Effect of active vitamin D treatment on development of type 2 diabetes: DPVD randomised controlled trial in Japanese population

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ABSTRACT

OBJECTIVE
To assess whether eldecalcitol, an active vitamin D analogue, can reduce the development of type 2 diabetes among adults with impaired glucose tolerance.

DESIGN
Double blinded, multicentre, randomised, placebo controlled trial.

SETTING
Three hospitals in Japan, between June 2013 and August 2019.

PARTICIPANTS
People aged 30 years and older who had impaired glucose tolerance defined by using a 75 g oral glucose tolerance test and glycated haemoglobin level.

INTERVENTIONS
Participants were randomised to receive active vitamin D (eldecalcitol 0.75 μg per day; n=630) or matching placebo (n=626) for three years.

MAIN OUTCOMES
The primary endpoint was incidence of diabetes. Prespecified secondary endpoints were regression to normoglycaemia and incidence of type 2 diabetes after adjustment for confounding factors at baseline. In addition, bone densities and bone and glucose metabolism markers were assessed.

RESULTS
Of the 1256 participants, 571 (45.5%) were women and 742 (59.1%) had a family history of diabetes. The mean age of participants was 61.3 years. The mean serum 25-hydroxyvitamin D concentration at baseline was 20.9 ng/mL (52.2 nmol/L); 548 (43.6%) participants had concentrations below 20 ng/mL (50 nmol/L). During a median follow-up of 2.9 years, 79 (12.5%) of 630 participants in the eldecalcitol group and 89 (14.2%) of 626 in the placebo group developed type 2 diabetes (hazard ratio 0.87, 95% confidence interval 0.67 to 1.17; P=0.39). Regression to normoglycaemia was achieved in 145 (23.0%) of 630 participants in the eldecalcitol group and 126 (20.1%) of 626 in the placebo group (hazard ratio 1.15, 0.93 to 1.41; P=0.21). After adjustment for confounding factors by multivariable fractional polynomial Cox regression analysis, eldecalcitol significantly lowered the development of diabetes (hazard ratio 0.69, 0.51 to 0.95; P=0.020). In addition, eldecalcitol showed its beneficial effect among the participants with the lower level of basal insulin secretion (hazard ratio 0.41, 0.23 to 0.71; P=0.001). During follow-up, bone mineral densities of the lumbar spine and femoral neck and serum osteocalcin concentrations significantly increased with eldecalcitol compared with placebo (all P<0.001). No significant difference in serious adverse events was observed.

CONCLUSIONS
Although treatment with eldecalcitol did not significantly reduce the incidence of diabetes among people with pre-diabetes, the results suggested the potential for a beneficial effect of eldecalcitol on people with insufficient insulin secretion.

TRIAL REGISTRATION
UMIN Clinical Trials Registry UMIN000010758.

Introduction
Diabetes mellitus is a major risk factor for various cardiovascular and renal diseases. The global prevalence of diabetes was 425 million adults in 2015, with an anticipated increase to 629 million by 2040.1 Moreover, a further 352 million people with impaired glucose tolerance are at high risk for developing diabetes and cardiovascular disease.1,2 Although lifestyle modifications may delay the development of type 2 diabetes,3,4 maintaining long term behavioural changes is difficult.5,6 Therefore, new strategies to reduce the incidence of type 2 diabetes are needed for people with impaired glucose tolerance.

Vitamin D receptors have been found in various cell types, including the pancreatic β cells,7,8 and active vitamin D is reportedly involved in insulin biosynthesis and secretion.7 Genetic studies in mice have shown that inter-organ communication and bone metabolism seem to be closely associated with insulin resistance.10,11 Observational studies
have shown an association between low serum 25-hydroxyvitamin D concentrations and increased incidence of type 2 diabetes.\textsuperscript{13,14} Although several intervention studies and a recent meta-analysis have suggested that vitamin D supplementation may have a beneficial effect on glycaemic control,\textsuperscript{15-18} relatively large scale clinical studies and other meta-analyses of randomised clinical trials have not supported this finding.\textsuperscript{19-23} Whether vitamin D supplementation is beneficial only for children with vitamin D deficiency is unclear,\textsuperscript{20} as is which bone metabolism markers may be associated with the improvement in insulin resistance after treatment. Hence, we did a prospective trial, the Diabetes Prevention with active Vitamin D (DPVD) study, to assess whether 0.75 μg per day of eldecalcitol, an active vitamin D analogue, could reduce the incidence of type 2 diabetes among people with impaired glucose tolerance.

