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The Effects of Cholecalciferol 1000 IU Supplementation on Handgrip Strength in Elderly with Vitamin D Deficiency

Pengaruh Cholecalciferol 1000 IU pada Kekuatan Genggam Tangan Lansia dengan Defisiensi Vitamin D

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ABSTRACT

Backgrounds: Vitamin D regulates muscle function by binding to vitamin D receptors (VDR) via genomic signaling pathways. The biologically active form of vitamin D (1,25-(OH)D) affects muscles by modulation of gene transcription and protein kinase signaling pathways that support proliferation and muscle growth. Aging will result in the interaction of vitamin D and VDR, affecting the regulation of muscle calcium channels, followed by a decrease in the stimulation of muscle contractions. Decreased synthesis and low vitamin D intake also affect serum level 25(OH)D. Maintaining vitamin D status in the elderly with vitamin D deficiency is expected to inhibit the decline in muscle strength and dysfunction.
Objectives: Determining the effect of giving cholecalciferol on handgrip strength.
Methods: An experimental study with randomized controlled trial (RCT) enrolled 54 elderly divided into treatment and control groups. The treatment group received cholecalciferol 1000 IU/day, and the control group received a placebo for 12 weeks. Both groups were examined for serum 25(OH) levels before and after treatment.
Results: Most samples in both groups (79.62%) showed vitamin D deficiency. There was an effect of 1000 IU cholecalciferol supplementation on serum 25(OH)D levels with a mean change of 3.8 ($p<0.001$), while the grip strength showed insignificant results with a mean change of 0.5 ($p=0.748$). No significant relationship existed between serum 25(OH)D level changes and handgrip strength ($r=0.02$; $p=0.87$).
Conclusions: Cholecalciferol supplementation of 1000 IU/day for 12 weeks increased serum vitamin D levels but did not increase grip strength.

INTRODUCTION

The Indonesian population pyramid in the last five decades shows that the percentage of the elderly population has doubled, reaching 9.60% or around 25.64 million people[1,2]. An increasing trend of health problems will follow an increase in older people. Sarcopenia is a health problem in the elderly due to aging, characterized by decreased function and muscle mass associated with a risk of disability, falls, and death[3].

The mechanism for sarcopenia is closely related to the underlying conditions, such as age, prolonged bed rest, sedentary lifestyle, chronic degenerative diseases, malignancy, and inadequate nutritional intake[4]. Each condition contributes differently to decreased muscle mass, strength, and quality. In addition, neurogenic components play a role, namely the presence of 2 types of muscle fibers; type I is a slow motor unit (slow type) rich in mitochondria and myoglobin, while type II is a fast fatigable motor unit (fast type). During aging, the size of type II fibers decreases compared to type I fibers. This is known through histochemical examination, which coincides with the atrophy of type II fibers. There is a disproportionate distribution so that myosin collects in the same fibers. The denervation of type II fibers and reinnervation of type I fibers affects the motor system, resulting in changes in muscle function, significantly decreasing skeletal muscle strength[3,5,6].

Vitamin D is in the spotlight after it has been shown to play an essential role in acute and chronic diseases, and previous studies have also mentioned the role of vitamin D in maintaining musculoskeletal function, although the results are still being debated[7,8]. The primary source of vitamin D, 90%, is obtained from the endogenous synthesis of vitamin D3 (cholecalciferol), and the rest is obtained from vitamin D2 (ergocalciferol) food intake. The intake of seafood, margarine, dairy products, and eggs is rich in vitamin D[9–11]. Several factors, including endogenous synthesis of vitamin D3, food intake, and supplementation, influence vitamin D status. The prevalence of vitamin D deficiency increases during aging. Even in the literature, it is stated that a decrease in serum vitamin D levels of less than 20 µg/mL in the Malay race reached 90.5%[12,13]. Research on vitamin D3 supplementation on musculoskeletal function in subjects with vitamin D deficiency needs to be carried out to add to the research base, which is still limited.

