Active vitamin D treatment in the prevention of sarcopenia in adults with prediabetes (DPVD ancillary study): a randomised controlled trial

Tetsuya Kawahara, Gen Suzuki, Shoichi Mizuno, Naoki Tominaga, Mikio Toda, Nagahiro Toyama, Tetsuya Inazu, Chie Kawahara, Yosuke Okada, Yoshiya Tanaka

Summary

Background Observational studies show inverse associations between serum 25-hydroxyvitamin D concentrations and sarcopenia incidence; however, it remains unclear whether treatment with vitamin D prevents its development. We aimed to assess whether treatment with active vitamin D (eldecalcitol [0·75 µg per day]) can reduce the development of sarcopenia among adults with prediabetes.

Methods This randomised, double-blind, placebo-controlled, multicenter trial as an ancillary study was conducted at 32 clinics and hospital sites in Japan. Participants were assigned (1:1) by using a central randomisation method in which a randomisation list was made for each hospital separately using a stratified permuted block procedure. The primary endpoint was sarcopenia incidence during 3 years in the intention-to-treat population defined as weak handgrip strength (<28 kg for men and <18 kg for women) and low appendicular skeletal muscle index (<7·0 kg/m² for men and <5·7 kg/m² for women in bioelectrical impedance analysis). Although the usual criterion of hypercalcaemia was 10·4 mg/dL (2·6 mmol/L) or higher, hypercalcaemia that was enough to discontinue the study was defined as 11·0 mg/dL or higher. This study is registered with the UMIN clinical trials registry, UMIN000005394.

Findings A total of 1094 participants (548 in the eldecalcitol group and 546 in the placebo group; 44·2% [484 of 1094] women; mean age 60·8 [SD 9·2] years) were followed up for a median of 2·9 (IQR 2·8–3·0) years. Eldecalcitol treatment as compared with placebo showed statistically significant preventive effect on sarcopenia incidence (25 [4·6%] of 548 participants in the eldecalcitol group and 48 [8·8%] of 546 participants in the placebo group; hazard ratio 0·51; 95% CI 0·31 to 0·83; p=0·0065). The incidence of adverse events did not differ between the two groups.

Interpretation We found that treatment with eldecalcitol has the potential to prevent the onset of sarcopenia among people with prediabetes via increasing skeletal muscle volume and strength, which might lead to a substantial risk reduction of falls.

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For the Japanese translation of the abstract see Online for appendix 1

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Introduction

Sarcopenia is a condition associated with loss of skeletal muscle mass, muscle strength, and physical function, resulting in frailty and a propensity for falls and fractures. In older adults, it increases the risk of long-term care and death, and affects the prognosis of various diseases.[1,2]

The global prevalence of sarcopenia varies between 10% and 27% according to the classification and cutoff point used to define the condition.[3] In addition, the prevalence of severe sarcopenia ranges from 2% to 9%.[3] It has also been reported that prediabetes and diabetes are independent risk factors for sarcopenia.[4] In the context of an increasing global ageing population, preventing sarcopenia has become an urgent social matter that needs to be addressed.[5]

It has been shown that early intervention in sarcopenia can extend healthy life expectancy, reduce care and medical costs, slow disease progression, and even improve sarcopenia.[6] Although lower serum 25-hydroxyvitamin D concentrations have been associated with a higher incidence of sarcopenia in observational studies,[7] clinical intervention studies with vitamin D supplementation have reported inconsistent results in muscle mass gain, muscle strength, and body fat loss.[8–11] Additionally, two meta-analyses have shown inconsistent conclusions about physical performance.[12,13] However, the total sample size of both meta-analyses was small, and the heterogeneity of various factors (eg, therapeutic effect and supplementation dose) was observed; therefore, a large interventional study is needed. Most importantly, there have been no large-scale randomised controlled trials using an active form vitamin D analog. Eldecalcitol, an active vitamin D analog, has superior effects in increasing bone density and inhibiting vertebral fractures compared with other active vitamin D, such as alfacalcidol,[14,15] and is the

Research in context

Evidence before this study

There are various diagnostic criteria for sarcopenia, such as the Asian Working Group for Sarcopenia 2019, the European Working Group on Sarcopenia in Older People 2, and the Foundation for the National Institute of Health, with each cutoff value being slightly different. However, they all share the same diagnostic criteria items of skeletal muscle mass and grip strength. Evidence from observational studies has shown associations between low blood vitamin D concentrations and increased sarcopenia incidence. Clinical trials of vitamin D supplementation have not shown a consistent benefit for muscle mass and strength. We searched PubMed and Clinical Trial Registrations on Sept 30, 2023, using the search terms "vitamin D", "active vitamin D", and "sarcopenia". We searched for clinical trials published between database inception and Sept 30, 2023, in English, and found 31 randomised controlled trials evaluating changes in muscle mass, muscle strength, and physical performance as elements of sarcopenia with vitamin D supplementation. These results have shown inconsistent conclusions about muscle mass gain and muscle strength. Furthermore, there are no interventional studies that have investigated the effect of vitamin D supplementation on the prevention of sarcopenia.

Added value of this study

Our Diabetes Prevention with active Vitamin D for sarcopenia study is, to our knowledge, the first randomised clinical trial to assess the preventive effect of active vitamin D on sarcopenia development. In this study, we have showed that treatment of eldecalcitol, which is an active form vitamin D analog, increased grip strength and skeletal muscle mass compared with placebo, and thus had a possibility of preventive effect on the development of sarcopenia. In addition, it was found that eldecalcitol treatment had a possibility of risk reduction of falls, which is one of the sarcopenia-related clinical events.