**Methods**

This randomised, double blind, placebo controlled trial evaluated the effect of eldecalcitol on incidence of type 2 diabetes in people with impaired glucose tolerance in Japan. It was designed and supervised by the steering committee and approved by the institutional review boards at three participating centres. The trial protocol has been previously published.\textsuperscript{24} Written informed consent was obtained from all participants before enrolment in the trial.

**Study participants**

Male and female patients who were aged 30 years or older and had impaired glucose tolerance were recruited to the study. We defined impaired glucose tolerance as meeting all three of the following glycaemic criteria: fasting glucose concentration <126 mg/dL (7.0 mmol/L), two hour glucose concentration 140-199 mg/dL (7.8-11.0 mmol/L) during a 75 g oral glucose tolerance test, and glycated haemoglobin <6.5% (48 mmol/L).\textsuperscript{25,26} The complete list of inclusion and exclusion criteria, published previously,\textsuperscript{27} is provided in the supplementary appendix.

**Randomisation and masking**

Sub-investigators in the three trial hospitals applied to the assignment centre for registration and treatment assignment. Participants were assigned to one of two treatment groups in a one to one ratio by using a central randomisation method. A responsible person at the assignment centre made a randomisation list for each hospital separately by using a stratified permuted block procedure before the first participant’s entry. The number of strata was eight according to sex (male, female), age (30-54 years, ≥55 years), and 75 g oral glucose tolerance test two hour post-load plasma glucose (<170 mg/dL, ≥170 mg/dL), because we considered these factors to affect the incidence of diabetes. The block sizes were six for five permute cycles and four for the next five permute cycles, and the last 17 participants were allocated using two block sizes—that is, a total of 417 participants per hospital. On the basis of the assignment list, which was kept in a locked safe located in the assignment centre, the responsible person enrolled and allocated participants to either the eldecalcitol group or the placebo group in the order of registration. The assignment list was inaccessible to the investigators or sub-investigators for the duration of the trial except in the event of emergencies. The key was retrieved only after the trial concluded and data were fixed. Participants were randomly assigned to take a single, once daily, hard gel pill containing either 75 μg of eldecalcitol or matching placebo, which looks exactly the same. A standard dose of 0.75 μg of eldecalcitol is used for the prevention and/or treatment of osteoporosis in Japan. Eldecalcitol and placebo were prescribed by a sub-investigator (physician) at every three monthly visit and exchanged for the prescription at an independent pharmacy that had no association with any members of the DPVD Research Group. The placebo was purchased from Sunsho Pharmaceutical, which was responsible for the manufacturing, packing, and distribution of the placebo. This company had no role in the design or conduct of the trial.

**Procedures**

Study visits were scheduled at three month intervals, with the follow-up period concluding after three years. A routine clinical examination, including measurement of fasting plasma glucose and glycated haemoglobin, was performed at each study visit. Each participant received a brief (five to 10 minutes long) talk on appropriate calorie intake from diet and exercise at each study visit, using an information sheet. A 75 g oral glucose tolerance test, serum 25-hydroxyvitamin D and 1,25-dihydroxyvitamin D concentrations, and bone mineral density were measured at baseline and at yearly intervals. Serum 25-hydroxyvitamin D and 1,25-dihydroxyvitamin D concentrations were measured by liquid chromatography-tandem mass spectrometry at LSI Medience Corporation (Tokyo, Japan). All data were collected in the assignment centre.

**Outcomes**

The primary endpoint was the development of type 2 diabetes, defined as meeting at least two of the following criteria: glycated haemoglobin >6.5%, fasting plasma glucose concentration ≥126 mg/dL, two hour post-load plasma glucose concentration ≥200 mg/dL (11.1 mmol/L), or random plasma glucose concentration ≥200 mg/dL. The first secondary endpoint was the regression to normoglycaemia, defined as meeting all three glycaemic criteria—glycated haemoglobin <6.5%, fasting plasma glucose concentration <110 mg/dL (6.1 mmol/L), and two hour post-load plasma glucose concentration <140 mg/dL—or both of the following criteria: glycated haemoglobin <5.7% and fasting plasma glucose concentration <100 mg/dL.\textsuperscript{27} The other secondary endpoint was the hazard ratio of eldecalcitol compared with placebo for the incidence of type 2 diabetes after adjustment for 11 confounding factors at baseline: age, sex (male/female), presence or
absence of hypertension (systolic blood pressure ≥140 mm Hg, diastolic blood pressure ≥90 mm Hg, or both), body mass index, family history of diabetes (yes/no), glycated haemoglobin, fasting plasma glucose, two hour plasma glucose, 25-hydroxyvitamin D, homoeostasis model assessment of insulin resistance (HOMA-IR), and insulinogenic index.

