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Effect of vitamin D supplementation on serum 25(OH) D levels and blood pressure among the elderly in a nursing house: A double-blind, randomised placebo-controlled trial

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ABSTRACT

Introduction: Hypertension is the most common cardiovascular disease, especially in the elderly. Previous studies have reported that vitamin D plays a role in blood pressure. This study aimed to analyse the effect of vitamin D supplementation on serum 25(OH)D levels and blood pressure. **Methods:** This was a double-blind, randomised placebo-controlled trial (RCT) on elderly subjects. Serum 25(OH)D levels were examined using chemiluminescent immunoassay (CLIA) method, while blood pressure was checked using a digital sphygmomanometer. Supplementation was given once per day for eight weeks; the control group was given a placebo, while the treatment group was given 2,000 IU vitamin D_3 for subjects with insufficiency and 4,000 IU for subjects with deficiency. **Results:** A total of 62 subjects aged 60-89 years participated and were randomised into 30 control and 32 treatment group subjects. Data analysis showed that vitamin D supplementation significantly increased 25(OH)D levels in treatment group (Δ=18.2±5.2 ng/mL) compared to control group (Δ=4.2±2.5 ng/mL) (p<0.001). However, vitamin D supplementation did not cause significant reduction in systolic blood pressure (Δ=-4.6(-25 - -0.5) mmHg for control group and Δ=-9.2(-20 - -27) mmHg for treatment group; p=0.109), and diastolic blood pressure (Δ=-7.2(-16 - -2) mmHg for control group and Δ=-8.4(-14.5 - -8.5) mmHg for treatment group; p=0.559). **Conclusion:** Vitamin D supplementation significantly increased serum 25(OH)D levels, but did not significantly reduce systolic and diastolic blood pressures in the elderly. Elderly people need to regularly check their vitamin D levels so that the provision of supplementation can be timely and their quality of life can be improved.

Keywords: blood pressure, elderly, serum 25(OH)D level, vitamin D supplementation

INTRODUCTION

Hypertension is the most common cardiovascular disease and it affects most people. Data from the World Health Organization (WHO) in 2015 showed that 1.13 billion people worldwide suffer from

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hypertension, which increased yearly (Bloch, 2016). Approximately 9.4 million people die yearly from hypertension and its complications (Whelton *et al.*, 2017). The incidence of hypertension is higher in people of developing countries compared to developed countries, with around 75% of people with hypertension living in developing countries (Hamdan *et al.*, 2012). According to data from the 2018 Basic Health Research (Riskesdas), the prevalence of hypertension in Indonesia was 34.1%, with a mortality rate of 42,7218 deaths. Hypertension mainly affects the age groups of 55-64 years (55.2%), 65-74 years (63.2%), and >75 years (69.5%) (Ministry of Health Indonesia, 2018).

Indonesia is currently entering a period of an ageing population with an increase in life expectancy, followed by an increase in the number of elderly. The increase in the number of elderly in Indonesia from 2010-2019 amounted to 7.9 million (2.1%) and will continue to increase to 48.2 million by 2035. As such, everyone will need to start paying attention to the needs and health of the elderly so that they can remain healthy, independent, active, and productive (Ministry of Health Indonesia, 2019). Based on Riskesdas's 2018 data, the most common diseases suffered by the elderly are non-communicable diseases such as hypertension, dental problems, joint disease, mouth problems, diabetes mellitus, heart disease, and stroke. In the elderly, there are also functional changes in the body that can affect nutrient bioavailability, including vitamin D (Ministry of Health Indonesia, 2018).

Several studies have shown that vitamin D is associated with cardiovascular disease, especially hypertension. Vitamin D plays a role in suppressing renin production so that the renin-angiotensin-aldosterone system is not activated and blood pressure does not increase (Zhang *et al.*, 2020). Vitamin D deficiency can be defined by low serum levels of 25-hydroxy vitamin D (25(OH)D) and can be prevented by increasing vitamin D synthesis through sun exposure, consuming foods rich in vitamin D, and supplementation (Whelton *et al.*, 2017).

Previous studies have also shown that vitamin D supplementation significantly increased serum 25(OH)D levels. Still, there are inconsistent results in blood pressure reduction among the elderly when the administration of vitamin D supplementation was the same for all subjects regardless of their previous serum 25(OH)D level status. This study was conducted to better analyse the effect of vitamin D supplementation on serum 25(OH)D levels and blood pressure in elderly people with hypertension compared to placebo based on their serum 25(OH)D level status.