Implications of all the available evidence

Our study can have an effect on future treatment guidelines for sarcopenia prevention because, until now, the only evidence recommended in guidelines has been adequate protein intake and moderate exercise. In the context of an increasing global ageing population, eldecalcitol treatment could play an important role in the prevention of sarcopenia. To validate and expand our findings, we plan to conduct a clinical trial targeting older people regardless of sarcopenia and prediabetes in the future.

approved for the treatment of osteoporosis in Japan and China. Therefore, we aimed to investigate whether an active vitamin D treatment would result in a lower sarcopenia risk than a placebo among adults with prediabetes in an ancillary study of the Diabetes Prevention with active Vitamin D (DPVD) trial.[16]

Methods

Study design

The DPVD trial was a multicentre, randomised, double-blind, placebo-controlled trial investigating the effect of active vitamin D treatment (eldecalcitol 0·75 µg per day) on the primary prevention of type 2 diabetes incidence among adults with prediabetes conducted at 32 clinics and hospital sites in Japan. The selected vitamin D dose is used for osteoporosis prevention and treatment in Japan and China, with a favourable safety and efficacy profile.[17] Study participants agreed not to take any additional vitamin D supplements or active vitamin D drugs during the study period.[16] In this ancillary study, DPVD for sarcopenia, we examined the effects of active vitamin D treatment compared with placebo on sarcopenia development. Study eligibility criteria were determined by diabetes-related indicators, the power calculation for sample size was based on the primary outcome of the incidence of type 2 diabetes in the DPVD trial, and this study used the same participants as the DPVD trial; however, a separate protocol was created in advance (appendix 2). The study protocol was approved by the Institutional Review Boards of University of Occupational and Environmental Health, Kokura Medical Association Health Testing Center, and Fujisawa City Hospital.

See Online for appendix 3

See Online for appendix 2

Participants

Male and female participants were eligible for inclusion if they were aged 30 years or older and had prediabetes without sarcopenia. Hospitals and clinics in the vicinity of the three study centres invited their patients to participate in our study. We defined prediabetes as meeting all three of the following glycaemic criteria: fasting glucose concentration of less than 126 mg/dL (7·0 mmol/L), 2 h glucose concentration 140–199 mg/dL (7·8–11·0 mmol/L) during a 75 g oral glucose tolerance test, and glycated haemoglobin of less than 6·5% (48 mmol/L).[18] Sarcopenia was defined as weak handgrip strength (<28 kg for men and <18 kg for women) and low appendicular skeletal muscle index (<7·0 kg/m² for men and <5·7 kg/m² for women in bioelectrical impedance analysis) based on the definition from the Asian Working Group for Sarcopenia 2019.[2] The definition criteria of the European Working Group on Sarcopenia in Older People 2[5] and the Foundation for the National Institute of Health[19] have been presented in appendix 3 (p 8) with the complete inclusion and exclusion criteria (appendix 3, p 2). Participants were followed up every 3 months on an outpatient visit, with study completion at the sarcopenia onset, or until the 3-year follow-up visit. Written informed consent was obtained from all

participants before enrolment in the trial. Data on gender were self-reported by the study participants through free-text.

Randomisation and masking

Patients were randomly assigned (1:1) to either the active vitamin D group (once-daily hard-gel pill containing 0·75 μg of eldecalcitol) or the matching placebo group, with both pills looking the same. Eldecalcitol and placebo were prescribed by a sub-investigator (physician) every 3-month 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, Fujinomiya city, Japan, 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.

Sub-investigators (appendix 3, p 11) in the three trial hospitals (University of Occupational and Environmental Health, Kokura Medical Association Health Testing Center, and Fujisawa City Hospital) applied for registration and treatment assignment to the Assignment Center. Participants were assigned by using a central randomisation method in which a randomisation list was made for each hospital separately using a stratified permuted block procedure by TI at the Assignment Center before the first participant's entry. The number of strata was eight according to sex (male and female), age (30–54 years and ≥55 years), and 75 g oral glucose tolerance test 2 h post-load plasma glucose levels (<170 mg/dL and ≥170 mg/dL). Based on the assignment list, which was kept in a locked safe located in the Assignment Center, TI 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. All data obtained from the trial were collected in the Assignment Center. The key was retrieved only after the trial concluded and data were fixed.

Procedures

In every 3-month outpatient visit, all participants' body weight, waist circumference, and handgrip strength were measured. Handgrip strength was measured twice on each side using a handgrip dynamometer (Takei Scientific Instruments, Niigata, Japan). We used the maximum value in the analysis. In addition, the volumes of skeletal muscle and body fat were measured with a body composition analyser (InBody720, InBody Japan, Tokyo, Japan) using direct segmental multi-frequency bioelectrical impedance analysis.[20] Before the shipment of the InBody analysers to the three study centres, the manufacturer measured the same sample for these analysers. After confirming that there was no difference in the measured values, they were shipped to each centre. Every year, one sample was measured ten times at each centre, and the manufacturer calibrated the analysers to ensure that the coefficient of variation was the same at all centres. Serum 25-hydroxyvitamin D and 1, 25-dihydroxy vitamin 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 sarcopenia. Secondary endpoints were the incidence of falls, the changes in handgrip strength, and that in body composition: fat mass index, lean mass index, and appendicular skeletal muscle index during the 3-year study period. However, the incidence of falls is post-hoc because it was established as a secondary endpoint after the study was completed. Falls were defined as unintentionally coming to rest on the ground, floor, or other lower level. The sub-investigator (appendix 3, p 11) interviewed participants for falls during outpatient visits every 3 months. In subgroup analyses, we examined the treatment effect after stratifying a risk factor for sarcopenia separately (ie, age, sex, BMI, fat mass index, lean mass index, appendicular skeletal muscle index, baseline serum 25-hydroxyvitamin D levels, and baseline serum 1, 25-dihydroxy vitamin D levels).

