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 Tampere
 1.9.2008

Effects of vitamin D and exercise in prevention of falls

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Key words: exercise, falls, physical functioning, vitamin D, mobility function, neuromuscular functioning, quality of life.

Avainsanat: liikunta, kaatumiset, fyysinen toimintakyky, D-vitamiini, liikkumiskyky, hermolihasjärjestelmän toiminta, elämänlaatu.

Introduction

The rise in the number of the elderly over the next few decades will be accompanied by an increased number of people with disease and chronic illness. Older people are less resistant to injury, whether from physiological events (e.g. heart attack) or environmental trauma (e.g. bone fracture), and they are less resistant to infection.¹ However, if ageing is combined with extended years of healthy life it could also produce desirable social, economic and health benefits. Health maintenance for people throughout the life, such as exercise and proper nutrition, contribute to lifelong wellbeing.²

Osteoporosis, with the main outcome problem of fractures, is a multifactorial disease characterized by low bone mineral density (BMD) and decreased bone strength. Often these people also have neuromuscular deficiencies resulting in increased risk of falls. Falls are the leading cause of unintentional injury and death. Approximately 30% of community living people aged 65 years or older fall each year the number being even higher in institutions. Although less than one fall in 10 results in a fracture, 20% of fall incidents require admissions to hospital.³⁻⁵ Since a greater propensity to fall will increase the risk of fracture and other injuries considerably, fall prevention is widely seen as the most essential element in the planning of effective injury and fracture prevention among any elderly population.^{3, 6, 7}

Preventing falls and injuries among older adults is really challenging. There is, however, strong evidence from randomized controlled trials and subsequent systematic reviews and meta-analyses that regular strength and balance training for elderly adults living in the community can reduce the risk of both noninjurious and injurious falls by 15-50%.^{3, 7, 8} Randomized controlled trials indicate that not only individually tailored training but also more untargeted group exercise programs are effective in preventing falls,⁹⁻¹² particularly if the training program involves Tai Chi or other exercises which challenge balance.^{12, 13} Thus, it seems prudent to recommend regular weight-bearing and other exercises for community-dwelling older adults, not only to maintain their functional ability, bone health and muscular performance, but also increase their balance confidence to keep them safely on their feet and avoid breaking their bones.¹⁴⁻¹⁸

Hypovitaminosis D is becoming widespread around the world regardless the latitude. Serum 25-hydroxy vitamin D (S-25-OHD) concentration, which is the best indicator of vitamin D status, has been shown to decrease in elderly Finnish women in wintertime.^{19, 20} It has been estimated that ambulatory elderly women require on average 18 µg vitamin D a day to maintain adequate vitamin D status (S-25-OHD above 50 nmol/L) during winter. To reach 60 nmol/L, which is a typical concentration in summer, the total mean intake should be approximately 24 µg, while actually it is only one third being about 8 µg.^{19, 21} This low intake may be a problem, since a higher S-25-OHD concentration is linked to higher bone mass in all ages, while inadequate intakes of vitamin D and calcium lead to reduced calcium absorption, higher bone turnover and increased bone loss and risk of fractures.²²⁻²⁵ Even more important may be that there is fair evidence that S-25-OHD level is inversely associated with falls.^{24, 26, 27} In randomized controlled trials the incidence of falls was almost halved and musculoskeletal function improved among elderly people with a combination of vitamin D and calcium compared with calcium supplement alone.^{28, 29} Falling may, at least partly, be a consequence of impaired neuromuscular function associated with vitamin D deficiency, since abnormal motor performance, increased body sway, and quadriceps weakness have been reported in those with low vitamin D status. Vitamin D receptors are known to be present in muscle tissue. Furthermore, the number of fast type II muscle fibers decreases with age, and these fibers are the first to be recruited in balance disturbance to avoid falling.^{30, 31}