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Over the last decades, the association between increasing age and subsequent decline in muscle mass and decreased circulating vitamin D levels has been extensively studied. Vitamin D must bind to the vitamin D receptor (VDR) to achieve effects in skeletal muscle mediated by genomic pathways. Campbell et al., 2008 reported a decrease in VDR in muscle cells directly related to increasing age and loss of muscle mass. This finding aligns with a study from Haslam et al., 2014 that lower serum vitamin D concentrations are associated with decreased muscle strength compared to those with higher concentrations. Supplementation in vitamin D deficiency is reported to affect the musculoskeletal system positively[6,7,14].

Handgrip strength, commonly called the Hand Grip Strength (HGS) examination, describes the maximum strength that comes from a combination of intrinsic and extrinsic muscles of the musculoskeletal system. The handgrip strength examination results can represent a picture of muscle strength. HGS is often used as a screening tool because it is a straightforward, non-invasive, inexpensive, and reliable way to assess muscle strength[15–17]. In a study by Cavalcante et al., 2015 supplementation of vitamin D3 6600 IU/week in postmenopausal women can increase HGS, but different results were obtained in the study by El Hajj et al. (2019) where supplementation of 10,000 IU three times a week did not affect muscle strength[18,19]. Meta-analysis of 81 RCT studies conducted by Bolland et al., 2018 concluded that there is little justification for giving vitamin D supplementation > 800 IU/day to maintain and support musculoskeletal health[20]. However, further and in-depth studies must be included in clinical guidelines. Previous studies that have not been conclusive regarding the optimal dose of vitamin D supplementation for the musculoskeletal system are one of the considerations in determining the daily dose of 1000 IU in this study.

Vitamin D deficiency status management, both preventive and curative, especially in the elderly, is expected to prevent or slow down the incidence of sarcopenia, so it is necessary to consider giving vitamin D supplementation. The results of the Bolland et al. 2018 meta-analysis study stated that it is necessary to prepare clinical guidelines regarding the optimal dose of vitamin D3 to be able to provide effects on muscle function, and most experimental studies are conducted in Western countries that have different demographics and population characteristics from Indonesia, so we consider it necessary to carry out RCTs regarding supplementation in the elderly. We are interested in investigating the effect of cholecalciferol on handgrip strength in the elderly.

METHODS

This type of research was experimental with a randomized controlled trial (RCT) design. Examination and data collection was carried out at the Dharma Bhakti Kasih Nursing Home Surakarta in the period August - November 2020, and obtained permission from the Health Research Ethics Commission, Faculty of Medicine, Diponegoro University (No. 246/EC/KEPK/FK-UNDIP/XI/2020). The population in the study were all residents of the orphanage who were over 60 years old, and the subjects taken were those who met the inclusion and exclusion criteria. The inclusion criteria included being over 60 years old; being able to stand for examination; having a serum 25(OH)D level of less than 30 ng/mL according to recommendations from The Endocrine Society; optimal criteria being above 30 ng/mL so that supplementation is given to subjects with insufficiency criteria to deficiency or serum vitamin D levels of less than 30 ng/m; no history of hospitalization in the last one month; and willing to become research subjects. Subjects were excluded if they had severe illnesses that could affect the synthesis and metabolism of vitamin D, such as a history of kidney and liver disease, consumption of vitamin D supplementation in the last two months, and conditions that prevented the subject from continuing participation.

According to the inclusion criteria, sampling was carried out by purposive sampling method. The research sample size was calculated using the sample size test formula for experimental design, so the minimum number of samples was 24. This study used 27 samples to anticipate a 10% dropout.

$$n1 = n2 = \left(\frac{(Z\alpha + Z\beta)\,.\,S}{(X1 - X2)}\right)^2$$

Description:

n = minimum number of subjects
α = type I error (specified)
β = type II error (specified)
$x1-x2$ = desired clinical difference (clinical judgment)
S = standard deviation of the average difference (from the library)

Preliminary data collection was carried out in both groups, consisting of primary data taken through interviews in the form of self-identity and characteristics through filling out questionnaires. Some of the questionnaires in this study were the Semi-Quantitative Food Frequency Questionnaire (SQ-FFQ) to see an overview of the variety of foods containing vitamin D consumed by the subjects and the International Physical Activity Questionnaire (IPAQ) to describe the physical activity of the last seven days. The next stage will be collecting anthropometric data by measuring body weight and height to obtain body mass index (BMI) data, measuring handgrip strength using a Jamar dynamometer, and measuring serum levels of 25(OH)D by taking venous blood. Subjects who met the inclusion criteria were randomly grouped by the person in charge of the orphanage into the treatment and control groups without the researcher knowing. The person in charge of the orphanage will give numbers to all the elderly, then 60 samples will be randomly selected, then the group distribution data will be submitted to the researcher.

