clinical sign of vitamin D deficiency myopathy. We will perform a detailed documentation of self-reported musculoskeletal pain at each visit and test the hypothesis that high dose monthly vitamin D (active group I and active group II), compared to a standard monthly supplementation dose (control group), improves musculoskeletal pain (measured as intensity and number of areas that ache) in ambulatory, pre-frail community-dwelling older adults with a history of a fall. For this endpoint, we will use the McGill Pain map *(see attachment 7)* collaborate with the international expert on pain and ageing, Suzanne G. Leveille. She is Professor of Medicine at the Harvard Medical School in Boston[41].

We also test the benefit of high-dose monthly vitamin D (active group I and II) compared to standard monthly dose of vitamin D3 on **blood pressure**. Blood pressure rises with increasing age and reaches systolic levels of 147 mmHg in women and 144 mmHg in men of age 60[42, 43] and these blood pressure increases are correlated with increased morbidity and mortality. Lowering systolic blood pressure in older hypertensive individuals by 10-12 mmHg reduced cardiovascular events by 32%[44] and cardiovascular mortality by 27%[45]. We recently published data on two large prospective cohort studies including 38’388 men from the Health Professionals' Follow-Up Study and 77’531 women from the Nurses' Health Study followed for 16 to 18 years. In this prospective cohort study 25-hydroxyvitamin D levels were inversely associated with risk of incident hypertension[46] *(see attachment 8)*. Individuals with mean 25-hydroxyvitamin D levels of 75 nmol/l or higher, which is the expected target level in active group I and II, the risk of incident hypertension was reduced 6.1-fold among men (95% confidence interval [CI]: 1.00 to 37.8) and 2.7-fold among women (95% CI: 1.05 to 6.79). The results of these observational studies are supported by two RCTs, in which vitamin D treatment reduced blood pressure in older community-dwelling women and [47] and hypertensive subject[48]. This is the first trial to test whether a high-dose monthly supplementation will improve blood pressure in older individuals with a history of a fall. **Even if high-dose monthly vitamin D would reduce blood pressure to a small degree, applied to a population, this effect would be enormous.**

**Prevention of repeat falls is a prominent goal in the care of older individuals.** Similar to increasing anti-fracture benefits with higher achieved 25-hydroxyvitamin D levels, our recent meta-analysis on double-blind RCTs *(in press at the British Medical Journal[10]*) found increased anti-fall efficacy with higher achieved 25-hydroxyvitamin D levels. This will be the first trial to test whether a high-dose monthly vitamin D supplementation (active group I and II) will reduce falls in older individuals with a history of a fall.
Improving bone density and muscle mass are important clinical endpoints within the clinical goal of disability prevention. This will be the first trial to test whether a high-dose monthly vitamin D supplementation (active group I and II) will improve bone density at the hip and spine, as well a muscle mass at the extremities in older individuals with a history of a fall. Both endpoints will be assessed by DEXA whole body composition. We will use the muscle mass measurement by DEXA for the definition of sarcopenia. In addition we will use a composite measure of sarcopenia including both muscle mass and strength, as suggested by a recent expert panel (REFERENCE). We will then assess the risk of sarcopenia with monthly high-dose vitamin D (active group I and II) compared to monthly standard dose vitamin D.

Lowering health care utilization / improving quality of life are important components to assess optimal health care cost allocation. We will measure quality of life by the EuroQol at baseline and at 6, 12, and 18 month of the trial. In addition, we will work with the health insurance companies to assess all outpatient and inpatient costs 1 year before and over the course of our trial. We will then compare healthy care utilization between the higher dose monthly vitamin D groups (active group I and II) compared to the control group, while controlling for health care costs in the previous year before the trial was initiated. Eventually, this cost analysis will help to make a better case for reimbursement of strategies that optimize vitamin D status in elderly fallers. We will also compare the rate of hospital admission between treatment and control groups.

Decreasing bone resorption is an important surrogate marker for bone health. We will measure serum N-telopeptides and other markers of bone resorption and remodeling at baseline, 6 and 12 month.

Decreasing upper and lower respiratory tract infections have been observed in individuals with better vitamin D status[49, 50], however this has not been tested in a randomized controlled trial. The vitamin D receptor is present on cells of the immune system[51] and there is an emerging recognition of the role of vitamin D in the immune response to infectious agents, such as tuberculosis bacteria[52] or viruses[49, 50].
LONGTERM BENEFIT

This project was designed to answer an urgent need as today’s strategies in optimizing vitamin D status in older persons are insufficient [13]. Intermittent dosing will improve adherence and simplify vitamin D supplementation in nursing homes. We test a monthly dose of vitamin D high-enough to increase 25-hydroxyvitamin D concentrations to the desirable range of at least 75 nmol/l. As vitamin D has a calcium-sparing effect, the higher dose will also enhance intestinal calcium uptake from natural calcium sources, which will decrease the need for additional calcium supplementation. In order to make a long-term impact with this project, we have addressed the only Swiss company that produces a vitamin D mono preparation (VIDe3-drops) to work with us and provide our study medication plus the willingness to develop a monthly product.

The results of the study will be widely distributed and discussed in clinical working groups to implement the monthly supplementation in guidelines and clinical practice. Additionally, the endpoints, the dose, the intermittent application of vitamin D and its combination with 25(OH)D supplementation in active group II, and the chosen target population of pre-frail older individuals make this trial unique and highly relevant. Therefore, results are of interest to the scientific world and will be of interest to a general medical journal. Given that vitamin D supplementation is inexpensive, well-tolerated, and recommended in all older individuals, we will organize an information event for older persons (Öffentlichkeitsanlass) and the results will be communicated to the media.
DETAILED METHODS

We propose a double-blind, randomized controlled trial to test the effectiveness of a

(1) **Active I** *(n = 70)*: monthly high-dose vitamin D$_3$ supplement dose (60'000 IU/month, equivalent to 2000 IU daily),
(2) **Active II** *(n = 70)*: or a monthly standard vitamin D$_3$ supplement dose combined with 25(OH)D (24'000 IU/month, equivalent to 800 IU daily) **PLUS** 300 mcg 25(OH)D, equivalent to 10 mcg per day)
(3) **Control** *(n = 70)*: compared to a standard vitamin D$_3$ supplement dose (24'000 IU/month, equivalent to 800 IU daily).

The *standard therapy group* will receive 24'000 IU of vitamin D once a month, which is the current recommended daily intake for adults aged 70 and older at risk for osteoporosis. The *active group 1* will receive 60'000 IU once a month (equivalent to 2000 IU/day), which is the currently defined safe upper intake of vitamin D established by the Institute of Medicine of the National Academy of Sciences. The *active group 2* will receive 24'000 IU of vitamin D once a month in combination with 300 mcg of 25(OH)D once a month. All individuals will be advised to consume calcium from natural food sources in a daily dose of 600-800 mg a day, including milk products. The maximal intake of supplemental calcium is restricted to 250 mg per day in the double-blinded phase of the trial (month 1-12).

**PRIMARY ENDPOINT**

(1) *lowering the risk of functional decline*, proportion of individuals with functional decline based on binary repeated measure assessment across 4 lower extremity tests
(2) **25-hydroxyvitamin D levels in late winter** (season of lowest expected 25(OH)D level) and **late summer** (season of highest expected 25(OH)D level) – Percent of participants reaching desirable 25-hydroxyvitamin D levels in late winter and in late summer.

**SECONDARY ENDPOINTS**

(3) *improving dual task performance*,
(4) *improving muscle strength*
(5) *reducing muscle pain*,
(6) *improving blood pressure*,
(7) *reducing the rate of falling*
(8) *improving bone density*
(9) *improving muscle mass, reducing the risk of sarcopenia*
(10) *lowering health care utilization / improving quality of life*
(11) *decreasing bone resorption*
(12) decreased any, upper and lower respiratory infections, infections that led to hospital admission
SAFETY ENDPOINTS
Serum calcium adjusted for albumin, serum creatinine at baseline, 2 weeks, 6 months, and 12 months follow-up in all participants.

HYPOTHESES:

(1) **Primary I:** Our primary hypothesis I is that there will be a higher proportion of individuals with functional decline (binary repeated measure assessment across 4 lower extremity tests) in the control group compared to both active groups over time (month 6 and 12).

(2) **Primary II:** Our primary hypothesis II is that both active groups are superior to the control group in enhancing serum 25-hydroxyvitamin D levels in both late summer and late winter.

   In a secondary analysis, we will also test whether the combination group (active group II) is superior to the high-dose vitamin D₃ supplement dose (active group I) in enhancing serum 25-hydroxyvitamin D levels in both late summer and late winter.

**Secondary:**

(3) We hypothesize that dual task performance is better in active group I and II compared to the monthly control group over time (month 6 and 12).

(4) We hypothesize that muscle strength (knee extensor, knee flexor, grip) is higher in active group I and II compared to the monthly control group over time (month 6 and 12).

(5) We hypothesize that muscle pain (McGill Map) is less in active group I and II compared to the monthly control group over time (month 6 and 12).

(6) We hypothesize that systolic and diastolic blood pressure is lower in active group I and II compared to the monthly control group over time (month 6 and 12).

(7) We hypothesize that the rate of falls is lower in active group I and II compared to the monthly control group over time (6 and 12 months).

(8) We hypothesize that bone density at the hip and spine is higher in active group I and II compared to the monthly control group at month 12.

(9) We hypothesize that extremity muscle mass is higher in active group I and II compared to the monthly control group at month 12. We also hypothesize that the risk of sarcopenia is lower in active group I and II compared to the monthly control group at month 12.

(10) We hypothesize that health care utilization is lower in active group I and II compared to the monthly control group over time (12 months). We also hypothesize that quality of life is higher in active group I and II compared to the monthly control group over time (6 and 12 months).
We hypothesize that bone resorption is lower in active group I and II compared to the monthly control group over time (6 and 12 months).

We hypothesize that the rate of any infections, upper and lower respiratory infections, and infections that led to hospital admission is lower in active group I and II compared to the monthly control group over time (6 and 12 months).

**COMPARISONS:** Each of the active groups will be compared to control. We will also compare active group I to active group II.