**Statistical analysis**

We assessed the intention-to-treat population, comprising all participants who were randomised and received at least one dose of the study drug, for the primary analysis. However, we also show the results of Cox regression analyses using the per protocol population and the “complete” population in the sensitivity analyses. The complete population was a study population with a complete set of measurements throughout the three year study period, which excluded participants who dropped out other than those who achieved the normal glucose tolerance status. We analysed progression to diabetes and regression to normoglycaemia with the log-rank test and two by four $\chi^2$ test, respectively. We compared treatments by estimation of hazard ratios and 95% confidence intervals. Additionally, we did Cox regression analysis using a multivariable fractional polynomial (mfp) method by an mfp package for R with eldecalcitol and the 11 baseline covariates, described above.28 We did subgroup analyses of continuous covariables by using splines with an mgcv package for R.29

Values were missing for covariates such as body weight, blood pressure, glycated haemoglobin, plasma glucose concentrations. To evaluate the time trends of covariates, we used a multiple imputation method for replacing missing values separately in each group with other plausible values by creating multiple filling-in patterns to avoid bias caused by missing data.30 In this study, we replaced each missing value with a set substituted plausible value by 20 filled-in complete datasets by using a multiple imputation by chained equation method.31 In the imputation process, we used the following covariates to create 20 complete datasets: age, sex, body mass index, blood pressure, family history of diabetes, glycated haemoglobin, plasma glucose, HOMA-IR, lipids concentrations, serum 25-hydroxyvitamin D concentrations, and serum 1,25-dihydroxyvitamin D concentrations in each group. We used Rubin’s rules to calculate standard errors.32 These standard errors take into account the variability in results between imputed datasets and reflect the uncertainty associated with the missing data.33 We averaged estimated associations in each of the imputed datasets together to give overall estimated associations. We also did a repeated measure analysis of variance and Dunnett test for the time trends of measurements.

In the original trial design, approximately 750 patients were needed on the basis of the following assumptions: 8.4% per year incidence of diabetes in the placebo group, participant accrual period of 2.3 years, study duration of 5.3 years, and a 7% dropout rate. The study had 80% power to detect a 36% lower rate of the primary endpoint in the active vitamin D group than in the placebo group, with a two sided type I error.
of 0.05. However, in the middle of the study, regression to normoglycaemia occurred, and the dropout ratio of participants who reached the normoglycaemic state was greater than anticipated, suggesting that the number of participants developing diabetes would be much smaller than originally planned. Therefore, we amended the protocol so that the cumulative incidence of type 2 diabetes in the control group was 16.9% (6.0% annually)—that is, the active vitamin D group was 11.1% (3.8% annually) and the dropout ratio was 12% in the recruitment phase of the study. Thus, the relative risk reduction was assumed at 36%. As a result, 625 participants were needed in each group (a total of 1250).

We used R software, version 4.0.5, for statistical analyses. We considered two sided P values less than 0.05 to be statistically significant.

**Patient and public involvement**

Patients and the public were not involved in setting the research question or outcome measures or in the writing of the results. However, patient representatives asked us to measure bone mineral densities for all participants yearly. As a result, we added the annual measurement of bone mineral density to the protocol.

**Results**

From 1 June 2013 through 31 August 2015, a total of 3875 participants were recruited from 32 institutions in Japan (fig 1), and 1256 participants were randomly assigned to receive either eldecalcitol (630 participants) or placebo (626 participants) (621 participants had impaired glucose tolerance alone and 635 had impaired glucose tolerance with impaired fasting glucose). Of the 1256 participants, 45.5% were women and 59.1% had a family history of type 2 diabetes. The mean age of participants was 61.3 (range 30-78) years. No clinically relevant differences in baseline characteristics existed between the two groups (table 1; supplementary table A). The mean serum 25-hydroxyvitamin D concentration at baseline was 20.9 ng/mL (52.2 nmol/L); 43.6% of participants had concentrations of <20 ng/mL (50 nmol/L). The classification of vitamin D concentrations in Japan is ≥30 ng/mL (≥75 nmol/L) as normal, 20 to <30 ng/mL (50 to <75 nmol/L) as insufficiency, and <20 ng/mL (<50 nmol/L) as deficiency.34-36 The trial was finished in August 2019. The median follow-up was 2.9 (interquartile range 2.8-3.0) years.