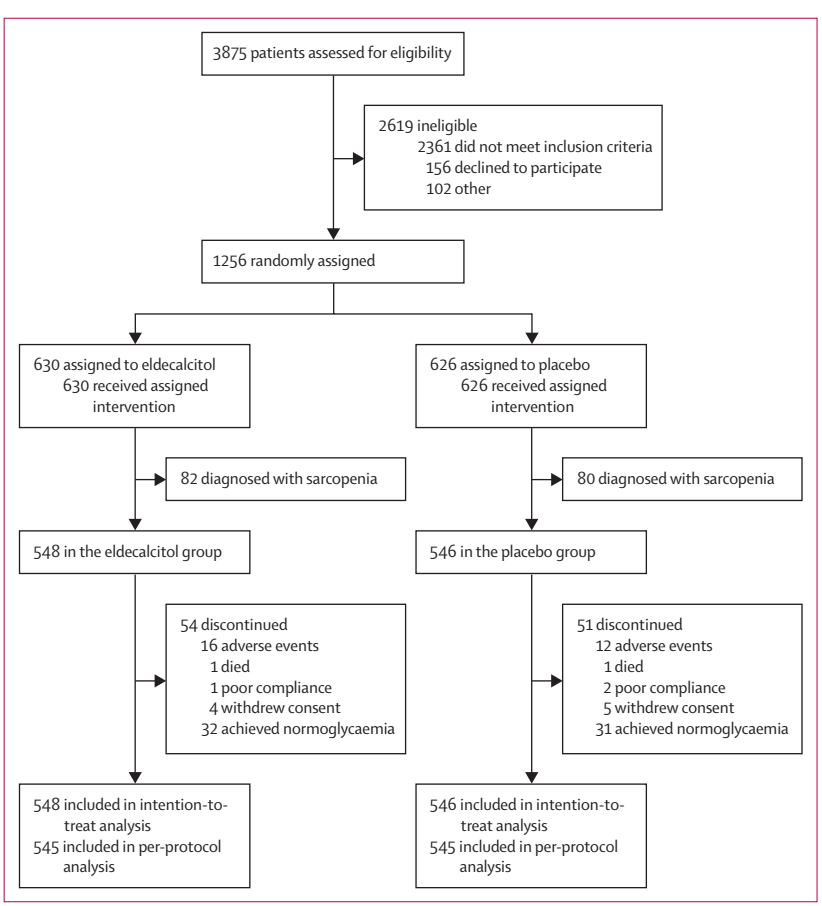

Figure 1: **Trial profile**

Statistical analysis

The sample size and power calculation were originally based on the primary outcome of the incidence of type 2 diabetes in the DPVD trial. However, if the accumulating incidence of sarcopenia in the control group was 9·3% (3·2% annually) for 3 years,[21] and dropout ratio was assumed to be 12%,[16] 546 participants in each group (a total of 1092) would be sufficient to detect a 50% reduction in sarcopenia development by eldecalcitol treatment under 80% statistical power at a 5% significant level (two-sided).

Prespecified efficacy analyses were based on the intention-to-treat population. A log-rank test and Kaplan–Meier analysis were used to estimate the time distribution to sarcopenia and incidence of falls. The treatment effect was expressed by hazard ratios (HRs) and 95% CI using a Cox regression model. In addition, the results of Cox regression analyses using the per-protocol population, and the adjustment for age, sex, and BMI were presented as sensitivity analyses. We used *t* tests and analyses of variance to compare continuous variables across randomised groups and χ^2 tests to compare proportions. The results of the prespecified intention-to-treat analyses in which missing data were imputed used the last-observation-carried-forward method. In addition, as a post-hoc analysis, we performed the multiple imputation of missing values by means of chained equations with fully conditional specification in R software (version 4.05); data were assumed to be missing at random (appendix 3, p 3).[22] In this study, we evaluated the changes during 3 years in covariates (body composition measures) using the results of these two methods. We also conducted a repeated measure ANOVA and Dunnett test for the time trends of measurements. As statistical analyses were not adjusted for multiple hypotheses testing, secondary endpoints and subgroup analysis should be interpreted with caution. We considered two-sided p values less than 0·05 to be statistically significant. This trial is registered with the UMIN clinical trials registry, UMIN000005394.

	Total (N=1094)	Eldecalcitol group (N=548)	Placebo group (N=546)
Sex			
Female	484 (44·2%)	245 (44·7%)	239 (43·8%)
Male	610 (55·8%)	303 (55·3%)	307 (56·2%)
Ethnicity			
Japanese	1094 (100%)	548 (100%)	546 (100%)
Age (years)	60·8 (9·2)	60·7 (9·0)	60·9 (9·4)
BMI (kg/m²)*	24·5 (2·5)	24·5 (2·5)	24·5 (2·3)
Fat mass index (kg/m²)	7·2 (2·1)	7·2 (2·1)	7·3 (2·1)
Female	7·5 (2·1)	7·5 (2·1)	7·5 (2·1)
Male	7·0 (2·0)	7·0 (2·0)	7·1 (2·0)
Lean mass index	17·3 (1·0)	17·3 (0·8)	17·3 (1·1)
Female	16·9 (0·8)	16·8 (0·8)	16·9 (0·9)
Male	17·5 (1·0)	17·5 (0·9)	17·4 (1·2)
Appendicular skeletal muscle index (kg/m²)	7·9 (0·9)	7·9 (1·2)	8·0 (1·3)
Female	7·2 (1·1)	7·2 (1·1)	7·3 (1·2)
Male	8·5 (1·0)	8·5 (1·0)	8·5 (1·1)
Grip strength (kg)	29·9 (7·1)	29·9 (7·4)	29·9 (6·9)
Female	23·1 (3·3)	23·2 (3·2)	23·0 (3·3)
Male	35·3 (5·0)	35·3 (5·0)	35·3 (5·0)
Family history of diabetes	651 (59·5%)	331 (60·4%)	320 (58·6%)
Glycated haemoglobin (%)	5·9 (0·2)	5·9 (0·2)	6·0 (0·2)
Unintentional falls in the past year	228 (20·8%)	115 (21·0%)	113 (20·7%)
Current smoker	64 (5·9%)	32 (5·8%)	31 (5·7%)
25-hydroxy vitamin D (ng/mL)	20·7 (6·0)	20·8 (6·1)	20·7 (6·0)
Distribution (ng/mL)			
0 to <12	88 (8·0%)	46 (8·4%)	42 (7·7%)
≥12 to <20	477 (43·6%)	235 (42·9%)	242 (44·3%)
20 to <30	549 (50·2%)	284 (51·8%)	265 (48·5%)
≥20 to ≥30	68 (6·2%)	29 (5·3%)	39 (7·1%)
1, 25-dihydroxy vitamin D (pg/mL)	41·2 (29·7–56·0)	41·0 (29·0–56·2)	41·5 (30·9–55·9)

Data are n (%), mean (SD), or median (IQR). Percentages might not total 100 because of rounding. *A total of 8·5% (93 of 1094 participants) were underweight (<22 kg/m²), 62·7% (686 participants) were normal weight (≥22 to <25 kg/m²), 25·8% (282 participants) were overweight (≥25 to <30 kg/m²), and 3·0% (33 participants) had obesity (≥30).