MATERIAL AND METHODS

Ethics statement

This study was approved by the Ethics Committee of Faculty of Medicine, Universitas Indonesia – Dr. Cipto Mangunkusumo Hospital, Jakarta on March 13, 2023, with certificate number KET-314/UN2.F1/ETIK/PPM.00.02/2023. All subjects had signed an informed consent before starting the study and all data collected in this study were kept confidential. Presentation of study results in scientific meetings/conferences and publications in scientific journals will not include subjects' name.

Study design and population

This was an experimental, randomised, double-blind, placebo-controlled trial of elderly with vitamin D insufficiency or deficiency and hypertension. Subjects were the elderly living in the Budi Mulia I Nursing Home between

April 2023 and June 2023. Inclusion criteria included: age of ≥60 years; a resident in Panti Sosial Tresna Werdha Budi Mulia I at recruitment and for an eight-week study period; systolic blood pressure >120 mmHg and/or diastolic >80 mmHg; serum 25(OH)D levels <30 ng/mL; and ability to give written informed consent. Exclusion criteria included: bedridden, malnourished (Mini Nutrition Assessment-Short Form (MNA-SF) score <8), hypercalcemia (calcium level >10.4 mg/dL), suffering from cancer / autoimmune / kidney or liver diseases, and consumed vitamin D supplementation >400 IU for four weeks.

Following informed consent, a screening evaluation of demographic and laboratory assessments were performed. A total of 69 subjects attended the baseline interview. The interview included collecting information on demographic status (age, sex, education level, co-morbidities, intake of drugs/vitamins, sun exposure, MNA-SF questionnaire). Blood pressure was measured after resting with a digital sphygmomanometer, with an average result from two -time measurements. Serum 25(OH)D level was measured using blood samples from the subject's cubital fossa after sterilising the area with alcohol cotton. As much as 5 ml of blood specimen was taken and stored in a vacutainer ethylenediamine tetraacetic acid (EDTA), labelled with the subject's identity. 25(OH)D level was examined using the chemiluminescent immunoassay (CLIA) method. Blood pressure and laboratory tests were performed prior to initiating therapy and after eight weeks.

Randomisation and treatment allocation

Subjects were randomly assigned to receive either 2,000 IU vitamin D_3 for subjects with insufficiency [25(OH) D level 20-30 ng/mL] and 4,000 IU for subjects with deficiency [25(OH) D level <20 ng/mL] or an identical placebo supplement containing Saccharum lactis (a lactose powder with no pharmacological activity). One individual (pharmacist) was assigned to randomise the subjects; this individual did not participate in recruitment, data collection or analysis. Subjects, nursing home staffs, investigators, and analysts were also blinded to group assignment. Nursing home staffs made sure all subjects took their vitamin D_3 or placebo supplementation every day. There was no cross-over and all subjects were analysed in per-protocol manner.

An eight-week vitamin D supplementation was chosen because of pharmacokinetic evidence indicating that the loading dose of vitamin D is 8-10 weeks (Michael *et al.*, 2011). Vitamin D_3 or placebo oral capsules were distributed to subjects. Capsules for the first four weeks were distributed one day after randomisation, followed by capsules of vitamin D_3 (or placebo) for the next four weeks distributed on the fourth week. Evaluation of side effects were checked every two weeks.

Outcomes

The primary outcome measures were systolic blood pressure, diastolic blood pressure, and serum 25(OH)D level. All assessment were collected in the morning after breakfast at baseline and 8 weeks after.

Statistical analysis and sample size

All analyses were conducted using the IBM SPSS Statistics for Windows version 20.0 (IBM Corp, Armonk, New York). Normality of data was tested using the Kolmogorov-Smirnov test; normal distribution data (p>0.05) were presented in mean±standard deviation (*SD*), while abnormal distribution data (p<0.05) were shown in median. Equality of baseline characteristics were performed using

Chi-square test for categorical scale, independent *t*-test or Mann-Whitney U test for numeric scale. Within group comparisons were performed using the paired *t*-test or Wilcoxon signed-rank test. Between group comparisons were performed using independent *t*-test. A $p<0.05$ was considered statistically significant. Comparison of two mean calculation estimated that a minimum of 31 subjects in each arm would enable us to detect a change in blood pressure and serum 25(OH)D level. The sample size was sufficient to detect approximately 10% reduction.