**Primary outcome**

During the three year follow-up period, 79 (12.5%) of 630 participants in the eldecalcitol group and 89 (14.2%) of 626 in the placebo group developed diabetes. We found no difference between treatment groups (hazard ratio for eldecalcitol versus placebo 0.87, 95% confidence interval 0.67 to 1.17; P=0.39) (fig 2, top panel).

**Secondary outcomes**

Similarly, we found no difference between treatment groups in regression to normoglycaemia. By the end of the study, 145 (23.0%) of 630 participants in the eldecalcitol group and 126 (20.1%) of 626 in the placebo group achieved normoglycaemia (hazard ratio 1.15, 0.93 to 1.41; P=0.21) (fig 3).

We did a multivariable Cox regression analysis after adjusting for 11 prespecified covariates (age, sex, hypertension, body mass index, family history of diabetes, glycated haemoglobin, fasting plasma glucose, two hour plasma glucose, 25-hydroxyvitamin D, HOMA-IR, and insulinogenic index) by using a multivariable fractional polynomial method. Figure 2 (bottom panel) shows the Kaplan-Meier curve after adjustment. We showed that eldecalcitol was effective for preventing the development of type 2 diabetes after adjustment for these covariates (hazard ratio 0.69, 0.51 to 0.95) at the significant level of P=0.020.

**Sensitivity analyses**

Sensitivity analyses for the per protocol population and complete population assessed the robustness of the primary outcome based on the intention-to-treat population. The result showed hazard ratios for eldecalcitol of 0.88 (0.65 to 1.19; P=0.39) and 0.88 (0.65 to 1.19; P=0.39) for the per protocol and complete populations, respectively, which were substantially the same as the primary analysis. In addition, the distributions of parameters related to glucose metabolism at the beginning of the study did not differ between the intention-to-treat and complete populations (supplementary table B).