**BLINDING/RANDOMIZATION:**
Treatment will be double blinded

4. *Active I (n=70):* monthly drink solution with 60'000 IU vitamin D 3 plus 3 placebo capsules

5. *Active II(n=70):* monthly placebo drink solution plus 2 capsules with 24’000 IU vitamin D3 and 1 capsule with 300 mcg of 25(OH)D.

6. *Control (=n70):* monthly drink solution with 24’000 IU vitamin D 3 plus 3 placebo capsules

**Month 0-12 (RCT):** Randomization will be computer-based by the study statistician (Prof. John E. Orav; Dept of Biostatistics, Harvard School of Public Health) in blocks of 6 and stratified by gender. Each time a patient meets the inclusion and exclusion criteria and is willing to participate, has studied and signed the written informed consent, we will call an independent randomization center to provide the study identification number and the blinded study medication. The hospital pharmacy at the Waid city hospital will serve as the randomization centre. There will be a direct communication between the director of the pharmacy and the study statistician regarding the randomization list of the trial. Each time a participant is recruited, the study staff will contact the pharmacy to provide the randomization number and prepare the study medication with a clear indication on the label of the study medication marking both the study ID and the randomization code. Then the study staff will walk to the pharmacy and pick up the study medication (separate building) for the study participant.

**Visit 6 (=Month 18, end of open follow-up):** 10 participants (5 men and 5 women) of each treatment-group (*Activ I, II and Control*), who completed the RCT-part (month 0-12) of the study will be randomly (computer based) selected by the study statistician (Prof. John E. Orav; Dept of Biostatistics, Harvard School of Public Health) and invited to participate at visit 6 in the study center. If one of the randomly selected persons refuses to come to the visit the next man/women on the randomization-list will be invited.
SETTING / RECRUITMENT:
We will enroll 210 community-dwelling men and women aged 70 years and older who report a fall in the last 12 months (with or without fracture). Participants will be recruited via newspapers and magazines, posters sent to all general practitioners in Zurich, flyers and posters at the University Hospital and other Hospitals in Zurich, as well as public events where older individuals participate (Geriatric lectures).
Participants have to be mobile and able to use public transportation to attend the clinical visits at the Centre on Aging and Mobility.

INCLUSION CRITERIA
- Age 70+
- Fall in the last 12 months before screening (with or without a fracture)
- Living at home (community-dwelling)
- Men or women
- Mobile with or without walking aid – have to be able to use public transportation to attend the clinical visits at the trial centre
- Score of at least 27 at the screening Folstein Mini Mental test
- Patient understands the study procedures, alternative treatments available and risks involved with the study, and voluntarily agrees to participate by giving a written informed consent.
- Patient meets the entry minimal requirements based on routine clinical laboratory safety screening tests and the Folstein mini mental status (score 27+ required) performed at the Screening Visit.
- Patient is willing to perform all study tests, attend all required office visits, and provide blood and urine samples.

EXCLUSION CRITERIA
- Serum calcium adjusted for albumin of > 2.6 mmol/l
- Pathologic fracture in the last year (except for fractures due to osteoporosis)
- Chemo therapy / Radiation due to cancer in the last year
- Treatment which has an effect on bone metabolism (e.g. PTH, calcitonin, chronic cortisone intake > 5mg/day in the last 12 months (except for inhalation and sporadic infiltration))
- Oral vitamin D intake of more than 800 IU per day
- Unwilling to stop calcium supplementation and vitamin D supplementation during the trial (maximal additional calcium supplementation = 250 mg per day; maximal additional vitamin D supplementation 200 IU/day, if medically indicated or the patient withdraws his declared intention to stop vitamin D supplementation during the study)
- Severe visual or hearing impairment
- Unwilling or unable to take study medication
• Diseases with a risk of recurrent falling (e.g. Parkinson’s disease/syndrome, Hemiplegia after stroke, symptomatic stenosis of the spinal canal, polyneuropathy, epilepsy, recurring vertigo, recurring syncope)
• BMI ≥ 40
• Estimated creatinine clearance < 15 ml/min (estimated Creatinine Clearance Cockcroft and Gault)
• Malabsorption syndrome (celiac diseases, inflammatory bowel disease)
• Diseases that may enhance serum calcium: sarkoidosis, lymphoma, primary hyperparathyroidism
• Kidney stone in the last 10 years
• Abnormal indices of calcium metabolism, uncontrolled hypocalcemia.
• Patient heavily consumes alcohol containing products defined as greater than (> 3 drinks (beer, wine, or distilled spirits) of alcoholic beverages per day.
• Patient is unlikely to adhere to the study procedures, to keep appointments, or is planning to relocate during the study.
• Patients who are planning a stay in a “sunny” location (e.g. winter sun resort) for more than two months per year
• Medication which has an effect on 25-hydroxyvitamin D level (e.g. certain anticonvulsants (e.g. Phenobarbital, Carbamazepin, Phenytoin))
• M. Paget (Ostitis deformans)
• Inflammatory arthritis (e.g. rheumatoid arthritis, reiter syndrome, psoriasis arthritis)
• Participation in a study in the last 6 month, except for studies without drug-application, or any influence of the study-medication can be excluded

ENROLLEMENT STEPS / INFORMED CONSENT - VISITS
If potential participants pass a first phone interview where we assess inclusion and exclusion criteria they are invited to our screening visit. Those who pass the screening telephone and express interest in the trial will receive our patient information and the consent form by mail to read at their convenience. When participants have studied the patient information for at least 2 days, we will call them and set an appointment for the screening visit, provided they are interested to participate in the trial. At the screening visit, they will have the opportunity to ask and discuss concerns about the trial. Only after signing the written informed consent, the screening visit exams will be performed.
At the screening visit there will be a laboratory test for serum calcium, albumin, and creatinine. At the screening visit patient’s height and weight will be measured, and the MMS test plus clock test performed. Patients who have laboratory values in the normal range and reach a Mini Mental Score of at least 27 are invited for the baseline visit.
Visit 2, 4, and 5 are clinical tests with outcome assessments as listed in table 1.
Visit 3 at 14 days after initiation of treatment is the safety visit with assessment of serum calcium, serum albumin, and serum creatinine.
STUDY MEDICATION

Overview:
All individuals will receive 3 capsules and 1 drink solution as follows:
Active I: 60'000IU D3 as a drink solution\(^1\) PLUS
   3 capsules of placebo\(^2\)
Active II: 24'000IU D3 divided in 2 capsules\(^2\) PLUS
   300mcg HyD as a capsule\(^2\) PLUS
   1 drink solution of placebo\(^3\)
Control: 24'000IU D3 as a drink solution\(^1\) PLUS
   3 capsules of placebo\(^2\)

\(^1\) provided by Dr. Wild & Co AG
\(^2\) provided by DSM Nutritional Products Ltd
\(^3\) provided by Kantonsapotheke Zürich

WILD will provide 12 small glass bottles per patient (1 for each month of the trial period), which will contain the vitamin D solution as either 24'000 IU or 60'000 IU vitamin D3. The solution will come easy to open 5 ml glass bottles. The content will look the same, and taste the same. Participants will be asked to add the content of the bottle to half a glass of water, juice or milk, and drink it with breakfast once a month. The 5 ml solution will contain 2.76 g alcohol. For a comparison, a glass of red wine (2 dl) contains 21.6 g alcohol, about 8 times more. The content is well absorbed after being added to water, juice, or milk.

DSM will provide 36 capsules per patient (3 for each month of the trial). Those either contain placebo, 24'000 IU vitamin D3 (divided in 2 capsules), or 300 mcg 25(OH)D.

The Kantonsapotheke Zürich will provide the placebo drink solution (The glass bottles will be provided by Wild to ensure the same appearance.)

At baseline, after all assessments have been performed, the participant is invited for a snack and we instruct how the vitamin D drink solution and capsules should be taken. Then additional 5 sets (drink solution bottles + capsules) are given to the patient with a month/date on them. At the 6 month visit, the same procedure will take place and participants will be given 6 more sets (drink solution bottles + capsules) of the study medication. Eventually, all participants will have received 12 bottles for 12 month of follow-up and 12 sets of 3 capsules. We ask all participants to bring back all used or unused drink solution bottles and capsules. All blood tests will be performed prior to the intake of the study medication. The study capsules will be provided by DSM and will contain either 24'000 IU vitamin D3 or 300 mcg 25(OH)D or placebo. All capsules will look and taste the same. DSM will also make a placebo solution for the small glass bottle using the carrier instructions of WILD. The study pills and drink solutions will be stored at 4 degrees celcius at the pharmacy of the Waid city hospital.
ASSESSMENT OF ADHERENCE TO MONTHLY STUDY MEDICATION

Adherence to vitamin D study medication will be assessed in 3 ways:

(a) 6-Monthly pill counts and assessment of the amount of drink solution left in bottles. Participants are asked to bring their pill container and drink solution bottles of the previous 6 months to the clinical visit or mail it.

(b) Participants (or care takers if needed) will be called every month by a study nurse to assess their adherence to the study medication.

(c) 25-OHD levels will be assessed at baseline, 6 and 12 months.

Efficacy analysis will be performed based on reported intake of study medication.

OPEN DESIGN FOLLOW-UP MONTH 13-18

In order to assess preference of intake (monthly versus daily), adherence to treatment with the daily vitamin D, and the efficacy to maintain 25-hydroxyvitamin D levels at the threshold reached after monthly high-dose (active group I and II) or standard vitamin D (control group), we will perform a 6-month open follow-up trial phase. This phase will start at month 13 after the double-blinded trial phase. All individuals will stop their monthly intake of vitamin D after dose 12 of the monthly course and switch to daily vitamin D (800 IU). We provide a 6 month supply of daily vitamin D as 8 drops per day (Vi-De 3®) for all participants. During the 6 months, we ask all participants to fill in a diary on their adherence to the tablets, side effects, falls and other adverse health events. The fall hotline will be available also during the 6 month open follow-up and we will call the participants every month as during the blinded trial phase to ensure adherence. There will be a final phone call in month 18 to assess adherence to daily vitamin D.