RESULTS

Six of the 69 research subjects who attended the initial screening session did not meet the inclusion criteria; only 63 subjects met the requirements of the study. Furthermore, the subjects were randomly divided into two groups – the control group and the treatment group. The 63 selected subjects followed the entire study procedure for eight weeks, but one subject dropped out due to death because of tuberculosis in the seventh week. Thus, the subjects with complete data included in the analysis were 62 (Figure 1).

Baseline characteristics

Baseline characteristics of research subjects can be seen in Table 1. The average age of subjects was 68 years, with the majority aged 60-74 years. Majority of subjects were females (42 subjects). The highest levels of education were primary education and secondary education. The most common co-morbidity was hypertension in 22 subjects. The drug consumed by subjects was anti-hypertensive in 12 people.

Sun exposure score was assessed using a questionnaire asking how long subjects were exposed to the sun per day and which parts of the body were exposed to the sun. The mean exposure score was 23, with 36 subjects exposed to the sun for 5-30 minutes per day. For

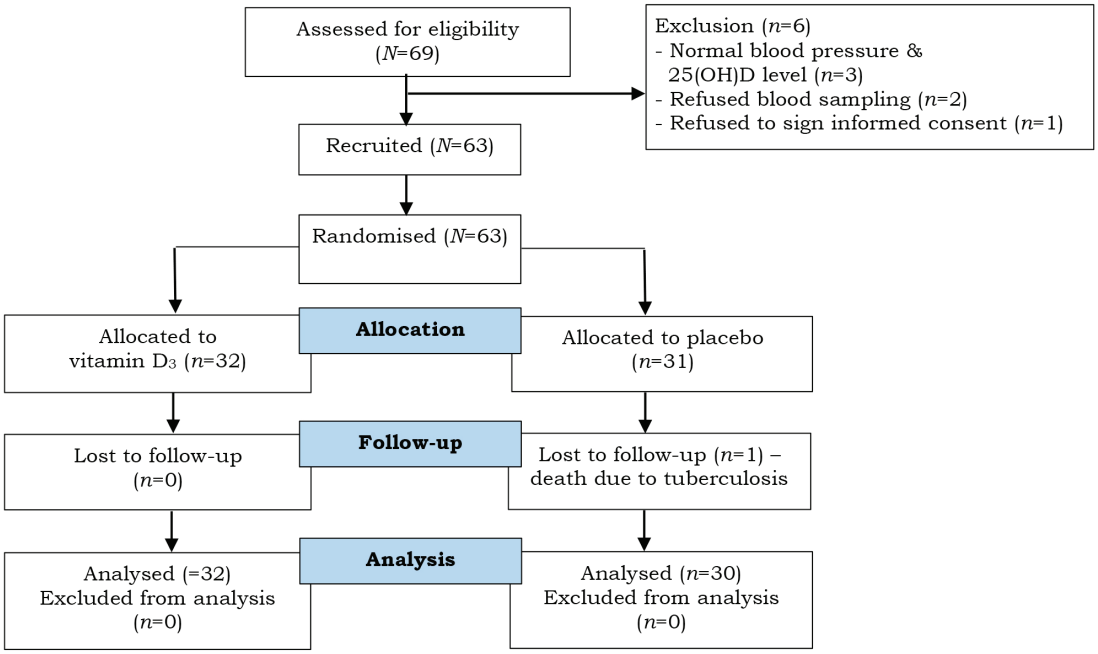

Figure 1. Flow chart of subject selection

Table 1. Baseline characteristics of research subjects

Characteristics	*Total (N=62)*		*Control (n=30)*		*Treatment (n=32)*		*p*
	n	*%*	*n*	*%*	*n*	*%*	
Gender							0.005†
Male	20	32.0	14	46.7	6	18.7	
Female	42	68.0	16	53.3	26	81.2	
Age							0.446†*
60-74 years	50	80.6	25	83.3	25	78.1	
75-90 years	12	19.3	5	16.7	7	21.9	
Education							0.268†*
No education	12	19.3	4	13.3	8	25.0	
Primary school	24	38.7	12	40.0	12	37.5	
Middle school	24	38.7	14	46.7	10	31.2	
High school	2	3.2	0	0.0	2	6.2	
Co-morbidity							0.689†*
Hypertension	22	35.5	10	33.4	12	37.5	
Diabetes mellitus	3	4.8	1	3.3	2	6.2	
Gout	9	14.5	3	10.0	6	18.7	
Osteo-arthritis	8	12.9	4	13.3	4	12.5	
Etc.	20	32.3	12	40.0	8	25.0	
Drug consumed							<0.001†
Antihypertension	12	19.3	8	26.7	4	12.5	
Sun exposure							0.454†*
Duration per day							
<5 minutes	4	6.4	2	6.7	2	6.2	
5 – 30 minutes	36	58.1	17	56.6	19	59.4	
>30 minutes	22	35.5	11	36.7	11	34.4	
Exposure area							
Face, hand	17	27.4	10	13.3	7	40.6	
Face, hand, arm	45	72.6	20	86.7	25	59.8	
Body mass index (kg/m^2)							0.213†*
Underweight (<18.5)	10	16.1	6	20.0	4	12.5	
Normal (18.5 – 22.9)	29	46.8	13	43.3	16	50.0	
Overweight (23 – 24.9)	10	16.1	7	23.3	3	9.4	
Obese I (25 – 29.9)	7	11.3	1	3.4	6	18.7	
Obese II (≥30)	6	9.7	3	10.0	3	9.4	
MNA-SF score							0.518‡*
Normal nutritional status (12-14)	16	25.8	8	26.7	8	25.0	