Table 1: **Baseline characteristics of the intention-to-treat population***

Role of the funding source

The funder of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report.

Results

From June 1, 2013, and Aug 31, 2015, a total of 3875 individuals were screened (figure 1), and 1256 were randomly assigned to receive eldecalcitol (630 participants) or matching placebo (626 participants). For this study, 162 participants with sarcopenia diagnosed by the Asian Working Group for Sarcopenia 2019 criteria were removed from the analysis. A total of 1094 participants (548 in the eldecalcitol group and 546 in the placebo group) were included in the intention-to-treat population.

Of the 1094 participants, 44·2% (484) were women and 59·5% (651 participants) had a family history of type 2 diabetes. Participants' mean age was 60·8 (range 30–77) years and BMI was 24·5 kg/m² (SD 2·5). Mean serum 25-hydroxyvitamin D levels were low (20·7 ng/mL [SD 6·0]; table 1; appendix 3, p 4). The trial was finished in Aug 31, 2019. The median follow-up period was 2·9 (IQR 2·8–3·0) years.

During the 3-year outpatient follow-up, 25 (4·6%) of 548 participants in the eldecalcitol group and 48 (8·8%) of 546 participants in the placebo group developed sarcopenia. Treatment of eldecalcitol, compared with that of placebo, had a significant preventive effect on the incidence of sarcopenia (HR 0·51, 95% CI 0·31–0·83; p=0·0065; figure 2). To assess the robustness of the primary outcome based on the intention-to-treat population, sensitivity analyses of the per-protocol population and the population after adjustment for

baseline age, sex, and BMI were performed. The results showed HRs for eldecalcitol treatment of 0·51 (95% CI 0·31–0·84; p=0·0071) for the per-protocol population and 0·50 (0·29–0·79; p=0·0043) for the after-adjustment population, which were consistent with the primary analysis findings (appendix 3, p 5). In addition, although this study investigated the incidence of sarcopenia according to the diagnostic criteria of the Asian Working Group for Sarcopenia 2019, the preventive effect of eldecalcitol on sarcopenia development was also proved using the criteria from the European Working Group on Sarcopenia in Older People 2[5] and the Foundation for the National Institute of Health.[19] The diagnostic criteria for sarcopenia in the Asian Working Group for Sarcopenia 2019, the European Working Group on Sarcopenia in Older People 2, and the Foundation for the National Institute of Health slightly differ. The participants who were diagnosed as sarcopenia according to these criteria were excluded from total of 1256 participants in the original DPVD study. As a result, 162 participants were excluded by the Asian Working Group for Sarcopenia criteria, resulting in 1094 participants; 57 were excluded by the European Working Group on Sarcopenia in Older People 2 criteria, resulting in 1199; and 49 were excluded by the the Foundation for the National Institute of Health criteria, resulting in 1207. 28 (4·7%) of 601 participants in the eldecalcitol group and 52 (8·7%) of 598 in the placebo group developed sarcopenia based on the European Working Group on Sarcopenia in Older People 2 criteria (HR 0·53, 95% CI 0·33–0·85; p=0·0064), and 27 (4·5%) of 606 participants in the eldecalcitol group and 51 (8·5%) of 601 in the placebo group developed sarcopenia based on the Foundation for the National Institute of Health criteria (HR 0·52, 95% CI 0·32–0·83; p=0·0058; appendix 3, p 9).

Eldecalcitol treatment also showed a significant reduction in the risk of falls compared with placebo, which occurred in 135 (24·6%) of 548 participants in the eldecalcitol group and 179 (32·8%) of 546 participants in the placebo group (HR 0·78, 95% CI 0·62–0·97; p=0·0283; figure 3).

Changes in BMI and waist circumference did not show significant differences between the eldecalcitol and placebo groups (BMI –0·72% *vs* –0·35%; p=0·34 and waist circumference –0·06% *vs* 0·02%, p=0·091). However, the fat mass index was significantly reduced by eldecalcitol treatment compared with placebo (–0·15% *vs* 0·31%, p=0·028). On the contrary, the appendicular skeletal muscle index was significantly increased in the eldecalcitol group compared with the placebo group (0·45% *vs* –1·72%; p<0·0001) as well as the handgrip strength (1·85% *vs* 0·45%; p=0·0003; figure 4). The results using multiple imputation method were consistent with the primary analysis findings (appendix 3, p 6).

In the subgroup analysis, we found a stronger preventive effect of eldecalcitol treatment on the development of sarcopenia in participants who were older (≥64 years), female, had a low appendicular skeletal muscle index (<7·4 kg/m²), and had low serum 25-hydroxyvitamin D levels (<18·3 ng/mL; appendix 3, p 7).

During the 3-year study period, serum 25-hydroxyvitamin D concentrations were not changed in both groups, whereas 1, 25-dihydroxy vitamin D concentrations were substantially decreased in the eldecalcitol group compared with the placebo group (0·94% *vs* 0·72%; p=0·37; –21·4% *vs* 0·43%; p<0·0001), in line with the parent study results (appendix 3, p 8).[16]