In prevention of fractures of elderly people, a strong focus should be targeted on improving the decreased muscle strength and the neuromuscular co-ordination to avoid falls instead of treating of low BMD, since most fractures are a direct consequence of falling.³² Although a recently published meta-analysis found little evidence that current multifactorial falls prevention programs could

prevent falls and related injuries,³³ it must be kept in mind that great majority of fall-prone elderly adults has more than one risk factor for falls. Furthermore, the fear of falling may result in restriction of physical activity and functional ability.^{16, 34, 35} Randomized controlled trials suggest that exercise may effectively improve many risk factors of falling, such as muscle strength, flexibility, balance, coordination, proprioception, reaction time and gait³⁶⁻³⁸ and prevent falling.^{3, 7, 8, 39} Regular moderate-to-vigorous exercise is also associated with reduced number of fractures.^{14, 17, 18} Also vitamin D has been proposed to protect against falls.²⁷ In spite of the strong evidence that both of these factors improve neuromuscular and cognitive function, and may reduce the risk of falls, these factors have not been evaluated together. Given the above, it is well justified to study the separate and combined effects of exercise and vitamin D in prevention of falls.

Purpose

Prevention of fractures includes reducing the number of falls, reducing the trauma associated with falls, and maximising bone strength. Nutritional factors, such as adequate intake of calcium and vitamin D, as well as physical activity are important not only in prevention of bone loss, but especially in preventing falls. In this study the primary purpose is to investigate both the separate and interactive effects of exercise and vitamin D supplementation on reducing falls and injuries in community-dwelling, independent-living women aged 70 years and older.

The primary outcomes of the study are the rate of falls, number of fallers and fall-related injuries. Rate of repeated falls and fallers, time to first fall, and fall-related medical consultations will also be reported. Changes in neuromuscular functioning (e.g. body balance, muscle strength), ADL- and mobility functions, bone status, fractures, cardiovascular risk factors, quality of life, fear of falling and institutionalization will be analysed as the secondary outcomes.

Study design and time schedule (Fig. 1)

The participants were randomly assigned into one of four groups: 1) exercise with vitamin D, 2) exercise with placebo, 3) no exercise with vitamin D, 4) no exercise with placebo. Duration of the intervention will be 24 months. After the intervention the subjects will be followed up for 2 years.

Methods to evaluate functional ability, quality of life, fear of falling (Falls Efficacy Scale-International, FES-I) and CHAMPS (activities questionnaire for older people) modified suitable for the Finnish culture were validated before the intervention in a randomized controlled trial.³⁶

Figure 1. Description of the time schedule.

2008	2009	2010	2011	2012	2013
Validation of questionnaires	Recruiting and randomization of the first 200 participants.	First 100 trainees start the training 2x a week, 100 referents start as controls. Recruiting and randomization of the other 200 participants.	First 100 trainees continue training once a week, and 100 trainees start training 2x a week, all 200 referents are included.	First 100 trainees and referents complete the study, other 100 trainees continue training once a week, and 100 referents continue	The rest 100 trainees and 100 referents complete the study. Start of reporting.

Subjects and methods

Screening for inclusion: A questionnaire was sent to 9370 70-79-year old women (born between 1930-1940) living in Tampere, inquiring whether they were interested in participating in this randomized, controlled intervention trial. Responders who express their interest (n= 1228) received a screening form *Health history questionnaire* (information of the self-reported health, previous falls, injuries, medication, diseases, and life style factors such as diet, physical activity, smoking and consumption of alcohol). The eligible women were then invited to a screening examination (n=433) (Table 1). The final screening of an individual qualified for the study required one visit which encompasses physician examination and completion of a health history questionnaire leaving 409 women for randomization using a computer-generated randomization list.

Table 1. Inclusion and exclusion criteria for the study.