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**Table 1 | Baseline characteristics of study participants. Values are means (standard deviations) unless stated otherwise**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Overall (n=1256)</th>
<th>Eldecalcitol (n=630)</th>
<th>Placebo (n=626)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years</td>
<td>61.3 (8.9)</td>
<td>61.1 (8.8)</td>
<td>61.4 (9.1)</td>
</tr>
<tr>
<td>No (%) female sex</td>
<td>571 (44.5)</td>
<td>288 (45.7)</td>
<td>283 (45.2)</td>
</tr>
<tr>
<td>Body mass index</td>
<td>24.3 (2.3)</td>
<td>24.1 (2.7)</td>
<td>24.5 (1.8)</td>
</tr>
<tr>
<td>Blood pressure, mm Hg</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Systolic</td>
<td>134.3 (11.0)</td>
<td>134.4 (12.4)</td>
<td>134.2 (9.4)</td>
</tr>
<tr>
<td>Diastolic</td>
<td>82.9 (9.1)</td>
<td>82.8 (10.3)</td>
<td>83.1 (7.6)</td>
</tr>
<tr>
<td>No (%) family history of diabetes</td>
<td>742 (59.1)</td>
<td>380 (60.3)</td>
<td>362 (57.8)</td>
</tr>
<tr>
<td>Glycated haemoglobin, %</td>
<td>6.0 (0.2)</td>
<td>5.9 (0.2)</td>
<td>6.0 (0.2)</td>
</tr>
<tr>
<td>Plasma glucose, mg/dL:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fasting state</td>
<td>109.9 (9.2)</td>
<td>110.0 (9.5)</td>
<td>109.8 (8.9)</td>
</tr>
<tr>
<td>30 min after oral glucose load</td>
<td>176.3 (20.1)</td>
<td>177.4 (19.8)</td>
<td>175.3 (20.2)</td>
</tr>
<tr>
<td>2 h after oral glucose load</td>
<td>168.4 (17.8)</td>
<td>168.9 (20.1)</td>
<td>168.0 (15.0)</td>
</tr>
<tr>
<td>Plasma insulin, μU/dL:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fasting state</td>
<td>6.9 (2.6)</td>
<td>7.0 (3.0)</td>
<td>6.8 (2.2)</td>
</tr>
<tr>
<td>30 min after oral glucose load</td>
<td>49.4 (23.2)</td>
<td>48.5 (24.9)</td>
<td>50.3 (21.3)</td>
</tr>
<tr>
<td>2 h after oral glucose load</td>
<td>63.4 (33.8)</td>
<td>64.9 (38.6)</td>
<td>62.0 (28.3)</td>
</tr>
<tr>
<td>Homoeostasis model assessment insulin resistance</td>
<td>1.89 (0.71)</td>
<td>1.89 (0.79)</td>
<td>1.88 (0.64)</td>
</tr>
<tr>
<td>Lipids, mg/dL:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low density lipoprotein cholesterol</td>
<td>170.2 (29.1)</td>
<td>128.8 (26.2)</td>
<td>171.8 (31.6)</td>
</tr>
<tr>
<td>High density lipoprotein cholesterol</td>
<td>56.3 (17.6)</td>
<td>57.5 (14.2)</td>
<td>55.1 (20.3)</td>
</tr>
<tr>
<td>Triglycerides</td>
<td>140.1 (42.9)</td>
<td>139.5 (47.2)</td>
<td>140.7 (38.2)</td>
</tr>
<tr>
<td>Serum 25-hydroxyvitamin D, ng/mL</td>
<td>20.9 (6.1)</td>
<td>21.0 (6.2)</td>
<td>20.7 (6.1)</td>
</tr>
<tr>
<td>Distribution, No (%):</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;20 ng/mL</td>
<td>548 (43.6)</td>
<td>270 (42.9)</td>
<td>278 (44.4)</td>
</tr>
<tr>
<td>20-29 ng/mL</td>
<td>622 (49.5)</td>
<td>322 (51.1)</td>
<td>300 (47.9)</td>
</tr>
<tr>
<td>≥30 ng/mL</td>
<td>86 (6.8)</td>
<td>38 (6.0)</td>
<td>48 (7.7)</td>
</tr>
<tr>
<td>Serum 1,25-dihydroxyvitamin D, μg/dL</td>
<td>47.7 (22.2)</td>
<td>48.8 (23.5)</td>
<td>46.7 (20.8)</td>
</tr>
</tbody>
</table>
We investigated confounding covariables by using spline curve analysis one by one for 11 continuous covariables: age, body mass index, systolic blood pressure, glycated haemoglobin, fasting plasma glucose, fasting immunoreactive insulin, two hour plasma glucose, 25-hydroxyvitamin D, HOMA-IR, and homoeostasis model assessment β cell function (HOMA-β), and insulinogenic index. We observed a confounding effect for glycated haemoglobin and two hour plasma glucose (supplementary figure A).

**Post hoc analysis**

As a post hoc analysis, we re-examined the interactions of nine continuous covariables with eldecalcitol one by one after adjusting for glycated haemoglobin and two hour plasma glucose by using multivariable fractional polynomial Cox analysis. As shown in supplementary figure B, interactions with the eldecalcitol effect were seen for HOMA-β, HOMA-IR, and fasting immunoreactive insulin (HOMA-β=fasting immunoreactive insulin×360/fasting plasma glucose–63; HOMA-IR=fasting immunoreactive insulin×fasting plasma glucose/405) After we divided the three covariables into three groups at their 33.3 centile and 66.6 centile values, we did Kaplan-Meier analyses and multivariable fractional polynomial Cox regression. Supplementary figure C shows that eldecalcitol had a significant preventive effect on the development of type 2 diabetes among the lowest divisions of HOMA-β (hazard ratio 0.35, 0.21 to 0.59; P<0.001), HOMA-IR (0.37, 0.20 to 0.67; P<0.001), and fasting immunoreactive insulin (0.41, 0.23 to 0.71; P<0.001). These results indicate that eldecalcitol had a beneficial effect on insufficient basal insulin secretion.