At risk of malnutrition (8-11)	46	74.2	22	73.3	24	75.0	
25(OH)D level (ng/mL)	20.4 (8.7 – 29.4)		23.5 (8.7 – 29.4)		16.7 (8.7 – 26.2)		<0.001‡
Calcium level (mg/dL)	9.5 (8.8 – 10.4)		9.5 (8.8 – 10.4)		9.5 (8.9 – 10)		0.681‡*
Blood pressure (mmHg)							
Systolic	134.6 (121-180)		133.9 (121-159.5)		135.3 (121-180)		0.787§*
Diastolic	89.4 (80–105)		89.6 (80-105)		89.2 (81.5–98.5)		0.594§*

MNA-SF score: Mini Nutrition Assessment-Short Form
†Chi-square test; ‡Independent *t*-test, §Mann-Whitney U test
*p>0.05 indicates equality

exposed body areas, 45 subjects reported face, hands, and arms. Calculation of body mass index found 29 subjects with normal weight. The results of malnutrition screening using the MNA-SF questionnaire found that 46 subjects were at risk of malnutrition.

For 25(OH)D levels before supplementation, 34 subjects experienced vitamin D insufficiency and 28 subjects experienced vitamin D deficiency, with an average 25(OH)D of 23.2 ng/mL before supplementation. Examination of blood calcium levels before supplementation showed normal results in all subjects, with an average calcium value of 9.5 mg/dL. Blood pressure was checked twice and the results were averaged. The results obtained were: 46 subjects had pre-hypertension, 14 subjects had grade I hypertension, and two subjects had grade II hypertension, with an average systolic blood pressure of 134.7 mmHg and diastolic blood pressure of 89.4 mmHg.

In this study, an equivalence test was carried out on the characteristics of subjects between the control and treatment groups. The results of the equivalence test on the characteristics of gender, age, education, co-morbidities, drugs consumed, sun exposure, BMI, MNA-SF score, 25(OH)D levels, calcium levels, and blood pressure can be seen in Table 1. The *p*-values for age (p=0.446), education (p=0.268), co-morbidities (p=0.689), sun exposure (p=0.454), BMI (p=0.213). MNA-SF score (p=0.518), calcium levels (p=0.618), and blood pressure (p=0.787 for systolic and p=0.594 for diastolic) were >0.05, meaning there was equality of characteristics between the control and treatment groups. Meanwhile, the *p*-values for gender, drugs consumed, and 25(OH)D levels were <0.05, so there was no equality in these characteristics of the subjects.

Distribution of subjects based on 25(OH)D level and blood pressure

The distribution of research subjects based on 25(OH)D levels before and after being given supplementation in the control and treatment groups can be seen in Table 2. The average level of 25(OH)D in 62 subjects was 20.4 ng/mL. The average systolic blood pressure in 62 research subjects was 134.7 mmHg and the average diastolic blood pressure was 89.4 mmHg.

