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Vitamin D and Longevity (VIDAL) Trial: Randomised Feasibility Study

Submission date
05/07/2011

Recruitment status
No longer recruiting

Registration date
02/08/2011

Overall study status
Completed

Last Edited
25/02/2020

Condition category
Nutritional, Metabolic, Endocrine

[X] Prospectively registered
[_] Protocol
[_] Statistical analysis plan
[X] Results
[_] Individual participant data

Plain English summary of protocol

Background and study aims
Vitamin D is essential for good health, because it helps our bodies to absorb calcium from the diet. There is a lot of evidence that having enough vitamin D can help prevent against many diseases, such as heart disease, bone diseases and cancer. Although vitamins generally come from the diet, in the case of vitamin D, the majority of people actually get most of it from sunlight. When the sun shines on our skin, a reaction in the body is triggered, producing an active form of vitamin D (known as vitamin D3). Studies have shown that many people in the UK suffer from a lack of vitamin D (vitamin D deficiency) because of the lack of sun exposure, especially in the older generation. A possible solution for this may be to take vitamin D supplements, to ensure that people are getting enough. A large study has been suggested to test the effects of taking vitamin D supplements over a 5 year period. This will aim to see if taking monthly vitamin D can reduce the levels of death and illness in people between the ages of 64-85. This initial study aims to find out whether or not a placebo (dummy pill) should be used in the final study.

Who can participate?
Adults between 65 and 84 years old, with a corrected serum calcium level of 2.65mmol/L, which are registered at one of the participating GP practices.

What does the study involve?
Each GP practice that is included in the study is randomly allocated into two groups. The practices in the first group included in a “placebo-controlled” trial. For these practices, the participants are either given the treatment of vitamin D3 supplements or a placebo (dummy pill), but they are not aware of which treatment they are receiving. Practices in the second group, are included in an “open-label” trial. This means that the patients and the researchers know which treatments are being given. Over the two year study period, the investigators assess which of the two types of study is more successful. Blood samples are taken from all participants in both study types in order to assess the vitamin D concentrations in the blood.

What are the possible benefits and risks of participating?
Not provided at time of registration.

Where is the study run from?
London School of Hygiene and Tropical Medicine (UK)

When is the study starting and how long is it expected to run for?
January 2012 to December 2013

Who is funding the study?
The NIHR Health Technology Assessment Programme (UK)

Who is the main contact?
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Contact information

Type(s)
Scientific

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Additional identifiers

Protocol serial number
HTA 08/116/48

Study information

Scientific Title
Feasibility study for a large randomised controlled trial measuring the effect of oral vitamin D on morbidity and mortality in men and women aged 65-84

Acronym
VIDAL

Study objectives
This is the feasibility study is that monthly oral vitamin D will reduce overall mortality in men and women aged 65-84.

Background
A consensus is emerging that circulating 25-hydroxyvitamin D (25(OH)D) concentration - the measure of vitamin D status - should be at least 75 nmol/l (30 ng/ml) for optimal health and increased life expectancy. Over eighty percent of the UK population aged over 65 years have levels of 25(OH)D below 75 nmol/l.

Several epidemiological studies report a correlation between low circulating 25(OH)D and the risk of developing various cancers, particularly colorectal cancer. Positive associations have however been reported between vitamin D status and risk of prostate cancer and pancreatic cancer, highlighting the need for large randomised trials. The epidemiological evidence that various other vitamins prevent cancer has been disproved in randomized trials. Associations between inadequate vitamin D status and increased risk of cancer reported in observational studies could thus be at least partly due to confounding, and no adequately powered trial has tested vitamin D in doses that are high enough to achieve serum 25(OH)D concentration > 75 nmol/l.

Evidence on vitamin D and heart disease from nested case-control studies includes elevated risk of myocardial infarction in men with low 25(OH)D levels in stored blood samples. A systematic review suggested that optimal serum 25(OH)D for all endpoints should exceed 75 nmol/l and that this can be achieved with the proposed dose without increasing health risks. Other effects of low circulating 25(OH)D may include compromised immunity. These pleotropic effects are supported by experimental studies. The active metabolite of vitamin D, 1,25-dihydroxyvitamin D, suppresses proliferation and induces differentiation of cancer cells in vitro, and its receptor and the enzyme that synthesises it are both expressed in many cell types. However, although the majority of observational studies report associations between vitamin D deficiency and susceptibility to a range of pathologies, some studies are null, and a few report opposite associations. The existing evidence is thus not sufficient as a basis for a universal policy of high-dose vitamin D supplementation.