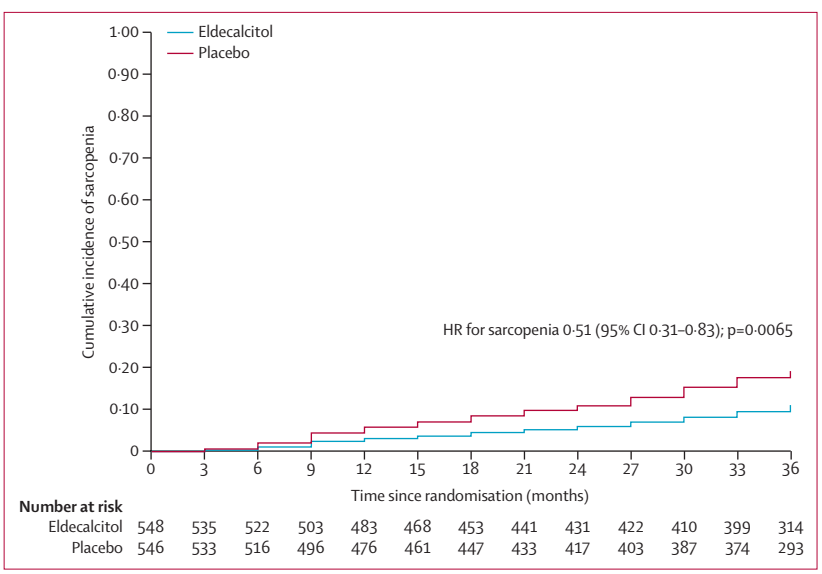

***Figure 2*: Kaplan–Meier plot for sarcopenia-free survival among adults with prediabetes**
The study's median follow-up was 2·9 years. The hazard ratio (HR) for new-onset sarcopenia between the eldecalcitol and placebo groups is derived from a log-rank test.

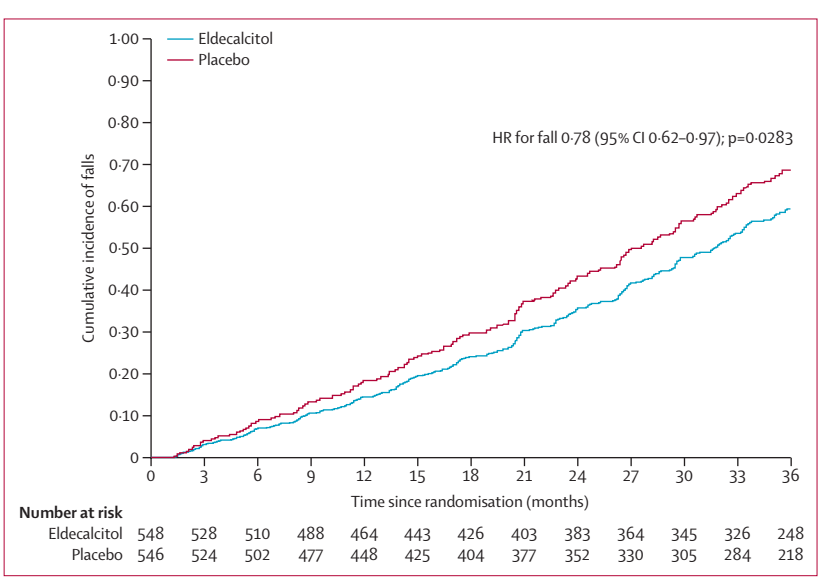

***Figure 3*: Kaplan–Meier plot for fall-free survival among adults with prediabetes**
The study's median follow-up was 2·9 years. The hazard ratio (HR) for new-onset falls between the eldecalcitol and placebo groups is derived from a log-rank test.

There were no significant differences in the incidence of adverse events between the eldecalcitol and placebo groups (table 2). The incidences of hypercalcemia, nephrolithiasis, and liver dysfunction resulting in discontinuation were slightly higher in the eldecalcitol group, but the difference did not reach statistical significance.

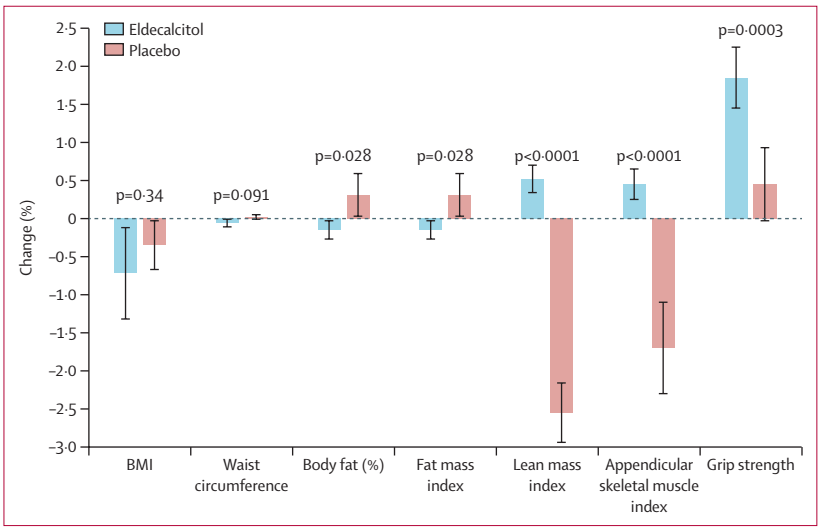

Figure 4: **Percentage change in body composition measures during 3 years**
Outcomes of adipose and lean tissues were assessed by bio-impedance analysis. T-bars indicate 95% CIs.

Discussion

In this study, treatment with eldecalcitol at a dose of 0·75 µg per day showed the possibility of reducing the incidence of sarcopenia among people with prediabetes via increasing the skeletal muscle volume and strength and reducing body fat mass after a median follow-up of 2·9 years. As a result, increasing skeletal muscle volume and strength and reducing body fat mass might lead to a significant risk reduction of falls.

It has been shown in in-vivo experiments in mice that insulin promotes protein kinase B (Akt) activation and phosphorylation of forkhead box protein O1 (FOXO1), leading to suppression of muscle degradation (ie, muscle maintenance and gain).[23] This pathway is suppressed in prediabetes and type 2 diabetes with insulin resistance. Observational studies have shown that the incidence of sarcopenia is higher in people with these diseases than in those without these diseases.[4] It has been shown in mice that active vitamin D enhances the Akt-FOXO1-mediated pathway and insulin action, resulting in preventing muscle atrophy.[24] These results in mice experiments are compatible with our results in humans.