In the control group, 25 subjects experienced vitamin D insufficiency and five subjects experienced vitamin D deficiency, with an average 25(OH) D level of 23.1 ng/mL. Subjects were then given placebo supplementation for eight weeks. The average 25(OH)D level after placebo was 27.3 ng/mL, with 11 subjects experiencing sufficiency, 16 subjects experiencing insufficiency, and three subjects experiencing deficiency. Whereas in the treatment group before supplementation, nine subjects experienced vitamin D insufficiency and 23 subjects experienced vitamin D deficiency, with an average 25(OH)D level of 17.9 ng/mL. After supplementation, the average level of 25(OH)D increased to 36.1 ng/mL, with 27 subjects experiencing sufficiency, three subjects experiencing insufficiency, and two subjects experiencing deficiency.

For blood pressure, in the control group, 22 subjects had pre-hypertension and 8 subjects had grade I hypertension. The average systolic blood pressure was 133.9 mmHg and diastolic blood pressure was 89.6 mmHg. After receiving placebo, the average systolic blood pressure became 129.3 mmHg and diastolic blood pressure 82.4 mmHg, with five normotension subjects, 21 subjects with pre-hypertension, and four subjects with grade I hypertension. Whereas in the treatment group before supplementation, 24 subjects had pre-

Table 2. Distribution of subjects based on 25(OH)D level and blood pressure, before and after supplementation

Variables	*Control group (n=30)*		*Treatment group (n=32)*		*p*
	n	*%*	*n*	*%*	
25(OH)D level					
Before supplementation					<0.001†
Insufficiency	25	83.3	9	28.1	
Deficiency	5	16.7	23	71.9	
After supplementation					<0.001†
Sufficiency	11	36.7	27	84.4	
Insufficiency	16	53.3	3	9.4	
Deficiency	3	10.0	2	6.2	
Blood pressure					
Before supplementation					0.315†*
Pre-hypertension	22	73.3	24	75.0	
Hypertension grade I	8	26.7	6	18.8	
Hypertension grade II	-	-	2	6.2	
After supplementation					0.680†*
Normotension	5	16.7	8	25.0	
Pre-hypertension	21	70.0	21	65.6	
Hypertension grade I	4	13.3	3	9.4	
Hypertension grade II	-	-	-	-	

†Chi-square test
*p>0.05 indicates equality

hypertension, six subjects had grade I hypertension, and two subjects with grade II hypertension. The average systolic blood pressure was 135.3 mmHg and diastolic blood pressure was 89.2 mmHg. After supplementation, the average systolic blood pressure was 126 mmHg and diastolic blood pressure was 80.8 mmHg, with eight normotension subjects, 21 subjects with pre-hypertension, and three subjects with grade I hypertension.

Changes in 25(OH)D levels and blood pressure

The normality of data distribution was tested using the Kolmogorov-Smirnov test. Data on 25(OH)D levels were normally distributed and analysed using paired *t*-test. As for systolic and diastolic blood pressures, the data were not normally distributed, so they were analysed using the Wilcoxon signed-rank test. Table 3 shows that in the control group, the level of 25(OH)D increased from 23.1±4.9 ng/mL to 27.3±7.3 ng/mL. After being analysed using paired *t*-test, the result showed a significant change (p<0.001). Likewise, in the treatment group, the level of 25(OH)D increased from 17.9±4.4 ng/mL to 36.1±9.8 ng/mL. The analysis using paired *t*-test also obtained a significant result (p<0.001).

The change in systolic blood pressure for the control group was 133.9(121-159.5) mmHg to 129.3(96-159) mmHg; the Wilcoxon signed-rank test showed a significant change (p<0.05). For the treatment group, the change was 135.3(121-180) mmHg to 126(101-153) mmHg, with a p<0.001 from the Wilcoxon signed-rank test, indicating a significant change. Similar results were also found for diastolic blood pressure, where the

change in the control group was 89.6(80-105) mmHg to 82.4(64-103) mmHg, with a $p<0.001$ from the Wilcoxon signed-rank test. In the treatment group, diastolic blood pressure reduced from 89.2(81.5-98.5) mmHg to 80.8(67-90) mmHg; the Wilcoxon signed-rank test also obtained a significant result ($p<0.001$).