A meta-analysis of published randomized trials on the effect of vitamin D on overall mortality (Autier and Gandini 2007, Arch Intern Med 167: 1730-7) showed a marginally significant reduction in overall mortality of 7% (95% CI 1%-14%: p<0.05). The meta-analysis included a British study of people aged 65-85 years randomised to 100,000 IU oral vitamin D3 or placebo every four months over five years. The authors¡¯ main recommendation was for large population-based randomised trials of prolonged vitamin D3 treatment at adequate dose, with total mortality as the primary endpoint.

The International Agency for Research on Cancer (IARC) Working Group on vitamin D and cancer reviewed the epidemiological evidence on vitamin D and cancer and concluded that the evidence was strong for colorectal cancer but inconclusive for other individual cancers (IARC Working Group on Vitamin D, 2008) Their report concluded: ¡°The only way to further address the cause-effect issue is to organise new randomized trials to evaluate the impact of vitamin D on all-cause mortality and on the incidence and mortality from common conditions including cancer. These trials should make sure that key parameters of vitamin D status (e.g., serum 25-hydroxyvitamin D levels before and in trial) can be assessed.¡±

Rationale For Current Study:
The proposed regimen (100,000 IU vitamin D monthly, equivalent to 3200 IU per day) is less than the current tolerable upper intake limit of 4000 IU/day for vitamin D in North America, defined as ¡°the highest daily level of chronic nutrient intake that is likely to pose no risk of adverse health effects to almost all individuals in the general population¡± (Institute of Medicine of the National Academies, 2011). Indeed a risk assessment based on a review of clinical trial data

concluded that a daily dose of at least 10,000 IU/day is safe, and the Institute of Medicine report accepts that this intake represents the NOAEL (no observable adverse effect level), which was adjusted for uncertainty to establish an upper limit of 4000 IU per day.

The main trial for which this is the feasibility study will be a randomized trial with 20,000 subjects followed for 10 years. A trial of that size will be needed to detect the 7% reduction that vitamin D supplementation might plausibly achieve in total mortality in healthy adults aged over 65 (Autier and Gandini 2007, Arch Intern Med 167: 1730-7). If self-administered vitamin D supplementation were shown to confer substantial health benefits it would be routinely recommended and widely adopted. This would also provide a rationale for a national policy of vitamin D supplementation for the general population, a review of the relative risks and benefits of sun exposure, and a revision of existing policy on vitamin D fortification of foods. If we show no benefit or unforeseen disadvantages this will also be a valuable contribution to knowledge.

An important public health priority is therefore to demonstrate the feasibility of a large randomized trial of prolonged vitamin D supplementation in older people, and to show that this will increase serum 25(OH)D to >=75 nmol/l in the majority of subjects. As well as demonstrating an expected increase in circulating 25-hydroxyvitamin D levels, the feasibility study will provide estimates of cost and establish the study design and procedures required for the main trial. An important feature of the feasibility study will be the comparison of a placebo control group with an open control group with no treatment. Randomized double-blind placebo-controlled trials are considered the gold standard, particularly where the endpoint is subjective, but an open control design may be acceptable where the main endpoint is overall mortality. The primary purpose of this feasibility study is to ascertain recruitment levels, but the study will also include a cluster randomized comparison of the effects of placebo versus open control trial design on the reliability of self-reported minor infections and adverse effects as well as on recruitment, participant acceptability and treatment compliance. The study will thus provide much needed evidence on an important methodological (and economic) issue in the design of pragmatic trials in preventive medicine.

Ethics approval required
Old ethics approval format

Ethics approval(s)
South East MREC, 10 August 2011

Study design
Randomised controlled trial, open or double-blind placebo control, and individual randomisation to vitamin D or control within each practice.