In a final telephone interview (month 18), we ask all participants how many days they took the daily supplements, and what intake regimen they prefer (daily or monthly). In addition a random sample of 30 patients from the 3 original groups (active groups I and II, control group) will be invited for a visit to test their 25-hydroxyvitamin D level, parathyroid hormone level, serum and urinary calcium, and serum albumin. The random sample of 10 subjects per arm will be selected by the study statistician based on a computer-based selection procedure among subjects that are still in the trial at month 17. If participants are unable to come to the 18 month visit, the next patient on the randomization list for each arm will be asked to come to the visit.

ZURICH FALL COHORT MONTH 19+

All participants will be followed with 6 monthly phone calls life-long to assess the need of care, nursing home admission, fractures, falls, mortality, and health care utilization.
(SERIOUS) ADVERSE EVENTS DEFINITION AND REPORTING

Definition of (Serious) Adverse Events

Adverse events
Adverse events (AEs) are defined as any untoward medical occurrence in a subject or clinical investigation subject administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal study product, whether or not related to the medicinal study product. An AE may also consist of a new disease, an exacerbation of a pre-existing illness or condition, a recurrence of an intermittent illness or condition, a set of related signs or symptoms, or a single sign or symptom.

AEs observed by the investigator and/or reported by the subject must be reported in the CRF during the entire study period, i.e. the period of time from the first (= signature of informed consent) to the last protocol-specific procedure regardless of the medicinal study product relation assessment.

For all AEs, sufficient information will be pursued and/or obtained so as to permit an adequate determination of the outcome of the event (i.e., whether the event should be classified as an SAE) and an assessment of the casual relationship between the AE and the investigational drug or study treatment(s).

Whenever available, the underlying disease or condition for which a therapeutic or diagnostic procedure is required should be reported as the AE term. Surgeries or other invasive procedures that had already been planned prior to the start of the study do not have to be documented as AEs. These planned procedures will be recorded in the CRF by the investigator at the baseline visit. It is not important if the condition was known before enrolment, only if the procedure was planned before.

Serious adverse event
An SAE is any untoward medical occurrence that at any dose results in
• results in death,
• is life-threatening,
• requires subject hospitalization or prolongation of current hospitalization,
• results in persistent or significant disability/incapacity, or
• any important medical event and any event which, though not included in the above, may jeopardise the subject or may require intervention to prevent one of the outcomes listed above.

Any other medically important condition that may be not immediately life-threatening or results in death or hospitalization but may jeopardize the subject or may require intervention to prevent one of the outcomes listed above should also usually (i.e. based on medical and scientific judgment) be considered serious. For example: intensive treatment at home for
allergic bronchospasm; certain laboratory abnormalities (e.g. blood dyscrasias); convulsions that do not result in hospitalisation; development of drug dependency or drug abuse
Recording of (Serious) Adverse Events

Clinical study subjects will be routinely questioned about AEs at study visits. The well-being of the subjects will be ascertained by neutral questioning ("How are you?"). The investigator is responsible for reporting all AEs occurring during the course of the study.

All observed or volunteered adverse drug events (serious or non-serious) and abnormal test findings, regardless of treatment group or suspected causal relationship to the investigational drug or study treatment(s) will be recorded in the CRF.

AEs or abnormal test findings felt to be associated with the study treatment(s) will be followed until the event (or its sequelae) or the abnormal test finding resolves or stabilizes at a level acceptable to the investigator.

An abnormal test finding will be classified as an AE if one or more of the following criteria are met:

• The test finding is accompanied by clinical symptoms.
• The test finding necessitates additional diagnostic evaluation(s) or medical/surgical intervention; including significant additional concomitant drug treatment or other therapy
  
  **Note:** simply repeating a test finding, in the absence of any of the other listed criteria, does not constitute an AE.
• The test finding leads to a change in study dosing or discontinuation of subject participation in the clinical study.

All AEs, serious and non-serious, will be fully documented on the appropriate CRF. For each AE, the investigator will provide the onset, duration, intensity, treatment required, outcome and action taken with the investigational product.

The intensity of AEs will be assessed as being

• mild (hardly noticeable, negligible impairment of well-being),
• moderate (marked discomfort, but tolerable without immediate relief), or
• severe (overwhelming discomfort, calling for immediate relief).

The investigator will determine the relationship of the investigational drug to all AEs as defined on the Adverse Event Reporting Form.

Assessment of (Serious) Adverse Events

The investigator will promptly review documented AEs and abnormal test findings to determine if

• the abnormal test finding should be classified as an AE,
• if there is a reasonable possibility that the AE was caused by the investigational drug or study treatment(s), and
• if the AE meets the criteria for an SAE.
The assessment by the investigator with regard to the study drug relation is done according to the following definitions:

**unlikely relation**

An AE, whose

- temporal relationship to drug administration makes a causal relationship improbable and
- in which other drugs or chemicals or underlying disease provides plausible explanations.

**possible relation**

An AE, which

- occurs within a reasonable time sequence to administration of the drug but
- could also be explained by concurrent disease or other drugs or chemicals.

Information on drug withdrawal may be lacking or unclear.

**likely relation**

An AE, which

- occurs within a reasonable time sequence to administration of the drug,
- is unlikely to be attributed to concurrent disease or other drugs or chemicals, and
- follows a clinically reasonable response on withdrawal (dechallenge).

Rechallenge information is not required to fulfill this definition.

**certain relation**

An AE, which

- occurs in a plausible time relationship to drug administration and
- cannot be explained by concurrent disease or other drugs or chemicals.
- the response to withdrawal of the drug (dechallenge) should be clinically plausible.
  The event must be pharmacologically or phenomenologically definitive, with use of a satisfactory rechallenge procedure if necessary.

**Reporting of Serious Adverse Events**

The Sponsor-Investigator is responsible for SAE reporting to Swissmedic and to the IEC, respectively, according to the following details.
The Sponsor-Investigator is responsible for:

- Compliance with the regulatory requirements of Swissmedic regarding prompt reporting of unexpected SAEs for which a causal relationship with the study drug or device cannot be ruled out.

- Reporting to Swissmedic of fatal and life-threatening SAEs if evaluated as “suspected”, “unexpected” and “drug related” (SUSAR):
  - without delay and no later than 7 calendar days following awareness that event meets criteria for a SUSAR;
  - follow-up information regarding the SUSAR within further 8 calendar days.

- Reporting to Swissmedic of non-fatal and not life-threatening SAEs if evaluated as “suspected”, “unexpected” and “drug related” (SUSARs):
  - promptly and no later than 15 calendar days following awareness that event meets criteria for a SUSAR.

- Sending yearly safety reports, starting one year after the date of notification to Swissmedic. These reports should contain:
  - A concise critical summary of the safety profile of the drug studied as well as the safety issues that have arisen;
  - A listing of all SUSARs that have occurred in Switzerland and at international level (if applicable);
  - Ideally all adverse drug reactions at international level.

The investigator is responsible for:

- Reporting to IEC any SAE which resulted in death:
  - immediately, i.e. within 24 hours.

- Reporting to IEC of fatal and life-threatening SAEs if evaluated as “suspected”, “unexpected” and “drug related” (SUSAR):
  - without delay and no later than 7 calendar days following awareness that event meets criteria for a SUSAR;
  - follow-up information regarding the SUSAR within further 8 calendar days.

- Reporting to IEC of non-fatal and not life-threatening SAEs if evaluated as “suspected”, “unexpected” and “drug related” (SUSAR):
  - promptly and no later than 15 calendar days following awareness that event meets criteria for a SUSAR.

An unexpected SAE refers to any AE, the nature or severity of which is not consistent with the applicable product information.
Follow-up of (Serious) Adverse Events

Subjects terminating the study (either regularly or prematurely) with

- reported ongoing SAE, or
- any ongoing AEs of laboratory values or of vital signs being beyond the alert limit

will return for a follow-up investigation. This visit will take place up to 30 days after terminating the treatment period. Follow-up information on the outcome will be recorded on the respective AE page in the CRF. All other information has to be documented in the source documents. Source data has to be available upon request.

For any AEs the outcome "unknown" is not acceptable, except if attempts to collect the information have been made and documented. In case of subjects lost to follow-up, efforts should be made and documented to contact the subject to encourage him/her to continue study participation as scheduled. In case of minor AEs a telephone call to the subject may be acceptable.

All new SAE or pregnancies that the investigators will be notified of within 30 days after discontinuation of study medication have to be reported in appropriate report forms and in the CRF if required. However, if the termination visit takes place more than 30 days after the subject has discontinued study medication, the reporting time has to be extended until the termination visit.

Follow-up investigations may also be necessary according to the investigator's medical judgment even if the subject has no AE at the end of the study. However, information related to these investigations does not have to be documented in the CRF but must be noted in the source documentation.
MEASUREMENTS

PRIMARY ENDPOINT/STATISTICAL ANALYSIS

A key target in healthy ageing and primary endpoint of the trial is the prevention of functional decline. With a history of a fall in the last 6 months, we have selected a pre-frail population, where functional decline is likely. The repeated sit-to-stand test (5 repeats) has been validated[55] and compared to overall function and activities of daily living [56] in a large population-based study in the US National Health and Nutrition survey III among community-dwelling individuals age 60 years and older. We have validated the timed-up-and-go test in community-dwelling and institutionalized older individuals and showed that the test is responsive to vitamin D treatment with a documented 11% improvement over 3 month in frail individuals compared to calcium alone[57]. We hypothesize that a higher proportion in the standard monthly group will have a more than 5% decrease in the timed up-and-go or the repeated sit to stand test at 12 months compared to the high-dose monthly group.

Statistical Analyses Prevention of Functional Decline

We will create binary variables for all 4 lower extremity tests (knee extensor and flexor strength, timed up-and-go, repeated sit-to-stand test): 0 = stayed the same or improved; 1 = got worse. Then we will use repeated measurements analyses across the 4 tests and time to assess the risk of functional decline over time. We will compare both active groups to the control group.

We will also use repeated measurement analyses to compare the score of the Short Physical Performance Test Battery, which consists of three components: balance (side-by-side, semitandem, and tandem stance for 10 seconds), timed 4 m walk, and chair stands (to rise from a chair with arms across their chest for five repetitions) for each active group compared with the control group.