Mean changes in 25(OH)D levels for the control and treatment groups are shown in Table 4. The mean change in 25(OH)D level in the control group was 4.2±2.5 ng/mL and 18.2±5.5 ng/mL for the treatment group. Independent *t*-test showed a significant change ($p<0.001$) in 25(OH)D levels between groups. For systolic blood pressure, the mean change in the control group was -4.6(-25 - -0.5) mmHg and -9.2(-20 - -27) mmHg in the treatment group. Independent *t*-test obtained no significant differences in systolic blood pressure change between groups ($p=0.109$). Likewise, with diastolic blood pressure, the mean change in the control group was -7.2(-16 - -2) mmHg and the mean change in the treatment group was -8.4(-14.5 - -8.5) mmHg; results using the independent *t*-test also obtained no significant differences in diastolic blood pressure change between groups ($p=0.559$).

Adverse event

In this study, no side effects were reported in each group. However, one research subject could not continue until the end of the study due to death (tuberculosis) in the seventh week. The subjects of this study had an initial screening examination with a serum 25(OH)D level of 26 ng/mL, calcium level of 9.5 mg/dL, blood pressure of 130/90 mmHg, normal nutritional status, and no co-morbidities. Subjects included in the control group were given placebo supplementation, so any adverse events could be considered unrelated to the administration of intervention in this study.

Table 3. Mean changes in 25(OH)D level, systolic and diastolic blood pressures

Variable	*Control group (n=30)*			*Treatment group (n=32)*		
	Before supplementation	*After supplementation*	*p*	*Before supplementation*	*After supplementation*	*p*
25(OH)D level	23.1±4.9	27.3±7.3	<0.001†*	17.9±4.4	36.1±9.8	<0.001†*
Systolic blood pressure	133.9 (121-159.5)	129.3 (96-159)	0.027‡*	135.3 (121-180)	126 (101-153)	<0.001‡*
Diastolic blood pressure	89.6 (80-105)	82.4 (64-103)	<0.001‡*	89.2 (81.5-98.5)	80.8 (67-90)	<0.001‡*

Value in mean±standard deviation (*SD*) or median (IQR, 25th-75th percentile)
†Paired *t*-test, ‡Wilcoxon signed-rank test
*$p<0.05$ indicates statistically significant

Table 4. Changes of 25(OH)D level, systolic and diastolic blood pressures between groups

Variable	*Control (n=30)*	*Treatment (n=32)*	*p*
Change in 25(OH)D level	4.2±2.5	18.2±5.5	<0.001†*
Change in systolic blood pressure	-4.6 (-25 - -0.5)	-9.2 (-20 - -27)	0.109†
Change in diastolic blood pressure	-7.2 (-16 - -2)	-8.4 (-14.5 - -8.5)	0.559†

Value in mean±standard deviation (*SD*) or median (IQR, 25th-75th percentile)
†Independent *t*-test
**p*<0.05 indicates statistically significant

DISCUSSION

25(OH)D is a marker to determine human vitamin D status. Vitamin D enters the blood, is assisted by vitamin D binding protein to the liver and is hydroxylated to 25(OH)D, which has the highest serum concentration and longer half-life (Hamdan *et al.*, 2012). The Institute of Endocrinology defines 25(OH)D levels below 20 ng/mL as vitamin D deficiency and 25(OH)D levels 20 - <30 ng/mL as vitamin D insufficiency (Larsen *et al.*, 2012). Various factors like age can cause vitamin D deficiency. One of the causes of vitamin D deficiency in the elderly is a decrease in the production of pre-vitamin D in the skin. Around 80-90% of vitamin D comes from sunlight. Therefore, outdoor activities will expose them to more sunlight. In this nursing home, the elderly routinely did morning exercise every day between 7 – 9 o'clock; this activity causes the elderly to be frequently exposed to sunlight.

Supplementation is one of the most effective ways to overcome vitamin D deficiency (Pfotenhauer & Shubrook, 2017). Because the subjects of this study were elderly, the safest dose of vitamin D_3 was used - a dose of 4,000 IU for subjects with deficiency and 2,000 IU for subjects with insufficiency for a supplementation duration of eight weeks, which was proven to provide a significant increase in 25(OH)D levels. In this study, there was a change in the average level of 25(OH)D in the control and treatment groups. The mean change in 25(OH)D level in the treatment group compared to the control group was also statistically significant. This is consistent with previous studies where there was a significant increase in 25(OH)D levels after vitamin D supplementation. In a study by Wood *et al.* (2012) where vitamin D supplementation was given to women aged 64±2 years at a dose of 1,000 IU per day for 48 weeks, there was a significant change in serum 25(OH) D level from 13±5.5 ng/mL to 55.9±5.5 ng/mL. A study by Pilz *et al.* (2015) also showed that vitamin D supplementation at a dose of 2,800 IU per day for 32 weeks in subjects aged 60.1±11.3 years who suffered from hypertension and 25(OH)D levels <30 ng/mL resulted in a significant change in 25(OH)D level from 22±5.5 ng/mL to 36.2±7.3 ng/mL. This is also consistent with the study of Husna *et al.* (2021) where a positive correlation was found between serum 25(OH)D level with a median duration of 40 minutes of sun exposure in elderly subjects (r=0.425, p=0.006). Farapti *et al.* (2020) said that vitamin D deficiency is common in the elderly due to lack of sun exposure and low intake of vitamin D.

