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Vitamin D supplementation to prevent infections: a sub-study of a randomised placebo-controlled trial in older people (RECORD trial, ISRCTN 51647438)

SIR—There is increasing interest in the influence of vitamin D on tissues other than bone [1]. Active vitamin D (1,25-dihydroxyvitamin D₃) is an important regulator of the immune system and has been most studied with regard to autoimmunity, where it acts as an immunosuppressant [2]. The influence of 1,25-dihydroxyvitamin D₃ on infection in vivo and in animal models has been little studied [3]. Mouse studies have suggested that 1,25-dihydroxyvitamin D₃ enhances Mycobacterium bovis killing [4], but increases the susceptibility to Toxoplasma gondii [5]. 1,25-dihydroxyvitamin D₃ directly regulates antimicrobial peptide gene expression, which could enhance host defence against infection [6–8].

Case control studies have found associations between vitamin D deficiency and tuberculosis in Asians in the UK [9] and severe acute lower respiratory and gastrointestinal infections in children in Ethiopia, Turkey, India and Jordan [10–13]. Peripheral blood T lymphocytes were significantly decreased in Turkish children with rickets [14], and children with rickets were found to have reduced neutrophil motility [15] and phagocytosis [16].

We have been unable to find any randomised controlled trials of vitamin D supplementation, which have examined the incidence of infection in at-risk groups. Rehman [17] reported reductions in respiratory infections and febrile illnesses in a group of Indian children with high alkaline phosphatase levels, but no clinical evidence of rickets as a result of vitamin D and calcium supplementation. A randomised trial of co-administration of intramuscular 1,25-dihydroxyvitamin D₃ with influenza vaccine was not found to enhance humoral immunity in healthy young volunteers, whose vitamin D status was not described [18].

At a conservative estimate, at least 8% of UK community-dwelling older people, and 32% of older people living in institutions have vitamin D deficiency (serum 25-hydroxyvitamin D₃ levels below 25 nmol/l) [19, 20]. However, there is some evidence that the optimal serum 25-hydroxyvitamin D₃ level for health could be as high as 90–100 nmol/l [21].

As an adjunct to the RECORD trial [22], a blinded, randomised, placebo-controlled trial of oral vitamin D₃ and/or calcium supplementation for the secondary prevention of osteoporotic fractures, we examined whether vitamin D was associated with a reduction in self-reported infections and antibiotic use.

Methods

Five thousand two hundred and ninety-two participants were randomised within a factorial design to 800 IU (20 µg) daily vitamin D₃, 1,000 mg calcium (calcium carbonate), both, or placebo, and followed up for 24–62 months. The trial was based in 21 centres in England and Scotland. Ethical approval was obtained from the Multicentre Research Ethics Committee for Scotland and each centre’s Local Research Ethics Committee. Participants gave written informed consent. Full details and main results of the trial are reported elsewhere [22].

In March 2002, when 25-hydroxyvitamin D₃ levels are lowest in older people in the northern hemisphere [19], all trial participants who were alive, or had not withdrawn from filling in questionnaires were sent a reply-paid postal questionnaire. This asked if they had had an infection or received antibiotics in the previous week.

We compared all participants who had been randomised to take vitamin D₃ with all participants who had not been randomised to D₃ (i.e. intention-to-treat analysis), using multiple logistic regression (adjusted for the trial minimisation factors of gender, age, type of enrolling fracture and time since fracture).

Results

Three thousand four hundred and forty-four participants responded to the questionnaire at a median (interquartile range) time of 18 (11–25) months since randomisation. Based on questionnaire responses, at least 55% of trial participants were still taking their tablets. Of the respondents randomised to vitamin D₃, 17.2% (300/1,740) reported an infection, compared with 18.8% (321/1,704) on placebo (adjusted odds ratio 0.84, 95% CI 0.64 to 1.09, \( P = 0.18 \)).

‘Per protocol’ analyses, based on tablet taking when completing the questionnaire, showed smaller odds ratios for infection (0.80, 95% CI 0.64 to 1.01, \( P = 0.06 \)) and antibiotic use (0.74, 95% CI 0.52 to 1.06, \( P = 0.10 \)).

Adverse events such as hypercalcaemia, renal stones and renal impairment were rare and did not differ between those people receiving vitamin D₃ or not.

Discussion

Although the observed differences were consistent with vitamin D reducing the risk of infection, the results were not statistically significant. ‘Per protocol’ analyses showed
smaller odds ratios for infection and antibiotic use, but the concern about such 'per protocol' analyses is that they are prone to bias, however, rates of tablet taking were similar for vitamin D3 and placebo groups. Non-compliance may therefore have reduced the protective effect. Our questions may also have been too crude, and it might have been preferable to ask participants to keep diaries for longer and to record the length, type and severity of infections.

Only 6% of the RECORD trial participants could not walk out-doors unaccompanied: hence, our participants were likely to have had higher sunlight exposure for vitamin D manufacture in the skin than less mobile older people and be less likely to benefit. The 25-hydroxyvitamin D3 level from a small sample of 60 trial participants in Southampton and Newcastle, measured from February to July before supplementation averaged 38 (SD 16) nmol/l by high-performance liquid chromatography [22], similar to the mean level for older people in institutions in recent UK surveys [19, 20]. After 1 year of supplementation in these participants 25-hydroxyvitamin D3 was 62 (SD 16) nmol/l.