The primary endpoint serum 25-hydroxyvitamin D concentration will be measured by radio-immuno assay (DIASORIN) and Mass Spectroscopy. The DIASORIN assay is the most widely applied assay for 25-hydroxyvitamin D, which allows our results to be compared nationally and internationally, while Mass Spectroscopy is the golden standard. Blood samples for 25-hydroxyvitamin D serum concentrations will be taken at baseline, at 2 weeks, and at 6 and 12 month in all individuals during the double-blinded trial phase and in a random sample of 30 patients in both groups 6 month after the follow-up open trial with daily oral vitamin D plus calcium. All samples will be stored at -80 degrees Celsius at the study centre. Our laboratory has great experience with this assay and we have published and validated its assessment earlier[14].

Statistical Analyses Primary Endpoint

We will use repeated measurements analyses to compare both active groups with the control group for 25-hydroxvitamin D levels over time while controlling for baseline 25-hydroxyvitamin D levels at baseline, gender, age, body mass index and potential other confounders.
We will also compare the risk of having 25-hydroxyvitamin D levels below 75 nmol/l in late summer and late winter for each active group compared with the control group.
SECONDARY ENDPOINTS / STATISTICAL ANALYSIS

Dual task performance identifies important deficits that combine function and cognitive abilities in older individuals. This will be the first trial to test whether high-dose vitamin D could improve dual task performance in older individuals. One prospective study found that older individuals who stop walking while talking have a high risk of falling [35]. Since then, dual tasking has been explored as an early assessment of impaired function among older individuals [36, 37]. The method of dual task performance was validated in an earlier study [53] among institutionalized older individuals. In the validation study, the balance device (sway star) indicated increased body sway while walking in response to a set of cognitive tasks [53]. The balance device is fixed to the test person as a belt around their waist. The device allows for exact balance assessment as the angle of sway and speed of correction in a pitch and role direction. The sway star balance method prospectively identified repeat fallers in an earlier trial performed in long-stay geriatric care patients [54].

Statistical Analyses Dual Task Performance

We will use repeated measurements analyses to compare both active groups with the control group for roll and pitch angle needed with every dual task tested while controlling for baseline roll and pitch angle, gender, age, body mass index and potential other confounders.

We will measure muscle strength at the lower extremities (knee extensor, knee flexor) and grip strength at baseline, 6 and 12 months. Knee extensor and knee flexor strength will be measured with a hand held gauge, and grip strength with the Martin vigoritmeter. All tests showed good reproducibility in an earlier trial of frail elderly individuals (intra-rater reliability between 0.68 and 0.94; inter-rater reliability between 0.89 and 0.96) [57].

Statistical Analyses Muscle Strength

We will use repeated measurement analyses for each strength test to compare active treatment I and II with control treatment while controlling for strength at baseline, gender, age, body mass index and potential other confounders.

We will measure muscle pain with the McGill Pain Map (attachment 7) at baseline, 6 and 12 months.

Statistical Analyses Muscle Pain

We will use repeated measurement analyses for area of muscle pain to compare active treatment I and II with control treatment while controlling for area of muscle pain at baseline, gender, age, body mass index and potential other confounders.

We will measure systolic and diastolic blood pressure with a standardized method after 5 minutes rest and in a seated position at baseline, 6 and 12 months.

Statistical Analyses systolic and diastolic blood pressure
We will use repeated measurement analyses for systolic and diastolic blood pressure to compare active treatment I and II with control treatment while controlling for blood pressure at baseline, gender, age, body mass index and potential other confounders.
Falls will be defined as “unintentionally coming to rest on the ground, floor, or other lower level.” Coming to rest against furniture or a wall was not counted as a fall[58]. The primary analysis will include the total number of falls per person over 12 months. We will truncate the total number of falls for outliers to the next highest fall frequency observed. Each fall will be documented with a fall protocol on the severity of the fall (injuries), circumstances, and associated health care utilization.

**Statistical Analyses Rate of Falls**
We will use Poisson regression to evaluate the effect of active treatment I and II compared with control on the rate of falling.

We will measure **bone density at the hip and spine** with DEXA at baseline and 12 months. DEXA will be measured with the Lunar iDXA device at the Waid City Hospital (Centre on Aging and Mobility, Zurich of University).

**Statistical Analyses Bone Density**
We will use general linear models for bone density of the hip and spine at 12 month follow-up to compare active treatment I and II with control treatment while controlling for bone density at baseline, gender, age, body mass index and potential other confounders.

We will measure **muscle mass** with DEXA at baseline and 12 months.

**Statistical Analyses Muscle Mass**
We will use general linear models for extremity muscle mass at 12 month follow-up to compare active treatment I and II with control treatment while controlling for muscle mass at baseline, gender, age, body mass index and potential other confounders.

**Sarcopenia** is the loss of muscle mass and quality. However, an internationally accepted definition is missing. Our group (Bischoff-Ferrari and Dawson-Hughes) proposed to validate various DEXA-based definitions of sarcopenia in another project. We will use the most valid definition established in the parallel project in the analyses of this project.

**Statistical Analyses Risk of Sarcopenia**
We will use logistic regression analysis to compare the active groups I and II with the control group in their risk of sarcopenia at 12 month follow-up, while controlling for prevalence of sarcopenia at baseline, gender, age, body mass index and potential other confounders.

We will measure **health care utilization** as cost of outpatient and inpatient claims to insurance companies in the 12 months before and after randomization. In addition, we will assess the rate of hospital admission and the rate of ambulatory care (MD visits, physiotherapy, Spitex) by monthly phone calls. Hospital admissions will be confirmed by hospital records and will be analyzed as the overall rate of hospital admission as well as in subgroups of hospital admission due to fall-related injuries, infections, and other. The quality of life will be assessed by the EuroQol Questionnaire at baseline, 6, and 12 months.
**Statistical Analyses Risk of Health care utilization**

We will use general linear models to compare the active groups I and II with the control group in their total health care utilization cost at 12 month follow-up, while controlling for total health care utilization costs in the 12 month prior to enrollment, gender, age, body mass index and potential other confounders.  
We will use Poisson regression to evaluate the effect of active treatment I and II compared with control on the rate of hospital admission overall as well as the following subgroups: fall-related fractures, infections, other.

We will measure **bone resorption** by serum N-teleopeptides plus other markers of bone remodeling at baseline, 6 and 12 months.  

**Statistical Analyses bone resorption**

We will use repeated measurement analyses for bone resorption markers to compare active treatment I and II with control treatment while controlling for blood pressure at baseline, gender, age, body mass index and potential other confounders.  

We will measure **the rate of upper and lower respiratory tract infections** at 12 months follow-up by monthly phone calls. Each infection will be documented with a protocol on treatment, duration, fever, MD visits.  

**Statistical Analyses Rate of upper and lower respiratory tract infections**

We will use Poisson regression to evaluate the effect of active treatment I and II compared with control on the rate of all infections, and specifically upper and lower respiratory tract infections.

**MONTHLY PHONE CALLS**

The study nurse will call every participant once a month to assess the following:
- Falls, fractures in the last month
- Hospital admission in the last month
- Infections in the last month
- MD visit, physiotherapy visit in the last month, Spitex
- Type of dwelling (new nursing home admission)
- Adherence to study medication in the last month
- Adverse events in the last month
ASSESSMENTS IN BLOOD (General health)
All blood and urine samples will be stored at -70°C at the Waid City Hospital for further analysis at the University hospital and ETH Zurich. Safety laboratory measures will be assessed at the laboratory of the Waid City Hospital.

At screening
- Creatinine, Calcium, Albumin
At baseline, 2 weeks, 6 and 12 months
- 25-hydroxyvitamin D
- Calcium, Albumin, Creatinine
At baseline, 6 and 12 months
- PTH
- Inflammatory markers (i.e. c-reactive protein, IL-6 receptor)
- Blood lipids
- Bone remodeling markers
- Serum ferritin
- Vitamins: Retinol, B12, B6, Folate, Homocysteine
- Undercarboxylated /carboxylated osteocalcin
- Minerals: Magnesium
- Sex Hormone Binding Globulin, Total Testosterone
At baseline and 12 months
- Haematology (Hb, Hk, Ec, Lc, Tc)
At baseline
- VDR genotype, ERa (Estrogen Receptor a), Collagen 1A1, ApoE
- FGF-23
- Transferrin receptor
At 18 months
- 25-hydroxyvitamin D, PTH, serum calcium, albumin, creatinine, bone remodeling markers

ASSESSMENTS IN URINE
At baseline, 2 weeks, 6 and 12 months
- Urinary calcium/creatinine ratio in spot urine
- Albumine
At 18 months
- Urinary calcium/creatinine ratio in spot urine
COMORBIDITY
We will ask participants to bring medical records from recent hospital admissions (last 5 years), we will also contact their general practitioners to give us a report on co-morbid conditions.
Co-morbid conditions will be assessed by the Sangha-Comorbidity Score based on an interview with the participant[59]. We will assess participants history of falls and fractures in the last 5 years prior to enrolment, based on the report of participants and their general practitioners. **We will use the SF-36 and the Geriatric Depression Scale to assess social function, well-being and mental health.**
At all visits any prescribed and over the counter medication or supplement will be assessed (type and dose).

NUTRITION
We will assess nutritional intake with a food frequency questionnaire, and malnutrition with the Mini Nutrition Assessment. In addition, we will ask questions regarding cooking (self or others) and food preparation, as well as what participants shop and usually keep in their fridge. We will ask about food and drink preferences (packages, taste, favourite foods), and assess what participants think are healthy food sources. We ask about diets in the past and present, smoking and alcohol intake.

CO-MEDICATION
Except for the drugs mentioned in the exclusion criteria there is no prohibited Co-medication during the study.
POWER ANALYSES
PRIMARY AND MAIN SECONDARY ENDPOINTS

Functional decline:
Another goal of the proposed study is to test the null hypothesis that the proportion of individuals with functional decline (binary repeated measure assessment across 4 lower extremity tests) is identical in the two populations. The criterion for significance (alpha) has been set at 0.050. The test is 2-tailed, which means that an effect in either direction will be interpreted.

With the proposed sample size of 70 and 70 for the two groups, the study will have power of 86.6% to yield a statistically significant result.
This computation assumes that the difference in proportions is 0.30 (specifically, 0.60 versus 0.30). This effect was selected as the smallest effect that would be important to detect, in the sense that any smaller effect would not be of clinical or substantive significance. It is also assumed that this effect size is reasonable, in the sense that an effect of this magnitude could be anticipated in this field of research[57].