Several intervention studies have investigated the effect of vitamin D supplementation on muscle strength and muscle mass as diagnostic criteria of sarcopenia and physical performance related to severe sarcopenia; however, the results are inconsistent.[8–11] Substantial increases in muscle mass and decreases in body fat mass

	Eldecalcitol (N=548)		Placebo (N=546)		Risk ratio (95% CI)	Risk difference (95% CI)
	Number of events	Event rate number/ 100 person-years	Number of events	Event rate number/ 100 person-years		
Discontinuations due to adverse events	17	1·03	13	0·79	1·30 (0·64 to 2·66)	0·24 (−0·41 to 0·89)
Laboratory tests						
Hypercalcaemia*	4	0·24	2	0·12	1·99 (0·37 to 8·84)	0·12 (−0·17 to 0·41)
Hypercalciuria†	3	0·18	2	0·12	1·50 (0·25 to 7·91)	0·06 (−0·20 to 0·32)
Increased serum creatinine levels‡	2	0·12	2	0·12	1·00 (0·14 to 3·05)	0·00 (−0·24 to 0·24)
Nephrolithiasis	2	0·12	1	0·06	1·99 (0·18 to 9·91)	0·06(−0·14 to 0·26)
Hives	1	0·06	2	0·12	0·50 (0·05 to 5·48)	−0·06 (−0·26 to 0·14)
Digestive symptoms	2	0·12	2	0·12	1·00 (0·14 to 3·05)	0·00 (−0·24 to 0·24)
Liver dysfunction	2	0·12	1	0·06	1·99 (0·18 to 9·91)	0·06(−0·14 to 0·26)
Death	1	0·06	1	0·06	1·00 (0·06 to 4·89)	0·00 (−0·24 to 0·24)
Serious adverse events	78	4·74	72	4·40	1·08 (0·80 to 1·45)	0·34 (−1·12 to 1·80)
Respiratory system	24	1·56	25	1·53	0·96 (0·55 to 1·65)	0·03 (−0·84 to 0·90)
Cardiovascular system	18	1·09	19	1·16	0·94 (0·50 to 1·78)	−0·07 (−0·80 to 0·66)
Gastrointestinal system	13	0·79	12	0·73	1·08 (0·50 to 2·34)	0·06 (−0·54 to 0·66)
Urogenital system	11	0·67	7	0·43	1·57 (0·61 to 4·01)	0·24 (−0·27 to 0·75)
Muscle-skeletal system	9	0·55	7	0·43	1·28 (0·48 to 3·42)	0·12 (−0·36 to 0·60)
Skin	3	0·18	2	0·12	1·50 (0·25 to 7·91)	0·06 (−0·20 to 0·32)

Table shows participants who received at least one dose of eldecalcitol or placebo. *Hypercalcaemia was defined as corrected serum calcium concentration higher than 11·0 mg/dL (2·7 mmol/L), as confirmed on repeat testing. Although the usual criterion of hypercalcaemia was 10·4 mg/dL (2·6 mmol/L) or higher, hypercalcaemia that was enough to discontinue the study was defined as 11·0 mg/dL or higher in this study. †Hypercalciuria was defined as fasting urine calcium: urine creatinine ratio of 0·28 or higher. ‡Increased serum creatinine concentration was defined as a serum creatinine concentration higher than 1·5 mg per deciliter or the upper limit of the normal range for clinical laboratory at each clinical site.

Table 2: **Frequency of adverse events in the safety population**

were observed in two studies[9,10] and in subgroup analyses of two other studies.[8,11] Similarly, results from the meta-analyses were inconsistent. One meta-analysis has reported a small but significant improvement in muscle strength and performance, but no increase in muscle mass by supplementation.[6] These effects were more noticeable for older women (aged ≥65 years) with a BMI of less than 25 kg/m² and low baseline serum 25-hydroxyvitamin D concentrations.[6] However, the other meta-analysis indicated that vitamin D supplementation worsened knee flexion strength, Timed Up-and-Go, and the short physical performance battery, and did not reduce the risk of falls and fractures.[25] In 2022, two meta-analyses showed inconsistent conclusions about physical performance. One meta-analysis[12] reported that vitamin D supplementation was effective in improving gait speed and grip strength as factors in the diagnostic criteria for sarcopenia, whereas the other meta-analysis[13] reported that it worsened short physical performance battery. However, both meta-analyses did not have large total sample sizes (269 for one meta-analysis[12] and 943 for the other[13]), and the heterogeneity of the various factors was observed.

Our study found a significant increase in muscle strength (handgrip strength) with eldecalcitol treatment. Muscle mass was slightly increased compared with its own baseline in the eldecalcitol group, whereas it was significantly decreased in the placebo group. As a result, eldecalcitol treatment significantly prevented the reduction of muscle mass by ageing.

The weight of our study population (mean BMI of 24·2 kg/m²) might have helped to prove the therapeutic effect of active vitamin D because (active) vitamin D is fat soluble and less effective in people with obesity. In addition, participants' serum 25-hydroxyvitamin D concentrations was relatively low (mean 20·7 ng/mL [51·8 nmol/L]) which might be another reason for the significant therapeutic effect seen. Furthermore, some reports have shown that active vitamin D is more effective than normal vitamin D in improving bone mineral density, fracture rate, physical performance, and Timed Up-and-Go.[26–28]

Falls is one of the sarcopenia-related clinical events. Several interventional studies have been conducted on the prevention of falls with natural vitamin D and active vitamin D, and meta-analyses have also showed inconsistent results. The meta-analysis[29] showed that vitamin D and active vitamin D prevent the incidence of falls, especially in patients with low serum 25-hydroxyvitamin D levels (20 ng/mL [50 nmol/L]).[29] On the contrary, null preventive effects or even worsening effects were reported for individuals with serum 25-hydroxyvitamin D concentrations greater than 40–45 ng/dL.[30] In addition, there are reports that high doses of vitamin D increases the risk of fractures and falls.[31] In this study, the participants' serum 25-hydroxyvitamin D concentrations were relatively low (mean of 20·7 ng/mL). Incidentally, the average of serum 25-hydroxyvitamin D concentrations of healthy male and female Japanese people are 20·3 ng/mL.[4] Thus, another reason for the preventive effect of active vitamin D on sarcopenia and falls in this study might be the vitamin D-insufficient status of the study population at baseline.

