**Research letters**

**Supplementary data**

Supplementary data are available online at *Age and Ageing* online.

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**References**


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**Vitamin D supplementation and type 2 diabetes: a study of a randomised placebo-controlled trial in older people (RECORD trial, ISRCTN 51647438)**

SIR—Studies in animals show that vitamin D deficiency is associated with impaired insulin sensitivity, and that insulin
secretion can be increased by vitamin D supplementation [1]. Epidemiological studies in man show associations between low vitamin levels and glucose intolerance [2].

Pittas et al. systematically reviewed the intervention trial evidence for the role of vitamin D and/or calcium in the prevention of metabolic syndrome and type 2 diabetes mellitus [2]. On the basis of evidence from small intervention trials or post hoc analyses of trials, they concluded that it was difficult to be definite whether or not vitamin D and/or calcium were important in the prevention of type 2 diabetes, and that effects might only be manifest in people who were particularly at risk of type 2 diabetes.

As an adjunct to the RECORD trial [3, 4], a blinded, randomised, placebo-controlled trial of oral vitamin D3 and/or calcium supplementation for the secondary prevention of osteoporotic fractures in older people, we examined whether vitamin D (with or without calcium) was associated with a reduction in self-reported development of diabetes, and starting tablets or insulin for diabetes as indicators of deteriorating glycaemic control.

Methods

In the RECORD trial, 5292 participants aged ≥ 70 years with a recent previous osteoporotic fracture were randomised from 1999 to 2002 within a blinded, factorial design to oral 800 IU (20 µg) daily vitamin D3, 1000 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. The participants gave written informed consent. Full details and main results of the trial are reported elsewhere [3].

The main outcome of the trial was new low-energy fracture [3]. The effects of vitamin D3 (with or without calcium) on the development of diabetes or initiation of tablets or injections for diabetes were prespecified secondary outcomes. At baseline and by annual postal or telephone questionnaire, the participants were asked if they had diabetes, or took tablets or injections for diabetes. All data on diabetes and medications for diabetes were therefore collected by self-report.

We compared all participants who had been randomised to take vitamin D3 with all those who had not been randomised to D3 (i.e. intention to treat analysis), using multiple logistic regression. Odds ratios and 95% confidence intervals were presented adjusted for the trial minimisation factors of gender, age, type of enrolling fracture and time since fracture. A corresponding, secondary, per protocol analysis was undertaken, based upon participants still reporting tablet consumption on >80% of days at 2 years post-randomisation. We also undertook post hoc analyses to test for an interaction effect between vitamin D3 and calcium under a per protocol basis.

Results

Participants’ baseline characteristics are given in Table 1. The mean age of participants was 77 years, 85% were females and 94% could walk out of doors unaccompanied. Their mean weight was 65 kg, 99% of participants were white, 8% reported already having diabetes, and the dietary calcium intake was < 700 mg/day in 39%.

A total of 2.5% (60/2416) of respondents randomised to vitamin D3 reported becoming diabetic compared with 1.6% (38/2447) randomised to placebo (adjusted odds ratio 1.11, 95% confidence interval 0.77–1.62, P = 0.57) (see Table 2). In the secondary, per protocol analysis, the adjusted odds ratio was 0.68 (95% CI 0.40–1.16, P = 0.16).

A total of 1.5% (37/2447) of respondents randomised to vitamin D3 started using tablets or injections to control diabetes compared with 1.6% (38/2447) randomised to placebo (adjusted odds ratio 0.97) (95% CI 0.62–1.54, P = 0.91). In the corresponding, per protocol analysis, the adjusted odds ratio was 0.78 (95% CI 0.41–1.50, P = 0.46).