Difference in proportions of individuals reaching desirable 25-hydroxyvitamin D levels of at least 75 nmol/l
One goal of the proposed study is to test the null hypothesis that the proportion positive is identical in the two populations. The criterion for significance (alpha) has been set at 0.010. The test is 2-tailed, which means that an effect in either direction will be interpreted.
With the proposed sample size of 70 and 70 for the two groups, the study will have power of 94.8% to yield a statistically significant result.
This computation assumes that the difference in proportions is -0.30 (specifically, 0.60 versus 0.90).

Difference in mean 25-hydroxy-vitamin D levels
One goal of the proposed study is to test the null hypothesis that the two population means for 25-hydroxyvitamin D are equal. The criterion for significance (alpha) has been set at 0.050. The test is 2-tailed, which means that an effect in either direction will be interpreted.
With the proposed sample size of 70 and 70 for the active group I and the control group, the study will have power of 94.0% to yield a statistically significant result. This computation assumes that the mean difference is -15.0 nmol/l (corresponding to means of 75 nmol/l versus 90.0 nmol/l) and the common within-group standard deviation is 25.0 nmol/l (which is conservative according to the literature). The comparison of active group II to control will have power exceeding 100% with a mean difference of -45.0 nmol/l (corresponding to means of 75 nmol/l versus 120 nmol/l).
It is assumed that this effect size is reasonable, in the sense that an effect of this magnitude could be anticipated in this field of research[12].
Rate of falls

The power calculation assumes a mean repeat fall rate of 1.1 falls per person based on data from the literature and our previous studies. We assume a Poisson distribution for the number of falls, as our primary regression analysis will be a Poisson regression analysis aiming to compare the numbers of falls between the two monthly groups. As both groups receive vitamin D we expect a reduction in the natural rate in both groups and a more pronounced reduction in the high-dose group.

Poisson assumption: $E(x) = \text{Var}(x)$, thus $s$ (standard deviation) is not equal between groups.

\[
\begin{align*}
\mu_1 \text{ (mean)} &= 0.9 & \mu_2 &= 0.4 \\
\text{Difference in means} &= 0.5 \\
n_1 \text{ (number of subjects)} &= 70 & n_2 &= 70 \\
s_1 \text{ (standard deviation)} &= \sqrt{0.9} & s_2 &= \sqrt{0.4} \\
s_1 &= 0.95 & s_2 &= 0.63
\end{align*}
\]

\textbf{Power = 85\% with significance level (alpha) = 0.05}

Drop-out Rate Estimation and impact on Power

With an expected drop-out rate of 14\%, we will maintain power at 80\%.

With a sample size of 60 per groups (10 drop-outs per arm), the study will have a power of 80\% to yield a statistically significant result for difference in mean 25-hydroxyvitamin D levels, difference in proportion of individuals reaching desirable 25-hydroxyvitamin D levels of at least 75 nmol/l, difference in proportion of individuals with functional decline, and difference in rate of falls.

Also, we will have partial information on 30 drop-outs, yielding more than adequate power for the study.
OPEN DAILY SUPPLEMENTATION FOLLOW-UP Month 13-18

AIMS
1. To assess whether monthly intake of vitamin D is preferred to daily intake.
2. To assess adherence to daily vitamin D supplementation.
3. To assess 25-hydroxyvitamin D and parathyroid hormone level in August after the 6-month daily intake of vitamin D compared to 25-hydroxyvitamin D and parathyroid hormone level in August after 6 month treatment with monthly vitamin D (active group I and II, control group).

HYPOTHESES
1. We hypothesize that a higher percentage of individuals prefer their monthly regimen compared to their daily regimen (all get a monthly regimen for 12 month and a daily regimen for 6 months).
2. We hypothesize that adherence to daily vitamin D is 60% or less.
3. We hypothesize that 25-hydroxyvitamin D levels are lower and parathyroid hormone level are higher in August after the 6-month daily intake of vitamin D compared to August after 6 month treatment with any monthly vitamin D group (active group I and II, control group).

FALL-COHORT: MONTH 19+

After 18 month of follow-up, participants will be followed in the life-long Zurich Fall Cohort with 6-monthly telephone assessments of function, malnutrition, adverse events (falls, fractures, hospital admission, nursing home admission), and need and cost of care.

Within the fall cohort we will be able to establish risk factors and quality care, as well as determinants of repeat falls and fall resulting in fractures among pre-frail older individuals. We will assess and follow all individuals life-long and assess long-term predictors of independence and good function including nutritional, medical, and social aspects.
ETHICAL CONSIDERATIONS

Declaration of Helsinki
The current revision of the Declaration of Helsinki (Seul 2008) is the accepted basis for clinical study ethics, and must be fully followed and respected by all engaged in research on human beings. Any exceptions must be justified and stated in the protocol. Independent assurance that subjects are protected can only be provided by an ethics committee/institutional review board and freely-obtained informed consent.

Good Clinical Practice (GCP)
Good Clinical Practice (GCP) is an international ethical and scientific quality standard for designing, conducting, recording and reporting trials that involve the participation of human subjects. Compliance with this standard provides public assurance that the rights, safety and well-being of trials subjects are protected consistent with the principles that have their origin in the Declaration of Helsinki (DoH), and that the clinical trial data are credible.

The Guideline for Good Clinical Practice of the “International Conference of Harmonization of technical requirements for registration of pharmaceuticals for human use” (ICH Harmonized Tripartite Guideline – Guideline for Good Clinical Practice, step 4, 10 June 1996, abbreviated ICH-GCP”) focuses on and is mainly applicable to clinical trials of investigational products administered in a pharmaceutical form.

DOCUMENTATION AND ARCHIVING
All data will be collected and stored at the Centre on Aging and Mobility, University of Zurich (Location: Waid City Hospital). Subject anonymity will be maintained upon all data archiving and analyses steps. After cessation of the whole study (finalized and signed research report) the original CRFs and the investigator file will be stored at the Centre on Aging and Mobility, University of Zurich (Location: Waid City Hospital) for at least 15 years. The documents will be kept confidential in a secure location. Members of the ethical committee and the authorities will be allowed to review the original data.

All data will be entered anonymously into a secured data bank by the study staff. The data bank can only be accessed by the study staff of the Centre on Aging and Mobility. Any access outside the study staff must to be confirmed by the PI of the trial (Prof. Heike Bischoff-Ferrari, MD, DrPH). All data will be entered into the trial data base continuously and data will be frozen after the last entry. All analyses will be performed by the PI of the trial in collaboration with the statistician of the trial (Prof. EJ Orav, Harvard University). The study statistician will break the randomization code only when all data have been entered and the trial has been terminated at month 18.

The Centre on Aging and Mobility will archive the protocol, documentation, approvals and all other essential documents related to the study, including certificates that satisfactory audit and inspection procedures have been carried out. Copies of all human study material will be archived for a period of at least 15 years.

Monitoring
The trial will be monitored by the Clinical Trials Center (Zentrum Klinische Forschung USZ, UZH), which will visit the investigational site on a regular basis, at least once before the first subject has been enrolled (Pre-study and initiation visit), several times during the course of the study, and at study completion (Close-out visit). The monitor has the responsibility of reviewing the ongoing study with the investigator to verify adherence to the protocol and to deal with any problems that arise. The investigatory will inform the ethical committee of any change to the study protocol or violation of the protocol during the course of the trial.
<table>
<thead>
<tr>
<th>TABLE 1: VISITS and ASSESSMENTS</th>
<th>Screening</th>
<th>Baseline Day 0</th>
<th>Safety check Day 14</th>
<th>6 month</th>
<th>12 month</th>
<th>18 months</th>
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<td><strong>Visit 1</strong></td>
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### TABLE 1a: Questionnaires

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### TIME LINE:

- ethical committee: July 2009
- Swissmedic: December 2009
- Preparation of forms and manuals: January-June 2009
- Recruitment: December 2009 – May 2010
- Screening (Visit 1): December 2009 – May 2010
- Visit 2: January -May 2010
- Visit 3: February-June 2010
- -Visit 4: July-November 2010
- -Visit 5: January-May 2011
- - Visit 6: July-November 2011
LITERATURE


Attachment 1:
CONFIDENTIAL

Plasma Pharmacokinetics: Comparison between Oral Supplementation Regimens with 25(OH)D and Vitamin D3.

Background: For vitamin D, a plasma concentration of 75 nmol/l 25-hydroxyvitamin D has been suggested as the desirable lower threshold for optimal fracture prevention. Studies with 800 IU vitamin D3 may bring about 50% of individuals up to 75 nmol/l, however variation between studies has been large. Alternatively, treatment with 25(OH)D may achieve a more efficient and stable increase of 25-hydroxyvitamin D plasma concentrations.

Aim: We compared the 25-hydroxvitamin D plasma pharmacokinetics between oral supplementation with 25(OH)D and vitaminD3, respectively, over 16 weeks.

Methods: In this prospective, double-blind, randomized study with seven parallel groups (n = 35; age 50 – 74 years, body mass index 18.6 – 30.0 kg/m²), five healthy postmenopausal women per group were supplemented with 20 g 25(OH)D or vitaminD3 daily, with 140 g 25(OH)D or vitaminD3 weekly, or on a single occasion with either 140 g 25(OH)D or vitaminD3 or both. 25-hydroxyvitamin D plasma concentrations were analyzed by a LC-MS/MS method.

Pharmacokinetics were assessed with a non-compartmental approach, and comparison between groups was performed using a bioequivalence testing method.

Results: For daily dosing, the area under the curve after the first dose (AUC0-24) was 28% higher with 25(OH)D compared to vitaminD3 (90% CI; 2%-62%), while after 16 weeks exposure, the AUC was 123% higher for 25(OH)D compared with vitaminD3 (90% CI 82%-174%). For weekly dosing, the AUC0-24 after the first dose was 67% higher with 25(OH)D compared with vitaminD3 (90% CI 32%-112%), while after 16 weeks exposure, the AUC was 178% higher with 25(OH)D compared with vitaminD3 (90% CI; 138%-225%). Desirable 25-hydroxyvitamin D levels of at least 75 nmol/l were achieved in all women in the daily and weekly 25(OH)D dosing groups after a mean of 16.8 days, while only 7 of 10 women in the vitaminD3 daily or weekly dosing groups achieved this threshold. Additionally, they achieved the threshold significantly later at a mean of 68.4 days.