The results of our subgroup analysis has suggested that active vitamin D exerted a more preventive effect on participants prone to sarcopenia than healthy people. It has been reported that muscle mass decreases by approximately 1% per year for every year of age in adults older than 30 years and by more accelerated rates in individuals older than 70 years.[32] Therefore, older people are prone to sarcopenia. In addition, adults with lower weight and a high percentage of body fat (ie, low muscle mass) are more likely to develop sarcopenia. These adults would need active vitamin D to maintain muscle mass and increase muscle strength. Although the prevalence of sarcopenia between sexes is not consistent, it is clear that women are susceptible to postmenopausal osteoporosis and that active vitamin D has a positive effect on bone mineral density.[16] A former report has also shown a strong correlation between bone mineral density and muscle mass,[33] with a tendency for more substantial active vitamin D effects in women than in men.

Regarding drug safety, although the usual criterion of hypercalcaemia is 10·4 mg/dL (2·6 mmol/L) or higher, in this study hypercalcaemia leading to study discontinue was defined as 11·0 mg/dl or higher. Eldecalcitol is originally a drug for treating osteoporosis, which affects the metabolism of serum vitamin D and phosphorus. Therefore, although there was no significant difference in the incidence of adverse events between the two groups in this study, previous clinical trials have showed that there was a slightly higher trend of hypercalcaemia in the eldecalcitol group compared with the placebo group.[15,16] We should not prescribe eldecalcitol unnecessarily and monitor hypercalcaemia carefully.

The strengths of this study were the large sample size, and high participant adherence. In addition, we have a protocol that was created separately from that of the DPVD study (appendix 2).

This study also has limitations. First, we only evaluated one active vitamin D dose (0·75 μg per day). Second, we measured muscle mass and fat mass using InBody720 (a bioimpedance analyser) with advantages in terms of simplicity and cost compared with dual-energy x-ray absorptiometry, magnetic resonance imaging, and computed tomography, but InBody720 is sometimes misunderstood to be inaccurate. However, this analyser has been assessed in normal populations, older adults, athletes, and haemodialysis patients, and closely correlates with the gold standard measurement by dual-energy x-ray absorptiometry, underwater weighing, and air displacement plethysmography.[20,34] Moreover, the tool is not based on statistical data of any specific population; therefore, it can accurately assess people with very

different body types. Third, under the Asian Working Group for Sarcopenia 2019 diagnostic criteria,[2] the diagnosis of sarcopenia can be made if there is either low grip strength or low physical performance (6 m walk, five time chair stand test, or Short Physical Performance Battery score) in combination with decreased appendicular skeletal muscle mass. However, the diagnosis of severe sarcopenia is made only when all three of these criteria are met. Although the reference values are different, the criteria of the European Working Group on Sarcopenia in Older People 2 and the Foundation for the National Institute of Health can also diagnose sarcopenia by low skeletal muscle mass and low grip strength.[5,19] Therefore, we diagnosed sarcopenia by measuring skeletal muscle mass and hand grip strength. Finally, although this study investigated sarcopenia incidence according to the diagnostic criteria of the Asian Working Group for Sarcopenia 2019 guideline, the preventive effect of eldecalcitol on sarcopenia development was also proved using the criteria of the European Working Group on Sarcopenia in Older People 2[5] or the Foundation for the National Institute of Health.[19] However, as this study was conducted only in a Japanese population, where individuals have a lower BMI and lower serum 25-hydroxyvitamin D concentrations than populations in other regions, such as Europe and North America, it is unknown whether the results apply to other ethnicities. In addition, the use of active vitamin D, especially eldecalcitol for the treatment of osteoporosis, is approved in Japan and China based on the following evidence,[14,15,17] but not internationally owing to the small number of clinical trials with active vitamin D in Europe and North America.

In conclusion, treatment with eldecalcitol, which is an active vitamin D analog, at a dose of 0·75 µg per day resulted in lowering risks of sarcopenia incidence and falls among adults with prediabetes. We plan to conduct a clinical trial targeting older people regardless of sarcopenia and prediabetes in the future.

Contributors

TK, GS, and TI conceived and designed the study and contributed to the writing of the protocol. TK, GS, NTom, MT, NToy, and CK were responsible for the collection and assembly of data. TI did the data management. TK, GS, SM, and TI accessed and verified the data. SM designed and performed the statistical analyses, and all authors discussed the analysis plan and results, and provided input to the manuscript. All authors were responsible for the revision of the Article for important intellectual content. All authors had full access to all data in the study and provided final approval to submit the manuscript for publication.

Declaration of interests

We declare no competing interests.

Data sharing

Data from this study will be made available upon reasonable request. For data access, please contact the corresponding author at dpvdtrial@mbox.med.uoeh-u.ac.jp.

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References

1 Janssen I. Influence of sarcopenia on the development of physical disability: the Cardiovascular Health Study. *J Am Geriatr Soc* 2006; **54:** 56–62.

2 Chen LK, Woo J, Assantachai P, et al. Asian Working Group for Sarcopenia: 2019 consensus update on sarcopenia diagnosis and treatment. *J Am Med Dir Assoc* 2020; **21:** 300–307.

3 Petermann-Rocha F, Balntzi V, Gray SR, et al. Global prevalence of sarcopenia and severe sarcopenia: a systematic review and meta-analysis. *J Cachexia Sarcopenia Muscle* 2022; **13:** 86–99.

4 Kaga H, Tamura Y, Someya Y, et al. Prediabetes is an independent risk factor for sarcopenia in older men, but not in older women: the Bunkyo Health study. *J Cachexia Sarcopenia Muscle* 2022; **13:** 2835–42.

5 Cruz-Jentoft AJ, Bahat G, Bauer J, et al. Sarcopenia: revised European consensus on definition and diagnosis. *Age Ageing* 2019; **48:** 16–31.

6 De Spiegeleer A, Beckwée D, Bautmans I, Petrovic M. Pharmacological interventions to improve muscle mass, muscle strength and physical performance in older people: an umbrella review of systematic reviews and meta-analyses. *Drugs Aging* 2018; **35:** 719–34.

7 Hassan-Smith ZK, Jenkinson C, Smith DJ, et al. 25-hydroxyvitamin D3 and 1,25-dihydroxyvitamin D3 exert distinct effects on human skeletal muscle function and gene expression. *PLoS One* 2017; **12:** e0170665.