Table 1. Baseline characteristics of participants

<table>
<thead>
<tr>
<th></th>
<th>With vitamin D3 (n = 2649)</th>
<th>Without vitamin D3 (n = 2643)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex, no. (%) female</td>
<td>2240 (84.6)</td>
<td>2241 (84.8)</td>
</tr>
<tr>
<td>White, no. (%)</td>
<td>2629 (99)</td>
<td>2623 (99)</td>
</tr>
<tr>
<td>Type of enrolling fracture, no. (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Proximal femur</td>
<td>459 (17.3)</td>
<td>445 (16.8)</td>
</tr>
<tr>
<td>Distal forearm</td>
<td>924 (34.9)</td>
<td>922 (34.9)</td>
</tr>
<tr>
<td>Other fractures</td>
<td>1266 (47.8)</td>
<td>1276 (48.3)</td>
</tr>
<tr>
<td>Weight, mean [SD] (kg)</td>
<td>65 [13]</td>
<td>65 [12]</td>
</tr>
<tr>
<td>Current smoker, no. (%)</td>
<td>298 (11.3)</td>
<td>320 (12.1)</td>
</tr>
<tr>
<td>Dietary calcium intake &lt;400 mg/day, no. (%)</td>
<td>277 (10.5)</td>
<td>256 (9.7)</td>
</tr>
<tr>
<td>Dietary calcium intake 400–699 mg/day, no. (%)</td>
<td>785 (29.6)</td>
<td>742 (28.1)</td>
</tr>
<tr>
<td>Could walk out of doors unaccompanied – no. (%)</td>
<td>2492 (94.4)</td>
<td>2487 (94.3)</td>
</tr>
<tr>
<td>Diabetic no. (%)</td>
<td>222 (8.4)</td>
<td>202 (7.6)</td>
</tr>
<tr>
<td>Steroids ≥ 7.5 mg prednisolone/d no. (%)</td>
<td>49 (1.9)</td>
<td>44 (1.7)</td>
</tr>
</tbody>
</table>
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Table 2. Diabetes outcomes

<table>
<thead>
<tr>
<th>Intention to treat analysis</th>
<th>Odds ratio (95% confidence interval)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Eligible</td>
<td>(n = 2416)</td>
<td></td>
</tr>
<tr>
<td>Developed diabetes, no. (%)</td>
<td>60 (2.5)</td>
<td>54 (2.2) 1.11 (0.77–1.62) 0.57</td>
</tr>
<tr>
<td>Eligible</td>
<td>(n = 2447)</td>
<td></td>
</tr>
<tr>
<td>Started tablets or injections for diabetes, no. (%)</td>
<td>37 (1.5)</td>
<td>38 (1.6) 0.97 (0.62–1.54) 0.91</td>
</tr>
<tr>
<td>Compliers at 2 years</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Eligible</td>
<td>(n = 1071)</td>
<td></td>
</tr>
<tr>
<td>Developed diabetes, no. (%)</td>
<td>24 (2.2)</td>
<td>34 (3.3) 0.68 (0.40–1.16) 0.16</td>
</tr>
<tr>
<td>Eligible</td>
<td>(n = 1083)</td>
<td></td>
</tr>
<tr>
<td>Started tablets or injections for diabetes, no. (%)</td>
<td>17 (1.6)</td>
<td>21 (2.0) 0.78 (0.41–1.50) 0.46</td>
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</table>

Our two post hoc analyses of developing diabetes, or initiation of tablets or injections also showed no evidence of an interaction effect between vitamin D and calcium (adjusted odds ratio 0.85, 95% CI 0.29–2.53, P = 0.77 and adjusted odds ratio 2.00, 95% CI 0.53 to 7.57, P = 0.31, respectively).

Conclusions

We did not find evidence that vitamin D3 in a daily dose of 800 IU, or in combination with 1000 mg calcium, was able to prevent the development of diabetes or an increase in the need for medication for diabetes. However, the confidence intervals do not rule out protective effects. The Women’s Health Initiative (WHI) also found that 400 IU vitamin D3 and 1000 mg calcium were not associated with a reduced risk of developing diabetes over a median follow-up period of 7 years in 33,951 women whose mean age was 62 years, where 50% of measured participants had a baseline 25(OH) vitamin D concentration of <44 nmol/l [5]. In the RECORD trial, the 25(OH) vitamin 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 [3], similar to the mean levels for men and women of similar age living in care homes in a recent English survey [6]. After 1 year of supplementation in these participants, 25(OH) vitamin D3 was 62 (SD 16) nmol/l.