Conclusion: Using the same doses, 25(OH)D treatment is more than 2-fold more potent in raising 25-hydroxyvitamin D levels over 16 weeks compared to vitaminD3. This pharmacokinetic study indicates that the target range for 25-hydroxyvitamin D plasma concentrations is achieved earlier, in a higher percentage, and for a longer time period after 25(OH)D intake than after intake of vitaminD3.
Oral supplementation with 25-hydroxyvitamin D3 versus vitamin D3: effects on 25-hydroxyvitamin D status, lower extremity function, and blood pressure

Heike A Bischoff-Ferrari, Bess Dawson-Hughes, J Henschkowski, Hannes B. Stähelin, E Stöcklin, S Wolfram, Ferrari SM, A Egli

Background: Raising 25-hydroxyvitamin D levels to at least 75 nmol/l has been identified as a desirable range for anti-fracture efficacy, optimal lower extremity function, and the prevention of incident hypertension.

Aim: To test whether 20 µg of oral 25-hydroxyvitamin D (25(OH)D) per day is more efficient in raising 25-hydroxyvitamin D levels compared to 20 µg of vitamin D3 per day. Secondary endpoints were the odds of maintaining or improving lower extremity function, as well as difference in mean blood pressure by treatment.

Methods: We enrolled 20 healthy postmenopausal women with 25(OH)D levels below 60 nmol/l. Mean age was 61.5 years (SD+/- 7.2). Women were randomized to either 20 µg of oral 25(OH)D per day or 20 µg of vitamin D3 per day (800 IU / day) in a double blind randomized controlled trial with a 16 week follow-up. 25-Hydroxyvitamin D levels were measured with LC-MS/MS on 13 visits. The odds of maintained or improved lower extremity function at 16 weeks follow-up was compared between the 25(OH)D and vitamin D3 treatment groups across 4 tests including knee extensor and flexor strength, the timed up and go test, and the repeated sit-to-stand test. Standardized blood pressure measurements were taken in a sitting position after a 5 minute rest on 13 visits.

Results: Over 16 weeks, mean 25-hydroxyvitamin D levels increased from 30.7 to 162.2 nmol/l in the 25(OH)D group and from 35.5 to 76.2 nmol/l in the vitamin D3 group. With 25(OH)D treatment, the odds of maintained or improved function across the lower extremity test battery was 2.79-fold higher than with vitamin D3 (95%CI: 1.18-6.58). For each of the 4 tests and controlling for age and body mass index, as well as baseline strength/function, the 25(OH)D treated group appeared to be better than the vitamin D3 group at 16 weeks with a significant difference for knee extensor strength (p = 0.03). Across time, and controlling for baseline blood pressure, 25(OH)D treatment resulted in a 6.1 mmHG decrease in systolic blood pressure compared to vitamin D3 (p = 0.0002). There was also a small and non-significant decrease in diastolic blood pressure with 25(OH)D compared to vitamin D3 (1.4 mmHG ; p = 0.24). No hypercalcemia was observed for 25(OH)D or vitamin D3 treatment at any time point.

Conclusions: 25(OH)D at a dose of 20 µg per day resulted in a safe, immediate and sustained increase in 25(OH)D levels in all participants. In addition, there appeared be a significant benefit of 25(OH)D on lower extremity function and systolic blood pressure if compared to vitamin D3.
Red flags are missed in the prevention of hip fractures: baseline results of the Zurich hip fracture trial

Author Block
H. A. Bischoff-Ferrari¹, H. B. Staehelin*², B. Dawson-Hughes³, A. Platz*⁴, U. Can*¹, S. Looser*¹, B. Bretschner*⁵, R. Theiler*⁵. ¹Rheumatology, University of Zurich, Zurich, Switzerland, ²Geriatrics, University of Basel, Basel, Switzerland, ³Tufts University, Boston, MA, USA, ⁴Traumatology, Triemli Stadtspital, Zurich, Switzerland, ⁵Rheumatology, Triemli Stadtspital, Zurich, Switzerland.

Abstract:
Background: From 1-2005 to 12-2007, we recruited 173 patients age 65 and older with acute hip fracture and a Folstein mini mental score of at least 15 into an ongoing double-blind RCT with vitamin D. 69% of hip fracture patients were admitted from home and 31% from institutions, 79% were women. Mean age was 86 year (± 6.9).

Aim: We present results from 3 self-reported “red flag” questions answered 3 to 7 days after the acute hip fracture that should have triggered vitamin D supplementation prior to the hip fracture event.

Results: Upon admission to acute care, only 12% of hip fracture patients enrolled had any dose of vitamin D including multivitamin formulations. Mean 25(OH)D was 31.3 nmol/l (± 19) in hip fracture patients admitted from home and 33.3 nmol/l (± 23) in those from institutionalized care. 51% of hip fracture patients admitted from home and 54% admitted from institutions had severe vitamin D deficiency (25(OH)D of less than 30 nmol/l). 48% of hip fracture patients admitted from home and 51% of those admitted from institutions reported that they had a previous fracture outside the hip prior to the acute hip fracture event. Of those admitted from home, 29% reported that they had fallen rarely and 20% that they had fallen repeatedly in the last 6 month prior to the acute hip fracture event. Similarly, of those admitted from institutions, 27% reported that they had fallen rarely and 34% that they had fallen repeatedly in the last 6 month prior to the acute hip fracture event. Furthermore, 33% of those admitted from home and 24% from institutions reported that they felt weakness in their legs 6 months prior to their acute hip fracture event.

Conclusion: Vitamin D supplementation for the prevention of falls and fractures is recommended in several guidelines, however, according to our data collected between 2005 and 2007, guideline practice is still low. The positive report of red flags including previous fractures, previous falls, and muscle weakness is common in patients with acute hip fracture and may help increase guideline practice in older individuals.
Severe vitamin D deficiency in Swiss hip fracture patients

H.A. Bischoff-Ferrari a,b,*, U. Can c, H.B. Staehelin a, A. Platz c, I. Hensekowskia a, B.A. Michel a, B. Dawson-Hughes b, R. Theiler c

* Department of Rheumatology, University Hospital, Zurich, Switzerland
b Jean Meyer United States Department of Agriculture, Tufts University, Boston, USA
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Received 15 September 2007; revised 15 October 2007; accepted 21 October 2007

Abstract

Background: Most clinical guidelines for the prevention of hip fractures recommend 800 IU vitamin D per day. This dose shifted serum 25-hydroxyvitamin D levels (25(OH)D) in previous studies to between 60 and 100 nmol/l.

Aim: To measure 25(OH)D levels and prevalence of vitamin D supplementation in individuals age 65 with acute hip fracture.

Methods: 222 consecutive hip fracture patients were investigated over a 12 month period. Mean age of patients was 86 years and 77% were women. Results: Mean serum 25(OH)D levels were low among hip fracture patients admitted from home (34.6 nmol/l), from assisted living (27.7 nmol/l), and from nursing homes (24 nmol/l). Severe vitamin D deficiency, below 30 nmol/l was present in 60%, 80% were below 50 nmol/l, and less than 4% reached desirable levels of at least 75 nmol/l. Consistently only 10% of hip fracture patients had any vitamin D supplementation on admission to acute care with significantly higher 25(OH)D levels among individuals supplemented with 800–800 IU/day (63.5 nmol/l). Controlling for age and gender, vitamin D supplementation, type of dwelling and season were independently and significantly associated with 25(OH)D levels.

Conclusion: These data provide evidence that current guidelines for the prevention of hip fractures need further effort to be translated into clinical practice.

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Keywords: Hip fracture; 25-hydroxyvitamin D; Elderly; Guideline practice

Introduction

Fractures contribute significantly to morbidity and mortality of older individuals. Among individuals age 60 years and older, the mortality-adjusted residual lifetime risk of fracture has been estimated to be 44–65% for women and 25–42% for men [1]. After age 75, hip fractures are the most frequent fractures with up to 50% of older individuals having permanent functional disability, 15 to 25% requiring long-term nursing home care and up to 20% dying within the first year after the event [2–4]. The exponential increase in hip fractures after age 75 translates into an estimated 1 in 3 women, and 1 in 6 men who will have sustained a hip fracture by their 9th decade [5]. With the aging of the population a world-wide increase in hip fractures has been projected [6]. For Switzerland, a 33% increase in hip fractures has been estimated from 2000 to 2020 [7].

Given the high frequency of falls and fractures at older age plus future demographic changes with a significant increase of the older segment of the population, well tolerated and inexpensive prevention strategies are needed. For vitamin D, there is evidence today that with a daily intake of 800 IU vitamin D about one fourth of all first hip and any first non-vertebral fractures could be prevented [8]. In addition, addressing the primary risk factor of hip fractures, recent short- and long-term trials with vitamin D found a significant

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doi:10.1016/j.bone.2007.10.026

Please cite this article as: Bischoff-Ferrari HA, et al, Severe vitamin D deficiency in Swiss hip fracture patients, Bone (2007), doi:10.1016/j.bone.2007.10.026
Absolute 25(OH)D serum concentrations by month of measurement

Legend:
The graph shows absolute mean 25(OH)D serum concentrations by month of measurement suggesting a seasonal swing with highest levels achieved in late summer and fall whereas lowest levels are achieved in spring months. Both, mean 25(OH)D levels of summer months (June, July, August: p-value = 0.02), and fall months (September, October, November: p-value = 0.01) differed significantly from spring levels (March, April, May). The arrow indicates the threshold for adequate vitamin D status at 75 nmol/l. **Mean 25(OH)D levels measured for each month were far below adequate 25(OH)D status.**
Attachment 5 (full article is attached):

Prevention of Nonvertebral Fractures With Oral Vitamin D and Dose Dependency

A Meta-analysis of Randomized Controlled Trials

Heike A. Bischoff-Ferrari, DrPH; Walter C. Willett, DrPH; John B. Wong, MD; Andreas E. Stuck, MD; Hannes B. Stochl, MD; E. John Orav, PhD; Anna Thomá, MD; Douglas P. Reid, MD; Jana Herschkovits, MD

Background: Antifracture efficacy with supplemental vitamin D has been questioned by recent trials.