Food intake and decreased nutrient bioavailability in the elderly can also inhibit vitamin D metabolism, which results in decreased levels of 25(OH) D (Russell, 2018). In this study, food weighing could not be analysed, so the subjects' intake data were only obtained based on the food menu list from the

nursing home. From the food menu list, food sources of vitamin D consumed by subjects were tempeh/tofu every day and gourami/mackerel/cob/catfish every two days without any additional vitamin D fortified foods. Tempeh and fish consumed by subjects had low vitamin D content, indicating that subjects had a low tendency to consume food sources of vitamin D. Based on the low consumption of vitamin D food sources, it can be concluded that the significant change in 25(OH)D level of the control group was because subjects routinely received sun exposure.

Vitamin D also has a vasoprotective effect, including slowing atherosclerosis, increasing endothelial function, and suppressing the renin-angiotensin-aldosterone system (Pilz *et al.*, 2015). The increased risk of cardiovascular disease, especially hypertension, is associated with vitamin D deficiency (Vaidya & Williams, 2012). Basic science research showed that vitamin D plays a role in hypertension by suppressing the renin-angiotensin-aldosterone system, the primary regulator of blood pressure, electrolytes, and volume homeostasis (Park *et al.*, 2014). Vitamin D can suppress renin production by suppressing gene transcription renin so that the renin-angiotensin-aldosterone system is not activated. In addition, vitamin D can also inhibit the expression of cyclooxygenase-2 (COX-2), so arachidonic acid is not converted into prostaglandins. As a result of the inactivated renin-angiotensin-aldosterone system, blood pressure does not increase (Hamdan *et al.*, 2012). In addition, vitamin D can affect endothelial function by increasing the production of nitric oxide, which plays a role in relaxing blood vessels and reducing blood pressure, as well as reducing inflammation in the endothelium so that it can repair the disturbed endothelial structure.

In this study, systolic blood pressure in the control group and treatment group decreased significantly. However, the change in systolic blood pressure in the treatment group compared to the control group was not statistically significant, meaning that vitamin D supplementation did not affect a significant reduction in systolic blood pressure. The same results were also obtained with diastolic blood pressure in the control and treatment groups, which experienced a significant decrease. Changes in diastolic blood pressure in the treatment group compared to the control group also did not yield statistically significant results, meaning that vitamin D supplementation had no significant effect on diastolic blood pressure reduction. The results of this study are similar to those of Wood *et al.* (2012), Gepner *et al.* (2012), Pilz *et al.* (2015), and Tomson *et al.* (2017), where there were no significant decreases in systolic or diastolic blood pressures. A study from Wood *et al.* (2012) conducted on 265 postmenopausal women aged 64±2 years who were given vitamin D at a dose of 1,000 IU/day for 48 weeks and divided into two seasons found no significant decrease in systolic and diastolic blood pressures. A study from Gepner *et al.* (2012) reported that 62 in 114 menopausal women in Wisconsin, USA, who were given 2,500 IU/day of vitamin D for 16 weeks also found a non-significant decrease in systolic and diastolic blood pressures. A study by Pilz *et al.* (2015) stated that the insignificant difference in blood pressure might be caused by a significant increase in triglyceride lipid profile due to vitamin supplementation, but these results still require validation and more examination on lipid profile. Conflicting results were found in several studies, with a significant decrease in systolic and diastolic blood pressures. A study from Larsen *et al.* (2012), which was conducted on 112