Based on data from studies of bone mineral density, lower-extremity function, falls, fractures, colorectal cancer and dental health, Bischoff-Ferrari and colleagues have argued that serum concentrations of 25-hydroxyvitamin D3 should be 75 nmol/l or more, with optimal levels at least 90–100 nmol/l [21]. In older people, an intake of ≥1000 IU (25 µg) vitamin D3 could bring 25-hydroxyvitamin D3 to 75 nmol/l in more than 50% of the population [21]. However, the studies contributing these data used different methods for determining serum 25-hydroxyvitamin D3 and rarely reported compliance. Currently available assays for 25-hydroxyvitamin D3 do not agree well, so that assay-specific decision limits have been suggested for assessing compliance and 25-hydroxyvitamin D3 status [23]. Further research is needed to assess the effect of a higher dose of vitamin D on infections in populations at high risk of insufficiency.

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**Key points**

- 1,25-dihydroxyvitaminD3 is an important regulator of the immune system.
- Vitamin D deficiency is common in older people in the UK, particularly in people living in institutions.
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- Daily supplementation with 800 IU vitamin D$_3$ (20 µg) was well tolerated by older people living in the community, with no detectable adverse effects.
- Supplementation was associated with fewer self-reported infections and antibiotics, but the estimated 10–15% reduction was not statistically significant.
- Further randomised trials of vitamin D and infections are warranted in at-risk populations.

Conflicts of interest statement

None declared for the authors. Conflict of interest statements for other members of the RECORD Trial Group are given in reference number 22.

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Record Trial Management Group

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References

Routine thrombolysis with intravenous tissue plasminogen activator in acute ischaemic stroke patients aged 80 years or older: a single centre experience

SIR—Treatment with intravenous tissue plasminogen activator (t-PA) in acute ischaemic stroke has been shown to improve outcome [1]. Little is known regarding the safety and efficacy of this treatment in patients aged 80 years and older, because this age group was underrepresented in clinical trials [1–4]. The NINDS trial [1] was the only trial without age limit and only 7% (n = 42) of the included patients were older than 80 years. However, about 30% of admitted ischaemic stroke patients are older than 80 years [5].

A number of previous observational studies compared the outcome of t-PA treatment in patients older than 80 years with their younger counterparts [6–12], and a recent systematic review suggested that t-PA is safe in older patients, despite a higher 3-month mortality and a less favourable functional outcome [13].

In this study, we compared the safety and outcome of t-PA treatment in patients aged 80 years and older with their younger counterparts in a prospective cohort from the University Medical Center Groningen (UMCG). In contrast to most previous studies, we not only investigated the 3-month mortality but also compared the early in-hospital mortality at 7 days between the two groups.

Methods

UMCG cohort

After participation in the European Cooperative Acute Stroke Study (ECASS) II, our centre started with t-PA treatment for eligible stroke patients and served as referral centre for regional community hospitals. An ongoing prospective registry of patients treated with t-PA was started in April 2002. This study analysed the period between April 2002 and January 2006. Inclusion and exclusion criteria were based on those of the NINDS trial.

Neurological deficit before start of t-PA treatment was recorded with the National Institute of Health Stroke Scale (NIHSS). All patients had a brain CT scan, blood investigation and electrocardiography. Baseline variables such as gender, age, vascular risk factors, serum glucose concentration and antiplatelet medication were recorded. Stroke-subtypes were defined into lacunar infarcts (LACI) and non-lacunar infarcts (total anterior circulation infarcts (TACI) and partial anterior circulation infarcts (PACI) and posterior circulation infarcts (POCI)) according to the Oxfordshire Community Stroke Project Classification [14].

Patients were treated with intravenous t-PA according to the NINDS protocol. After treatment, patients were monitored in a stroke unit, where early rehabilitation was started by a multidisciplinary team. We did not routinely perform a brain CT scan after each thrombolysis.

For the safety analysis, we defined the following outcome measures: incidence of symptomatic intracerebral haemorrhage (SICH), early in-hospital mortality within 7 days and 3-month mortality. SICH was defined as a neurological deterioration within 48 h following thrombolysis, with an intraparenchymal haematoma demonstrated by CT scan, which could explain the deterioration. Functional outcome was assessed after 3 months using the modified Rankin Scale (mRS). The mRS was divided into favourable outcome (mRS 0–1) and unfavourable outcome (mRS 2–6). Data were analysed separately in the young and old age groups and compared between both groups.

Statistical analysis

All statistical analyses were done using SPSS version 11.0. The Mann–Whitney U and the t-test were used for continuous and ordinal variables, and the χ² test, or Fisher exact test, for dichotomous variables. Confidence intervals for proportions were calculated using Wilson’s method. For the functional outcome and 3-month mortality, a multivariate analysis was done to adjust for possible confounders: NIHSS score, time from onset until treatment, stroke subtype (lacunar versus non-lacunar) and blood glucose concentration.

Results

UMCG cohort

Baseline characteristics

Between April 2002 and January 2006, 1029 consecutive ischaemic stroke patients were admitted to our department, of whom 142 received t-PA treatment within 3 h after onset. All patients were independent (mRS 0–2) before admission. Of the 142 treated patients, 111 (78%) were younger than 80 years and 31 (22%) were 80 years or older. Baseline characteristics of both groups are summarised in the Table 1.

The median NIHSS tended to be higher in the older group (15, range 6–22 versus 13, range 2–23), although this did not reach a statistical significant difference (P = 0.197).

Older patients had a longer onset to treatment time (mean time 158 min versus 145 min in younger patients, P = 0.022) and were less likely to have a lacunar stroke (3% versus 19% in the younger group, P = 0.046).