Methods: We performed a meta-analysis on the efficiency of oral supplemental vitamin D in preventing nonvertebral and hip fractures among older individuals >65 years. We included 12 double-blind randomized controlled trials (RCTs) for nonvertebral fractures (n=42,279) and 88 RCTs for hip fractures (n=10,086) comparing oral vitamin D with or without calcium, with calcium or placebo. To incorporate adherence to treatment, we multiplied the dose by the percentage of adherence to estimate the mean received dose (dose × adherence) for each trial.

Results: The pooled relative risk (RR) was 0.86 (95% confidence interval [CI], 0.77-0.96) for prevention of nonvertebral fractures and 0.91 (95% CI, 0.78-1.05) for the prevention of hip fractures, but with significant heterogeneity for both end points. Including all trials, antifracture efficacy increased significantly with a higher dose and higher achieved blood 25-hydroxyvitamin D levels for both end points. Consistently, pooling trials with a higher received dose of more than 400 IU/d resolved heterogeneity. For the higher dose, the pooled RR was 0.80 (95% CI, 0.72-0.89; n=33,705 subjects from 9 trials) for nonvertebral fractures and 0.82 (95% CI, 0.69-0.97; n=31,872 subjects from 5 trials) for hip fractures. The higher dose reduced nonvertebral fractures in community-dwelling individuals (−20%) and institutionalized older individuals (−13%), and its effect was independent of additional calcium supplementation.

Conclusion: Nonvertebral fracture prevention with vitamin D is dose dependent, and a higher dose should reduce fractures by at least 20% for individuals aged 65 years or older.

Arch Intern Med. 2009;169(6):551-561

Text:

The antifracture benefits of vitamin D have been questioned by several recent trials, leading to uncertainty among patients and physicians regarding recommendations for vitamin D supplementation. Two 2007 meta-analyses included most of these trials and concluded that vitamin D may not reduce fractures significantly or may do so only in combination with calcium and primarily among institutionalized older individuals. A third 2007 meta-analysis concluded that calcium with or without vitamin D may reduce total fracture risk by 12%, a result that was questioned by a more recent meta-analysis of high-quality trials of calcium supplementation alone in which calcium had a neutral effect on nonvertebral fractures and a possible adverse effect on hip fracture risk.

Apart from the mixed data on calcium, the recent meta-analyses with vitamin D did not consider heterogeneity by received dose (incorporating adherence) or achieved level of 25-hydroxyvitamin D.

A dose-response relationship between vitamin D and fracture reduction is supported by epidemiologic data showing a significant positive trend between serum 25-hydroxyvitamin D concentrations and hip bone density and lower extremity strength. In addition, greater antifracture efficacy with higher achieved 25-hydroxyvitamin D levels was documented in an earlier meta-analysis of high-quality primary prevention trials with supplemental vitamin D. Factors that may obscure a benefit of vitamin D are low adherence to treatment, low dose of vitamin D, or the use of less potent ergocalciferol (vitamin D3). Furthermore, open study design trials may bias results toward the null because vitamin D supplementation is available over the counter.

Our primary goal was to determine the antifracture efficacy of oral vitamin D supplementation among individuals aged 65 years or older by performing a systematic review of the literature and meta-analysis of high-quality, double-blinded RCTs. In addition, we specifically addressed anti-
Attachment 6 (full article is attached):

Calcium intake and hip fracture risk in men and women: a meta-analysis of prospective cohort studies and randomized controlled trials¹⁻³

Heike A Bischoff-Ferrari, Beiss Dawson-Hughes, John A Baron, Peter Burcickar, Rui Feng Li, Donna Spiegelman, Bonnie Specker, John E Orav, John B Wong, Hannes B Staehelin, Ellis O'Reilly, Douglas P Kiel, and Walter C Willett

ABSTRACT

Background: The role of total calcium intake in the prevention of hip fracture risk has not been well established.

Objective: The objective of the study was to assess the relation of calcium intake to the risk of hip fractures on the basis of meta-analyses of cohort studies and clinical trials.

Results: In women (7 prospective cohort studies, 170,991 women, 2,954 hip fractures), there was no association between total calcium intake and hip fracture risk [pooled risk ratio (RR) per 300 mg total Ca was 1.01 (95% CI: 0.97, 1.05)]. In men (5 prospective cohort studies, 60,656 men, 2,144 hip fractures), the pooled RR per 300 mg total Ca was 0.92 (95% CI 0.83, 1.03). On the basis of 5 clinical trials (n = 5,566 women, primarily postmenopausal, plus 107 men) with 814 nonvertebral fractures, the pooled RR for nonvertebral fractures between calcium supplementation (300–1,600 mg/d) and placebo was 0.92 (95% CI 0.81, 1.05). On the basis of 4 clinical trials with separate results for hip fracture (650 subjects with 139 hip fractures), the pooled RR between calcium and placebo was 1.64 (95% CI: 1.02, 2.64). Sensitivity analyses including 2 additional small trials with < 100 participants or pre-protocol results did not substantially alter results.

Conclusions: Pooled results from prospective cohort studies suggest that calcium intake is not significantly associated with hip fracture risk in women or men. Pooled results from randomized controlled trials show no reduction in hip fracture risk with calcium supplementation, and an increased risk is possible. For nonvertebral fractures, there was a neutral effect in the randomized trials.


KEY WORDS

Meta-analysis, hip fracture, nonvertebral fracture, calcium intake, calcium supplementation, cohort studies, randomized controlled trials

INTRODUCTION

Calcium supplementation or the consumption of calcium-rich foods such as milk is commonly recommended for the prevention of osteoporosis and fractures. These recommendations are primarily based on evidence from randomized controlled trials (RCTs) with bone density as the outcome. However, in a 2004 meta-analysis of RCTs, supplementation with 500–2000 mg Ca/d in postmenopausal women provided only a modest benefit for bone density: 2.05% difference in total-body bone density, 1.66% difference in lumbar spine bone density, and 1.64% difference in hip bone density (1, 2). The implications of such differences with respect to fracture risk prevention are unclear. In the same meta-analysis, limited evidence from RCTs (222 subjects in 2 trials) suggested only a modest and nonsignificant benefit of calcium supplementation for the risk of nonvertebral fractures [pooled risk ratio (RR) = 0.86; 95% CI: 0.43, 1.72]. Furthermore, an earlier meta-analysis published in 1997 that summarized observational studies in postmenopausal women found no clear benefit of a 300-mg increment in daily calcium intake for hip fracture risk [pooled RR among 28,513 women from 5 cohorts was 0.96 (95% CI 0.91, 1.02)] (3). Consequently, considerable uncertainty exists regarding optimal intakes of calcium, and this uncertainty is reflected in markedly different recommended daily intakes among countries. For example, for adults ≥50 y old, the recommended daily intake is 700 mg Ca/d in the United Kingdom and 1200 mg Ca/d in the United States (4).

¹ From the Departments of Nutrition (H.A.-F., E.O., and W.C.W.), Epidemiology (R.L. and D.S.), and Biostatistics (R.L. and D.S.), Harvard School of Public Health, Boston, MA; the Department of Rheumatology and the Institute for Physical Medicine and Rehabilitation, University Hospital Zurich, Zurich, Switzerland (H.A.-F.); the Jean Mayer USDA Human Nutrition Research Center on Aging, Tufts University, Boston, MA; the Division of Clinical Decision Making, Tufts-New England Medical Center, Boston, MA (H.B.W.); the Department of Geriatrics, University of Basel, Basel, Switzerland (H.B.W.); and the Institute for Aging Research, Hebrew SeniorLife, Harvard Medical School, Boston, MA (W.C.W.).

² Supported by grants from the Medical Foundation (Charles H. Fanninworth Trust; US Trust Company; Trustee and the Charles A King Trust; Fleet National Bank) and the International Foundation for the Promotion of Nutrition Research and Nutrition Education (ISPE), the Swiss Foundation for Nutrition Research (SFFFS), and the Swiss National Foundation (SNF) (Professors grant).

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Received June 22, 2002; Accepted for publication June 28, 2007.
Attachment 7:
McGill pain map

Overlay for scoring purpose
Vitamin D and Risk of Hypertension

Plasma 25-Hydroxyvitamin D Levels and Risk of Incident Hypertension

John P. Forman, Edward Giovannucci, Michelle D. Holmes, Heike A. Bischoff-Ferrari, Shelley S. Tworoger, Walter C. Willett, Gary C. Curhan

Abstract—Hydroxylation of 25(OH)D to 1,25-dihydroxyvitamin D and signaling through the vitamin D receptor occur in various tissues not traditionally involved in calcium homeostasis. Laboratory studies indicate that 1,25-dihydroxyvitamin D suppresses renin expression and vascular smooth muscle cell proliferation; clinical studies demonstrate an inverse association between ultraviolet radiation, a surrogate marker for vitamin D synthesis, and blood pressure. We prospectively studied the independent association between measured plasma 25-hydroxyvitamin D [25(OH)D] levels and risk of incident hypertension and also the association between predicted plasma 25(OH)D levels and risk of incident hypertension. Two prospective cohort studies including 613 men from the Health Professionals’ Follow-Up Study and 1198 women from the Nurses’ Health Study with measured 25(OH)D levels were followed for 4 to 8 years. In addition, 2 prospective cohort studies including 38,388 men and 77,531 women with predicted 25(OH)D levels were followed for 16 to 18 years. During 4 years of follow-up, the multivariable relative risk of incident hypertension among men whose measured plasma 25(OH)D levels were <15 ng/mL (i.e., vitamin D deficiency) compared with those whose levels were ≥30 ng/mL was 6.13 (95% confidence interval [CI]: 1.00 to 37.8). Among women, the same comparison yielded a relative risk of 2.67 (95% CI: 1.05 to 6.79). The pooled relative risk combining men and women with measured 25(OH)D levels using the random-effects model was 3.18 (95% CI: 1.39 to 7.29). Using predicted 25(OH)D levels in the larger cohorts, the multivariable relative risks comparing the lowest to highest deciles were 2.31 (95% CI: 2.03 to 2.63) in men and 1.57 (95% CI: 1.44 to 1.72) in women. Plasma 25(OH)D levels are inversely associated with risk of incident hypertension. (Hypertension. 2007;49:1063-1069.)