**Time trends of glycaemic status and body mass index**

With regard to glycaemic status at the end of the trial, plasma glucose and immunoreactive insulin concentrations at fasting state and after 120 minutes did not differ between the two groups (fig 4). However, plasma glucose concentrations after 30 minutes of loading were significantly improved from those at baseline in the eldecalcitol group. We observed no significant differences in glycated haemoglobin and insulinogenic index between the two groups. HOMA-IR was significantly lower and HOMA-β was significantly higher in the eldecalcitol group than in the placebo group after the three year treatment period. Body mass index did not differ significantly between the two groups after treatment.

**Time trends of bone metabolism markers**

Although serum 25-hydroxyvitamin D concentration did not differ between the two groups, serum 1,25-dihydroxyvitamin D and bone alkaline phosphatase concentrations were significantly lower with eldecalcitol compared with placebo (fig 5). In addition, bone mineral densities of the lumbar spine and femoral neck were significantly higher with eldecalcitol than with placebo. Serum osteocalcin concentrations were significantly higher with eldecalcitol than with placebo. We found no significant differences between the two groups in serum leptin, receptor activator of nuclear factor-κB ligand (RANKL), and osteoprotegerin concentrations.

**Adverse events**

A total of 26 (4.1%) participants in the eldecalcitol group and 21 (3.4%) in the placebo group discontinued the study owing to adverse events (hazard ratio 1.23, 0.70 to 2.16; P=0.47). Rates and types of adverse

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**Fig 2 | Kaplan-Meier curves for survival free from type 2 diabetes among adults with impaired glucose tolerance. Top: before adjustment for 11 covariables. Bottom: after adjustment for 11 covariables**

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**Fig 3 | Number of participants with impaired glucose tolerance who achieved normoglycaemia**

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**Fig 4 |**
events did not differ significantly between the two groups (table 2).

Discussion
In this DPVD trial, treatment with eldecalcitol (an active vitamin D analogue), at a dose of 0.75 µg per day, did not show a preventive effect on the incidence of type 2 diabetes, nor a beneficial effect on the rate of regression to normoglycaemia. However, we showed a preventive effect of eldecalcitol after adjusting for covariables (confounding factors) by using a multivariable fractional polynomial Cox regression analysis. The preventive effect of eldecalcitol on development of type 2 diabetes in a pre-diabetic population was seen especially among participants with insulin insufficiency. We believe that this discrepancy is a result of lack of statistical power, an unbalanced distribution of two hour plasma glucose concentrations between participants in the eldecalcitol and placebo groups, or both (supplementary figure D).

Fig 4 | Changes in glycaemic status and body mass index. Bars indicate standard error. HbA₁c=glycated haemoglobin; HOMA-β=homeostasis model assessment β cell function; HOMA-IR=homeostasis model assessment insulin resistance. *P<0.001 compared with placebo. †P<0.001 compared with baseline.
Firstly, we powered our trial to detect a 36% lower risk of diabetes with eldecalcitol than with placebo. However, eldecalcitol treatment decreased the risk of diabetes by a smaller effect size (13%). A meta-analysis published in 2020 showed that vitamin D supplementation was associated with an 11% lower risk of diabetes among 4896 patients with pre-diabetes. Therefore, we suspect that our research was underpowered to detect the beneficial effect of eldecalcitol before adjustment for unbalanced covariables.

Glucose intolerance is associated with insufficient insulin secretion, insulin resistance, or both. HOMA-\(\beta\) is a biomarker of insulin secretion, with a value of less than 40% indicating decreased \(\beta\) cell function. HOMA-IR is a biomarker of insulin resistance, and a value of 1.6 or above indicates that insulin is secreted from the pancreas but the target organ’s sensitivity to insulin is reduced and its action is slowed down—that is, insulin resistance. Fasting immunoreactive insulin represents the amount of basal insulin; the normal range in Japan is 2-10 μU/mL, but in Europe and the US it is 2.6-24.9 μU/mL, which is a little higher. Eldecalcitol showed its beneficial effect among the participants with the lower third of HOMA-\(\beta\), HOMA-IR, and fasting immunoreactive insulin values, of which cut-off values were 44.0%, 1.49, and 5.6 μU/mL, respectively. This suggests that eldecalcitol might have a preventive effect for development of type 2 diabetes in pre-diabetic patients with impaired basal insulin secretion. Our results are backed by basic experiments and mouse genetics.