Data were only collected by self-report, which was also used in the WHI trial [5]. The reported prevalence of diabetes at enrolment was 8%, lower than the figure of 10% reported for women aged 75–79 years and over in England [7]. This may reflect not only under-reporting but also a lower risk for type 2 diabetes in people with osteoporosis and lower body weight.

We did not collect data at baseline about body mass index or glycemic control. The participants’ mean weight was 65 kg, similar to the mean weight of 64.1 kg for a UK survey of women aged 75–84 years, for whom the mean body mass index was 26.7 kg/m2 [8]. Again, this would suggest that this was not a particularly high-risk population for type 2 diabetes.

In a post hoc analysis, one randomised trial [9] found that supplemental 700 IU vitamin D3 and 500 mg calcium daily over 3 years in 314 men and women with a mean age of 71 years reduced the rise in fasting plasma glucose over time in a sub-group of people with pre-existing impaired fasting glucose, but not participants with normal fasting glucose. In that trial, supplementation achieved a 25(OH) vitamin D level of 99 nmol/l standardised to the vitamin D external quality assurance scheme [10].

A recent randomised trial in the UK examined the effect of a single dose of 100,000 IU vitamin D3 or placebo in people with type 2 diabetes, a mean age of 64 years and a baseline 25(OH) vitamin D of 38 nmol/l [11]. Flow-mediated endothelial function was significantly improved by vitamin D2, but there was no significant difference between groups for glycaemic control or insulin sensitivity. An Australian trial utilised 100,000 IU vitamin D3 as two doses 2 weeks apart in people with a mean age of 55 years without type 2 diabetes with a mean 25(OH) vitamin D3 of 40 nmol/l [12]. Supplementation had no significant effect on insulin sensitivity or glucose tolerance. Thus, high-dose bolus oral supplementation was not found effective in people younger than the RECORD trial participants, who appeared to have similar pre-supplementation 25(OH) vitamin D3.

Based on data from studies of bone mineral density, lower extremity function, falls, fractures, colorectal cancer and dental health, Bischoff–Ferrrari and colleagues have argued that serum concentrations of 25(OH) vitamin D3 should be 75 nmol/l or more [13]. Neither the RECORD trial nor WHI attained these levels in people measured [14], and poor compliance may have contributed in the RECORD trial.

The results suggest that randomised controlled trials should concentrate on evaluating the use of vitamin D3 in higher doses in groups at high risk of developing type 2 diabetes.

Key points

- Epidemiological studies show an association between low serum 25(OH) vitamin D and impaired glycaemia, but vitamin D intervention trials have had mixed results.
- A large trial of daily 800 IU vitamin D3 and 1000 mg calcium in older people at high risk of another osteoporotic fracture did not suggest a protective effect against the development of type 2 diabetes or use of medication for type 2 diabetes.
Acknowledgements

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Conflict of interest

A Avenell designed and coordinated this substudy of the main RECORD trial. JA Cook, GS MacLennan and GC McPherson undertook data handling and statistical analyses. All contributed to the writing of this report. Conflict of interest statements for other members of the RECORD Trial Group are given in reference [2].

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References


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Impact of different diagnostic thresholds and the anaemia–ferritin–transferrin receptor model on the prevalence of anaemia and impaired iron status in older people

SIR—Anaemia is common in older people (defined here as aged 65 years and older). Prevalence increases with age [1]: a systematic review of the literature has shown a wide range of estimates in the older population, ranging from 2.9% to 61% in men, and 3.3% to 41% in women [2], depending on the setting, age groups and definitions used [3]. Thresholds defining diagnosis of anaemia are therefore crucial and have been the subject of considerable scientific debate [4, 5].

The WHO criteria for anaemia uses a haemoglobin (Hb) threshold of <12.0 g/dl (<7.5 mmol/l) for women and <13.0 g/dl (<8.1 mmol/l) for men [6]. However, these criteria were developed in 1968 based on statistical distributions equivalent to two standard deviations below the mean in a reference sample aged <65 years. A lower threshold [Hb <11.5 g/dl (<7.2 mmol/l) for both sexes], the Joosten’s criterion, has been suggested for older people to identify all causes of anaemia [5].