Figure 2. Predicted 25(OH)D levels had a diminished distribution compared with actual measured values; hence, predicted values were not directly comparable to measured values. A, Men: In 1980, the median (range) predicted 25(OH)D levels were 33.0 nmol/L (32.1 to 38.1) for decile 10 and 23.6 ng/mL (13.7 to 24.8) for decile 1. Decile 10 contained no black participants; decile 1 was 5.7% black. B, Women: In 1984, the median (range) predicted 25(OH)D levels were 33.7 ng/mL (32.6 to 37.6) for decile 10 and 21.4 ng/mL (7.3 to 22.6) for decile 1. Decile 10 contained no black participants; decile 1 was 8.8% black. P for trend was <0.001 in both men and women. Adjusted for age, BMI, physical activity, race, smoking status, family history of hypertension, and intakes of alcohol, vitamin D, folate, sodium, calcium, magnesium, and potassium. In women, we also adjusted for menopausal status.
Attachment 9:

Investigational product
Product name and formulation (Produktname Spanien = Hidroferol; Beipackzettel siehe nächste 2 Seiten)

**Product name:** 25-Hydroxyvitamin D$_3$, spray-dried form.

**Characterization:**
Powder, formulation given in Appendix II. 25-hydroxyvitamin D$_3$ and DL-alpha tocopherol are dissolved in triglycerides of medium chain fatty acids and then emulsified into an aqueous solution of modified starch, sucrose, and sodium ascorbate. The emulsion is atomized in a spray dryer in the presence of silicon dioxide. The resulting powder is collected and then filled into the containers. Ingredients and residual solvents comply with pharmacopoeia guidelines.

**Synonyms:**
- 25(OH)D$_3$
- 25(OH)D
- 25(OH) vitamin D
- Calcifediol
- Calcidiol
- 25-Hydroxycholecalciferol

**Product name:** Vitamin D$_3$, spray-dried form.

**Characterization:**
Vitamin D$_3$ and DL-alpha tocopherol are dissolved in triglycerides of medium chain fatty acids and then emulsified into an aqueous solution of modified starch, sucrose, and sodium ascorbate. The emulsion is atomized in a spray dryer in the presence of silicon dioxide. The resulting powder is collected and then filled into the containers. Ingredients and residual solvents comply with pharmacopoeia guidelines.

**Synonyms:**
- Cholecalciferol
- Calciol

The investigational product 25(OH) vitamin D will be given as hard gel capsules containing either 20 300 g active substance per capsule or placebo.
Ap Pierre Weller

Appendix I A Hidroferol In-Pack Information

Translated (Spanish-German) in-pack information for Hidroferol 0.1 mg/ml. Original given below.

Tropfen in Lösung
Calcifediol

Zusammensetzung
Calcifediol (25(OH)vitamin D) 0.1 mg
Hilfstoffe: Glicerol, tricaprilat/caprat, alpha tocopherol acetat 1 ml

Eigenschaften und Wirkungen

Dosierung
Erwachsene 5-50 Tropfen, oder mehr gemäss Indikationen
Kinder: Rachitis mit Hypokalzämie: 1-4 Tropfen pro Tag gemäss klinischem Bild.
Säuglinge: Resistente Rachitis, bis 100 Tropfen pro Tag

Anwendungsmöglichkeiten
Orale Anwendung, allein oder zusammen mit einem Löffel Milch oder Fruchtsaft.
Für Säuglinge: Nicht in die Trinkflasche geben, da die ölige Lösung an der Flaschenwand haften kann.

Kontraindikationen, Anwendungseischränkungen
HIDROFEROL darf nicht bei Anzeichen von Vitamin D-Intoxikation oder bei Hyperkalzämie verabreicht werden.

Interaktionen
Mit Schmerzmitteln und Hidatoinen muss die Dosierung angepasst werden

Unerwünschte Wirkungen
Mögliche Wirkungen sind wegen Überdosierung oder bei spezifischen individuellen Reaktionen.

Behandlung der Überdosierung oder Intoxikation

Packungen:
Tropfenzähler mit 10 und 20 ml

Warnung:
Ausserhalb der Reichweite von Kinder aufzubewahren. Rezeptpflichtig.
HIDROFEROL 0,1 mg/ml

Gotas orales en solución
Calcifediol

COMPOSICIÓN (cada ml, 25 gotas, contiene):
Calcifediol ........................................... 0,1 mg
Excipientes: Glicerol tricaprilato/caprato,
alfa-tocoferol acetato, c.s.p. ..................... 1 ml

INDICACIONES:

POSOLOGÍA:
Adultos: 5-50 gotas (1.200-12.000 UI de calcifediol) al día o más, según las indicaciones. Niños: Raquitismos carenciales con hipocalcemia: 1-4 gotas al día (240-960 UI de calcifediol), según los signos clínicos y biológicos. Niños y lactantes: Raquitismos resistentes: hasta 100 gotas al día (24.000 UI de calcifediol) en administración progresiva en función de los resultados y con vigilancia de la calcemia, calcuria y fosforemia.

NORMAS PARA SU CORRECTA ADMINISTRACIÓN:
Por vía oral, sólo o en una cucharada de leche o zumo. En lactantes no es conveniente administrarlo en el biberón, pues por su consistencia oleosa podría quedar adherido a las paredes.

CONTRAINDICACIONES Y PRECAUCIONES:
HIDROFEROL está contraindicado si apareciesen signos de hipervitaminosis, con aumento excesivo de la calcemia. Debe vigilarse periódicamente la calcemia y calcuria para evitar el riesgo de sobredosificación.

INCOMPATIBILIDADES:
No se han descrito.

INTERACIONES:
La terapia con metabolitos de la vitamina D3 presenta interacciones con barbitúricos e hidantoinas, que obligan a ajustar la dosis.

EFECTOS SECUNDARIOS:
Los efectos secundarios que pueden aparecer por administración de HIDROFEROL son debidos a sobredosificación o susceptibilidad individual, éstos pueden ser hipertensión, elevación del calcio sérico y
Attachment 10:

Packaging and labelling
The capsules are packaged in Duma bottles. Boxes of bottles and containers containing the capsules will be labeled bearing the following information:

Nur für den klinischen Versuch in Studie KEK Nr. 39/09
Study ID XX
Arzneimittel bei 2 – 8°C im Kühlshrank ausserhalb der Reichweite von Kindern aufzubewahren.
Chargennummer __________ Verfall Datum __________

Handling and storage conditions:
Store the products in original containers in a secured, dry storage area at 2-8 degrees celcius.

Dosage regimen:
Each supplement will be consumed orally. Once per month, drink one bottle (poor into water, juice, or milk) and two capsules with breakfast. No dose adjustment is planned.

Route of administration:
Supplement bottles and capsules will be taken orally with breakfast.

Treatment duration:
Duration of the supplementation will be 12 months.

Dispensing and accountability:
The trial centre (Waid City Hospital; Centre on Aging and Mobility) will fill in a Dispensing and Return Log in order to account for investigational product dispensed and returned by the subject. It will be kept up-to-date and list the study ID, the amount of investigational product and date dispensed to the subject and the amount of product and date returned. At each visit, the subjects will be given a container with a supply of supplements for the following months until the next visit. Subjects will be instructed to return the bottles and capsule containers on each visit.

Warnings and Precautions
Given the screening procedures where individuals at risk for hypercalcemia are excluded, and supplemental calcium intake is prohibited beyond 250 mg per day, there are no warnings regarding the supplement. In addition, all participants will be closely assessed for side effects and hypercalcemia. In addition, there will be a safety laboratory at 2 weeks after treatment initiation.

Concomitant treatments and restrictions
All additional medication use will be recorded in the CRF’s at each visit (BL, 6 months, 12 months, 10 month visit or telephone). If treatment for adverse events becomes necessary, the medication(s) will be reported on the concomitant medication section of the case report form (CRF), including generic name, indication, total daily dose, route and time/duration of administration.

Obtaining informed consent
Subjects who are foreseen to fulfill the inclusion / exclusion criteria for enrolment into the study will be asked to give informed consent prior to any study specific procedures. Both the subject (or legal representative) and investigator will sign and date the informed consent
All subjects who have signed the information consent form will be listed on the Subject Screening and Enrolment Log.
CONTRIBUTIONS / EXPERTISE OF CO-INVESTIGATORS

Prof. Bess Dawson-Hughes (Tufts University, Boston)
- Calcium and Vitamin D Metabolism / Dose-finding

Prof. Hannes B. Staehelin (University of Basel)
- Geriatric Assessments / Cognitive Tests

Prof. Reto Kressig (University of Basel)
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- Pain Assessment

Prof. Robert Theiler (Triemli Stadtpital, Zurich)
- Functional Assessments

Prof. Endel J. Orav (Harvard School of Public Health, Boston)
- Statistician / Trial Design

PD Nicolas Mueller (University Hospital Zurich)
- Infections Assessment

Prof. Richard Hurrell (ETH, Institute of Food Science and Nutrition)
- Assessment of other micronutrient deficiencies

Prof. Walter C. Willett (Dept. of Nutrition, Harvard School of Public Health)
- Food intake assessment

Prof. Walter Dick (University of Basel)
- Assessment of fall-related injuries -- fractures

Prof. José daSilva (University of Coimbra)
- Assessment of bone health and musculoskeletal pain

Advisors / Collaborators:
Prof. Andreas Maetzel: Health Economy
Dr. Daniel Grob: Geriatric Care – Need of Care in the Elderly
SIGNATURES

Sponsor

Prof. Dr. med. Heike A. Bischoff-Ferrari, MD, DrPH
25.01.2011___________________________ date, sign

Haupt-Prüfer

I certify that I read this study and understand and accept all parts.

Prof. Dr. Med. Heike A. Bischoff-Ferrari, MD, DrPH
25.01.2011___________________________ date, sign

The present study was created according to the criteria of ICH-GCP.