As expected, the serum 25-hydroxyvitamin D concentration was not changed and the 1,25-dihydroxyvitamin D concentration was decreased by eldecalcitol treatment in this study. Eldecalcitol, an active vitamin D analogue, does not affect the serum 25-hydroxyvitamin D concentration, but it suppresses the expression of the \(CYP27B1\) gene in the kidney, which promotes conversion of 25-hydroxyvitamin D to 1,25-dihydroxyvitamin D intracellularly. In addition, it is relatively stable in the cell and strongly enhances the expression of the \(CYP24\) gene, which suppresses 1,25-dihydroxyvitamin D production. As a result, the serum and intracellular 1,25-dihydroxyvitamin
D concentrations are decreased. However, eldecalcitol has a similar physiological effect to 1,25-dihydroxyvitamin D. Hence, it increased the bone mineral densities of the lumbar spine and femoral neck in this study.

We also measured the changes in various factors (osteocalcin, leptin, RANKL, and osteoprotegerin) that are reportedly associated with glucose metabolism as well as bone metabolism after treatment with vitamin D and active vitamin D. Serum osteocalcin is a bone formation marker, which affects insulin sensitivity and glucose metabolism. In the second year of the trial, serum osteocalcin concentrations began increasing significantly in the eldecalcitol group compared with the placebo group. Changes in serum osteocalcin concentrations by vitamin D supplementation were inconsistent in many previous studies. This may have been due to relatively short-term administration of vitamin D. Studies have shown that active vitamin D increases the bone mineral density and is not contained in any food; thus, the drug intake can be easily evaluated. In addition, the effects with active vitamin D seem to be stronger than with normal vitamin D. Studies have shown that active vitamin D treatment increased the bone mineral density, muscle strength, and mobility of participants. We also observed increased bone mineral density in this study. This finding might be associated with the improvement in participants’ activity.

Strengths and limitations of study
Our trial has many strengths including a large population size, outpatient follow-up every three months, high rates of follow-up, and high adherence to the trial regimen. Moreover, this is the first published randomised controlled trial to assess the preventive effect of active vitamin D treatment on the development of type 2 diabetes in a pre-diabetic population and showed its beneficial effect on participants with insufficient insulin secretion. The mean serum 25-hydroxyvitamin D concentration at baseline was 20.9 ng/mL in our trial, which was lower than what was obtained in previous studies (that is, 44.0 ng/mL and 28.0 ng/mL). From the result shown in supplementary figure A, eldecalcitol may be more effective in patients with vitamin D deficiency than in patients without vitamin D deficiency.

The trial also had some limitations. Firstly, we used eldecalcitol at a regular dose of 0.75 µg. This is the standard dose administered in the case of osteoporosis, rickets, and hypocalcaemia in Japan. In studies in osteoporosis, a dose of 0.75 µg has shown non-inferiority in increasing bone mass and in preventing bone fracture compared with a higher dose (1 µg) and non-inferiority compared with a lower dose (0.5 µg). In the onset of adverse events, however, whether it was an appropriate dose for prevention of diabetes in the context of this trial is unclear. Secondly, whether the results of this study apply to all ethnicities is unclear, because the study involved only Japanese participants. Latitude of living area, occupation, and racial or ethnic differences are important factors that affect serum 25-hydroxyvitamin D concentration. Thirdly, the allocation method in this multicentre collaborative study may have been inadequate to prevent the imbalance of a critical variable such as baseline two-hour plasma glucose concentration between the two groups. Therefore, a more sophisticated allocation method should be developed.
Conclusions
Treatment with eldecalcitol, an active vitamin D analogue, at a dose of 0.75 µg per day did not significantly reduce the incidence of diabetes and failed to increase the rate of regression to normoglycaemia compared with placebo among patients with impaired glucose tolerance who were at high risk for type 2 diabetes. Although our study suggested the potential for a beneficial effect of active vitamin D treatment on the prevention of type 2 diabetes after adjustment for confounding factors, this finding should be replicated in further populations before its significance for public health can be fully appreciated. Further research, such as an appropriately randomised study focused on pre-diabetic patients with insufficient basal insulin secretion or a meta-analysis including the results of this study, would be needed to determine whether vitamin D and/or active vitamin D is beneficial to people with pre-diabetes.

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Data sharing: Relevant anonymised patient level data are available from the corresponding author on reasonable request.

The lead author (the manuscript’s guarantor) affirms that the manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.

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