8 Chou SH, Murata EM, Yu C, et al. Effects of Vitamin d3 supplementation on body composition in the vitamin d and omega-3 trial (VITAL). *J Clin Endocrinol Metab* 2021; **106:** 1377–88.

9 Salehpour A, Hosseinpanah F, Shidfar F, et al. A 12-week double-blind randomized clinical trial of vitamin D_3 supplementation on body fat mass in healthy overweight and obese women. *Nutr J* 2012; **11:** 78.

10 El-Hajj Fuleihan G, Nabulsi M, Tamim H, et al. Effect of vitamin D replacement on musculoskeletal parameters in school children: a randomized controlled trial. *J Clin Endocrinol Metab* 2006; **91:** 405–12.

11 Mason C, Xiao L, Imayama I, et al. Vitamin D3 supplementation during weight loss: a double-blind randomized controlled trial. *Am J Clin Nutr* 2014; **99:** 1015–25.

12 Barbagallo M, Veronese N, Di Prazza A, et al. Effect of calcifediol on physical performance and muscle strength parameters: a systematic review and meta-analysis. *Nutrients* 2022; **14:** 1860.

13 Prokopidis K, Giannos P, Katsikas Triantafyllidis K, et al. Effect of vitamin D monotherapy on indices of sarcopenia in community-dwelling older adults: a systematic review and meta-analysis. *J Cachexia Sarcopenia Muscle* 2022; **13:** 1642–52.

14 Matsumoto T, Ito M, Hayashi Y, et al. A new active vitamin D3 analog, eldecalcitol, prevents the risk of osteoporotic fractures—a randomized, active comparator, double-blind study. *Bone* 2011; **49:** 605–12.

15 Liu H, Wang G, Wu T, Mu Y, Gu W. Efficacy and safety of eldecalcitol for osteoporosis: a meta-analysis of randomized controlled trials. *Front Endocrinol* 2022; **13:** 854439.

16 Kawahara T, Suzuki G, Mizuno S, et al. Effect of active vitamin D treatment on development of type 2 diabetes: DPVD randomised controlled trial in Japanese population. *BMJ* 2022; **377:** e066222.

17 Matsumoto T, Miki T, Hagino H, et al. A new active vitamin D, ED-71, increases bone mass in osteoporotic patients under vitamin D supplementation: a randomized, double-blind, placebo-controlled clinical trial. *J Clin Endocrinol Metab* 2005; **90:** 5031–36.

18 Seino Y, Nanjo K, Tajima N, et al. Report of the committee on the classification and diagnostic criteria of diabetes mellitus. *J Diabetes Investig* 2010; **1:** 212–28.

19 Studenski SA, Peters KW, Alley DE, et al. The FNIH sarcopenia project: rationale, study description, conference recommendations, and final estimates. *J Gerontol A Biol Sci Med Sci* 2014; **69:** 547–58.

20 Kim M, Shinkai S, Murayama H, Mori S. Comparison of segmental multifrequency bioelectrical impedance analysis with dual-energy x-ray absorptiometry for the assessment of body composition in a community-dwelling older population. *Geriatr Gerontol Int* 2015; **15:** 1013–22.

21 Cooper C, Dere W, Evans W, et al. Frailty and sarcopenia: definitions and outcome parameters. *Osteoporos Int* 2012; **23:** 1839–48.

22 Rubin DB, Schenker N. Multiple imputation in health-care databases: an overview and some applications. *Stat Med* 1991; **10:** 585–98.

23 Bhardwaj G, Penniman CM, Jena J, et al. Insulin and IGF-1 receptors regulate complex I-dependent mitochondrial bioenergetics and supercomplexes via FoxOs in muscle. *J Clin Invest* 2021; **131:** e146415.

24 Hirose Y, Onishi T, Miura S, Hatazawa Y, Kamei Y. Vitamin D attenuates FOXO1-target atrophy gene expression in C2C12 muscle cells. *J Nutr Sci Vitaminol* 2018; **64:** 229–32.

25 Bislev LS, Grove-Laugesen D, Rejnmark L. Vitamin D and muscle health: a systematic review and meta-analysis of randomized placebo-controlled trials. *J Bone Miner Res* 2021; **36:** 1651–60.

26 Papadimitropoulos E, Wells G, Shea B, et al. Meta-analyses of therapies for postmenopausal osteoporosis. VIII: meta-analysis of the efficacy of vitamin D treatment in preventing osteoporosis in postmenopausal women. *Endocr Rev* 2002; **23:** 560–69.

27 Rosendahl-Riise H, Spielau U, Ranhoff AH, Gudbrandsen OA, Dierkes J. Vitamin D supplementation and its influence on muscle strength and mobility in community-dwelling older persons: a systematic review and meta-analysis. *J Hum Nutr Diet* 2017; **30:** 3–15.

28 Ringe JD. Plain vitamin D or active vitamin D in the treatment of osteoporosis: where do we stand today? *Arch Osteoporos* 2020; **15:** 182.

29 Ling Y, Xu F, Xia X, et al. Vitamin D supplementation reduces the risk of fall in the vitamin D deficient elderly: an updated meta-analysis. *Clin Nutr* 2021; **40:** 5531–37.

30 Gallagher JC. Vitamin D and falls—the dosage conundrum. *Nat Rev Endocrinol* 2016; **12:** 680–84.

31 Sanders KM, Stuart AL, Williamson EJ, et al. Annual high-dose oral vitamin D and falls and fractures in older women: a randomized controlled trial. *JAMA* 2010; **303:** 1815–22.

32 Kim TN, Choi KM. Sarcopenia: definition, epidemiology, and pathophysiology. *J Bone Metab* 2013; **20:** 1–10.

33 Bijlsma AY, Meskers MC, Molendijk M, et al. Diagnostic measures for sarcopenia and bone mineral density. *Osteoporos Int* 2013; **24:** 2681–91.

34 McLester CN, Nickerson BS, Kliszczewicz BM, McLester JR. Reliability and agreement of various inbody body composition analyzers as compared to dual-energy x-ray absorptiometry in healthy men and women. *J Clin Densitom* 2020; **23:** 443–50.