Inclusion criteria	Exclusion criteria
<ul style="list-style-type: none"> - age between 70-79 years, living at home independently - had fallen at least once during the previous year - no contraindication to exercise - participant understands the procedures of the study, has been informed of X-ray radiation doses of the DXA and pQCT investigations, and amount of blood samples needed, and voluntarily agrees to undergo all measurements. 	<ul style="list-style-type: none"> - moderate-to-vigorous exercise more than 2 hours per week - regular use of vitamin D or calcium + vitamin D supplements - a recent fracture (during preceding 12 months) - contraindication or inability to participate in the exercise program - persons with a marked decline in the basic activities of daily living (ADL-test) - persons with cognitive impairments (Mini Mental State Examination, MMSE-test) - persons with degenerative conditions, such as Parkinson's disease.

Falls: The number of falls will be gathered with daily falls diaries. Diaries will be collected monthly by posting to the investigator. Ascertainment of the details of each registered fall will be done by the investigator. The definition of a fall is “an unexpected event in which the participants come to rest on the ground, floor or lower level.”⁴⁰ Injurious falls are those requiring medical attention and treatment.

Measurements

All measurements will be done at baseline, and at 12- and 24-month (the end point of the intervention). Blood samples and physical functioning will also be assessed at 6- and 18- month time points.

General health status and falls consequences: Information on the participant's health, medication, lifestyle (level of physical activity, use of alcohol, smoking, diet), quality of life, activity of Daily Living (ADL), mobility and cognitive functions will be assessed with appropriate methods and FES-I (Falls Efficacy Scale-international) in assessing fear of falling.

Anthropometry: Body height and weight will be measured with standard methods. Body composition (fat mass and lean mass) will be estimated with DXA (Lunar Prodigy Advance, GE Lunar, Madison, WI, USA). According to repeated measurements of 22 adults, the *in vivo* precision (coefficient of variation, CV%) was 1.3% for fat mass and 0.7% for fat-free mass (Sievänen, unpublished).

Bone measurements

Dual-energy X-ray absorptiometry (DXA): Bone mineral content (BMC) of the total body, lumbar spine and left proximal femur (femoral neck and trochanter) will be assessed with DXA (Lunar Prodigy Advanced, GE Lunar, Madison, WI, USA) accordant to our standard procedures. In addition, strength of the femoral neck will be analyzed from the DXA-measurements including cross-sectional area (CSA, an index of bone strength against compression), section modulus (Z, an index of bone strength against bending) and periosteal diameter.

Peripheral computed tomography (pQCT): In addition to DXA measurements, the left tibia will be measured with pQCT (Norland/Stratec XCT 3000, Pforzheim, Germany). The tomographic slices will be taken from the midshaft and distal part of the tibia. For the shaft region, the analyzed variables are BMC, cortical cross-sectional area (CoA, mm²), cortical density (CoD, g/cm³) and density-weighted polar section modulus or bending strength (BSI). For the distal tibia the variables are BMC, trabecular density (TrD, g/cm³) and BSI accordant to our standard procedures.⁴¹

Dietary intake: Dietary intakes of calcium and vitamin D will be assessed with a 7-day calcium intake diary⁴² and food frequency questionnaire⁴³ and calculated by Micro-Nutrica software (Social Insurance Institution, Helsinki, Finland).

Physical activity: CHAMPS (activities questionnaire for older people) will be used in assessing physical activity, and over the entire 2-year study period, the subjects will keep an exercise diary for type and duration of all physical activities. Diaries will be collected monthly by posting to the investigator. In addition, each subject's daily walking distance will be measured during the intervention with a pedometer (Omron HJ-112-E).

Physical performance and physical functioning: maximal leg-extensor strength and grip strength of the both forearms, and dynamic balance and reaction time will be measured by a standard methods used at the UKK Institute. In addition to self-rated questionnaire, timed up and go test (TUG) and validated test battery of Guralnik will be used in assessing physical functioning.^{44,45} The test battery is targeted for older adults.