elderly subjects at a dose of 3,000 IU/ day for 80 weeks showed a significant decrease in systolic blood pressure from 132±10 mmHg to 128±0 mmHg (Δ=-4) and diastolic blood pressure from 77±6 mmHg to 76±6 mmHg (Δ=-3). A study by Chen *et al.* (2014), which was conducted on 126 elderly subjects with grades I and II hypertension at a dose of 2,000 IU/ day for 24 weeks also found a significant decrease in systolic blood pressure from 132.1±9.4 mmHg to 125.9±9.4 mmHg (Δ=-6.2) and diastolic blood pressure from 75.1±9.1 mmHg to 70.9±9.1 mmHg (Δ=-4.2). Likewise, in the study of Hermawan & Andoko (2017), there was a significant decrease in systolic blood pressure from 172 mmHg to 153 mmHg (Δ=-19) and diastolic blood pressure from 93 mmHg to 83 mmHg (Δ=-10).

According to the research by Vaidya & Forman (2010), the inconsistent results of several RCT studies regarding the effect of vitamin D on reducing blood pressure could be due to the variability of study population, sample size, vitamin D dosage, and duration of supplementation. In previous studies, a duration of more than eight weeks of supplementation is required to obtain a significant reduction in blood pressure, whereas in this study the duration of supplementation followed the loading dose of vitamin D to increase serum 25(OH)D levels. Therefore, the duration of supplementation may have caused a non-significant decrease in systolic and diastolic blood pressures in this study.

An equivalence test on subject characteristics (baseline) of anti-hypertensive drugs consumed (p<0.001) was found. Out of a total of 12 subjects taking anti-hypertensives, eight subjects were in the control group. Inequality in the randomisation of subjects on these characteristics can affect the analysis results on reducing blood pressure, which was not significant in the treatment group compared to the control group. Study results by Jorde *et al.* (2010) also found no significant reduction in blood pressure because 21% of the study population took anti-hypertensive drugs. In this study, eight subjects in the control group were taking anti-hypertensives; which likely caused the decrease in blood pressure for the treatment group to be insignificant compared to the control group.

Limitations

This study had some limitations needed to be considered: (i) body composition was not measured, especially fat mass, so it did not consider the loading dose duration of vitamin D for subjects with obesity or sarcopenia; (ii) sun exposure score was only assessed at the beginning of the examination, so it was not known whether there was a change in the subjects' behaviour towards sun exposure and this could be a confounding factor in the increase of serum 25(OH)D levels in the control group; (iii) subjects who consumed anti-hypertensive drugs were only assessed at the beginning of the examination, so it was not known whether there were any additional subjects who consumed anti-hypertensive drugs during supplementation and this could be a confounding factor in the decrease of blood pressure in the control group; (iv) access to obtain food intake data by food weighing cannot be carried out, so no analysis was done in terms of food intake, especially food sources of vitamin D and its effect on serum 25(OH) D levels and blood pressure; (v) other factors that can cause hypertension, such as family history, smoking habit, salt consumption, and lipid profile (cholesterol, triglycerides) were not examined in this study.

CONCLUSION

Vitamin D supplementation significantly increased serum 25(OH)D levels but did not significantly reduce systolic and diastolic blood pressures in the elderly. Researchers and medical educationists are encouraged to continue to assess a more varied elderly population, a larger sample size (to eliminate confounding factors that may affect serum 25(OH) D levels and blood pressure), a longer duration of supplementation, food intake especially food sources of vitamin D on its effect on 25(OH)D levels, and other factors that can cause hypertension in the elderly. Also, the elderlies need to regularly have their health, nutritional status, and vitamin D levels checked so that the provision of therapy can be timely and their quality of life can be increased.

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Authors' contributions
Ferawaty, principal investigator, conceptualised and designed the study, led the data collection and analysis, prepared the draft of the manuscript; Diana S, advised on conceptualisation, study design, data analysis, interpretation, assisted in the drafting of the manuscript, and reviewed the manuscript; Noto D, advised on conceptualisation, study design, data analysis, interpretation, assisted in the drafting of the manuscript, and reviewed the manuscript; Dian NC, advised on conceptualisation, study design, data analysis, interpretation, assisted in the drafting of the manuscript, and reviewed the manuscript; Ninik M, advised on conceptualisation, study design, data analysis, interpretation, assisted in the drafting of the manuscript, and reviewed the manuscript; Nurul RMM, advised on conceptualisation, study design, data analysis, interpretation, assisted in the drafting of the manuscript, and reviewed the manuscript.

Conflict of interest
There is no conflict of interest in this research.

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