Primary study design
Interventional

Study type(s)
Treatment

Health condition(s) or problem(s) studied
Vitamin D supplement on morbidity and mortality

Interventions

Participants will receive either:
1. 100,000 IU monthly (average 3300 IU/day) of oral vitamin D3 or double-blind placebo control (800 participants)
2. 100,000 IU monthly (average 3300 IU/day) of oral vitamin D3 or open control (800 participants)

Intervention Type
Other

Phase
Not Applicable

Primary outcome(s)
1. The successful establishment of the procedures required to identify, invite and recruit eligible patients. Our target is to randomise 1,600 participants aged 65-84 through 20 GP practices.
2. Overall recruitment rate and comparison of recruitment rate in placebo versus open control studies
3. Overall level of compliance with study medication and comparison of placebo versus open control medication compliance (to evaluate whether participants taking open label vitamin D are more or less compliant than those who are unaware of IMP status)
4. Contamination: whether open controls are more likely to take vitamin D supplements than placebo controls
5. Overall level of attrition over 2 years and comparison of attrition rates in open label and placebo-controlled practices
6. Costs of placebo versus open control study designs to determine whether the extra costs of placebo would be justified in the main trial (participants randomised to an open untreated control arm may take supplements containing vitamin D more frequently than those on placebo)
7. Comparison of incidence of serious adverse events between vitamin D and control in placebo-controlled practices
8. Comparison between vitamin D and control of infections, GP prescriptions and frequency of GP visits:
8.1. In placebo-controlled practices, and
8.2. In open-label practices
This will provide an estimate of the bias in these measures in participants allocated to vitamin D in an open control design
9. Serum 25(OH)D concentration at recruitment and at 2-year follow-up in relation to potential determinants of vitamin D status including self-reported compliance with study medication
10. Cause-specific mortality and cancer incidence will be ascertained by flagging in the National Health Service Information Centre (NHS IC)
11. Hospital records will be collected by NHS number linkage with Hospital Episode Statistics (HES)

Key secondary outcome(s))
Before randomisation:
1. An online lifestyle questionnaire on foreign holidays, sunbathing, sunbed use and use of vitamin supplements will be completed at the GP practice by all participants (treated and control) before randomisation
2. A blood sample will also be taken, and corrected serum calcium will be assayed before randomisation to establish eligibility. Serum 25(OH)D will also be assayed. Aliquots (plasma and buffy coat) will be stored in liquid nitrogen for further analysis (subject to additional funding) including genetic studies.

At two years:
1. All 1600 participants will attend the GP practice 2 years after randomization. A further blood sample for 25(OH)D assay and a second copy of the same online questionnaire will be obtained to quantify differences in vitamin D status between the intervention and control groups in blinded versus open label studies.
2. Summaries of GP records for all participants will also be extracted for GP visits, prescriptions and infections for one year pre-randomisation and 2 years post-randomisation.

Completion date
31/12/2013

Eligibility

Key inclusion criteria
1. Aged between 65 and 84 years at enrolment
2. Contactable by telephone, able to attend enrolment at the GP surgery, and able to give informed consent
3. Baseline corrected serum calcium 2.65 mmol/L
4. Registered with one of the 20 participating GP practices

Participant type(s)
Patient

Healthy volunteers allowed
No

Age group
Senior

Sex
All

Total final enrolment
1615

Key exclusion criteria
1. Aged <65 or >84 years
2. No telephone
3. Terminal illness
4. Known active tuberculosis
5. Referral for suspected hepatic or renal dysfunction
6. Known sarcoidosis, hyperparathyroidism or nephrolithiasis
7. <3 years since remission from cancer (except non-melanoma skin cancer)
8. Taking >400mg daily vitamin D
9. Any other Investigational Medicinal Product (IMP) therapy within 4 months
10. Concomitant carbamazepine, phenobarbital, phenytoin, primidone, oral 1-alpha-hydroxylated vitamin D preparations (e.g. alfalcalcidol, calcitriol) or the combination of a thiazide diuretic (e.g. bendrofluazide, metolazone) with a calcium supplement

Date of first enrolment

01/01/2012

Date of final enrolment
31/12/2013

Locations

Countries of recruitment
United Kingdom

England

Study participating centre
Department of Non-Communicable disease Epidemiology
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Sponsor information

Organisation
London School of Hygiene & Tropical Medicine (UK)

ROR
https://ror.org/00a0jsq62

Funder(s)

Funder type
Government

Funder Name
The NIHR Health Technology Assessment Programme - HTA (UK) ref: 08/116/48

Results and Publications

Individual participant data (IPD) sharing plan

IPD sharing plan summary

Not provided at time of registration

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
Results article	results	01/02/2020	25/02/2020	Yes	No
Participant information sheet	Participant information sheet	11/11/2025	11/11/2025	No	Yes