Laboratory measurement: Serum 25-hydroxy-vitamin D (S-25-OHD) will be measured as a marker of vitamin D-metabolism. In addition, serum intact parathyroid hormone (S-iPTH) will be measured, as it is usually increased when S-25-OHD is low, and gives additional information on the severity of vitamin D deficiency. Genomic DNA sample will be taken for the assessment of the vitamin D receptor (VDR) gene polymorphism. As markers of cardiovascular health, risk factors of metabolic syndrome, e.g. waist circumference, blood pressure and serum lipids, markers of inflammation (hsCRP, IL-6, TNF- α), adipokines (leptin, adiponectin), cholesterol ester transfer protein, and oxidized LDL- and HDL-lipids will be determined.

Statistical analysis and power calculation: The incidence rate will be calculated as the number of falls divided by the time over which falls is monitored for each participant. Poisson regression models will be used to estimate incidence rate ratio between the two groups for falls and falls with injury. Between-group changes in neuromuscular functioning, functional ability, bone variables, cardiovascular risk factors, and quality of life will be analysed by analysis of covariance (ANCOVA) or logistic regression analysis.

The sample size and power calculations have been estimated for the primary outcome of this study, i.e., the rate of falls. We hypothesized that there will become a 30% difference in the rate of falls between the treatment groups (vitamin D vs. placebo, and exercise vs. non-exercise). Accordingly, 260 subjects in total should be recruited into the study (130 exercisers and 130 non-exercisers, 65 in each group with vitamin D supplement) in total will be needed to show that the intervention (exercise or vitamin D) would reduce the incidence rate of falls during the two years by 30% at a significance level of 0.05, and at a power of 80%, with a mean treatment time of 1.5 years. However, in order to increase chance to detect possible interaction of vitamin D and exercise, a total number of 400 subjects (100 subjects in each group) will be recruited into the study.

Intervention

Vitamin D supplements/placebo: The participants were randomly assigned to receive placebo (50% of the participants) or 20 μ g of vitamin D (50% of the participants) per day for two years. Both participants and outcome assessors are blinded to the group assignment of placebo or vitamin D during the study. Compliance will be confirmed with pill counts. A health status questionnaire will be administered to all participants at 6, 12, 18, and 24 months of follow-up to monitor safety. As standard safety markers, S-Ca and S-Pi will also be assayed in six month intervals. Calcium supplementation is not given since mean dietary calcium intake of elderly home-dwelling Finnish women is sufficient compared with the recommendation.¹⁹

Training program: Participants in the exercise groups (n=205, 50% of the participants, with vitamin D or placebo) participate in supervised training classes two times a week for 12 months, and once a week during the next 12 months. All supervised training sessions will be led by experienced exercise leaders of the UKK Institute. The training consists of strength, balance and mobility training. In addition to supervised training sessions, the exercisers have a home-training program

for daily training based on programs used in training sessions. The participants in the non-exercising group (n=204, 50% of the participants, with vitamin D or placebo) are asked to maintain their current level of physical activity.

Ethics issues

This study will be carried out conforming to the guidelines of good scientific practice and to provisions of the Medical Research Act. The aim of the study as well as risks and benefits has been clarified for those women recruited to the study. The same information has been given in a written format. Subjects agreeing to participate have signed the informed consent document. All collected data concerning the participants will be handled according to Finnish Personal Data Act. The use of data requires passwords and understanding of the matters confidentiality. All collected data will be preserved at the UKK Institute. The data will be preserved until year 2020 after which the personal identification numbers are deleted. The approval of the Pirkanmaa Hospital District Ethics Committee has been admitted for the validation of the questionnaires (R08125) and for the intervention protocol (R09090). The study protocol is registered in the ClinicalTrial.gov –register 29.9.2009 (NCT00986466).

Current status

For practical reasons, the trial started in two phases (201 participants were recruited in March 2010 and 208 participants in March 2011). The end-point measurements after the intervention will be carried out in spring 2012 for the first recruited sample, and 2013 for the last recruited sample. The last follow-up measurements will be done in 2014 and 2015, respectively. Currently we are doing the 18-mo measurements for the first recruited participants and 6-mo measurements for the last recruited participants. The study progresses according to schedule.

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