Giving cholecalciferol 1000 IU/day once a day

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at any time was carried out in the treatment group for 12 weeks. In comparison, the control group was given a placebo containing 3.6 mg sodium saccharin and 45 mg sodium cyclamate. Consumption of supplementation in both groups was confirmed by caregivers from the orphanage daily. All subjects received the same intake and physical activity from the orphanage. Final data collection was carried out after 12 weeks, measuring serum levels of 25(OH)D and handgrip strength.

All data collected were analyzed using descriptive analysis, namely univariate and bivariate. The significance of the effect of the intervention between treatment groups was analyzed using an unpaired t-test with a confidence interval value of $p<0.05$.

RESULTS AND DISCUSSION

All research methods are described in the flow, as shown in Figure 1. The total research subjects based on gender are shown in Table 1. Most subjects were 37 women (68.5%) compared to 17 male subjects (31.4%). There was no significant difference between the characteristics of the treatment group and the control group based on gender ($p>0.05$). Gender is related to serum 25(OH)D levels based on women's habit of avoiding sunlight, which is higher than men, while muscle strength is based on research by Alqahtani, 2019 that men have a higher handgrip strength value than women[15,21].

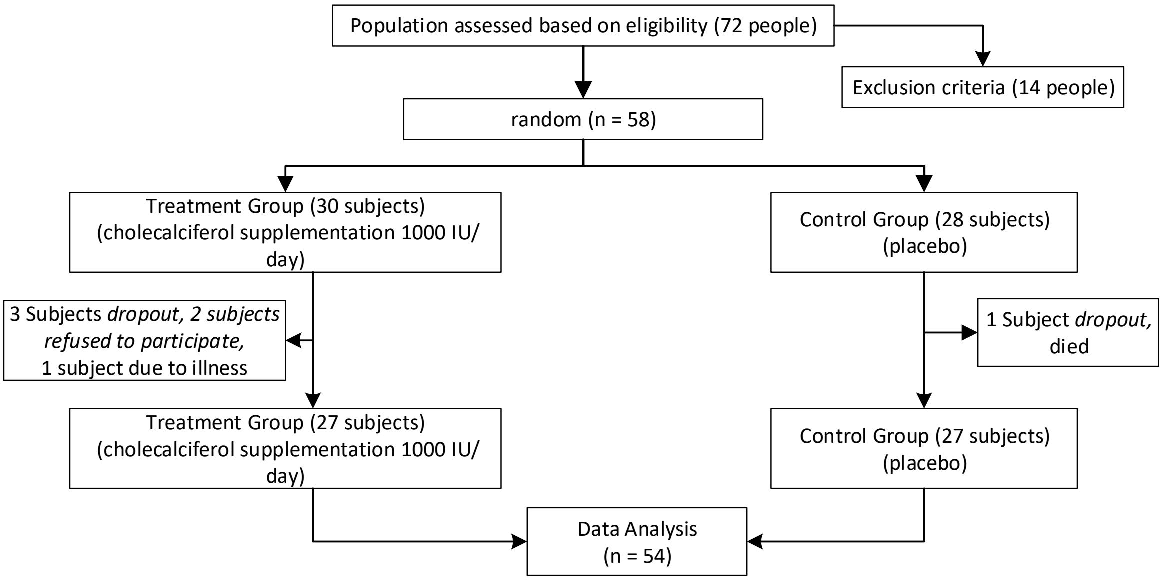

Figure 1. Research flow. The stages of the research methodology were as follows: The elderly population in the nursing home was 72 people, 14 people entered the exclusion criteria, and 58 subjects were divided into 2 groups in a double-blind randomized trial. Supplementation and placebo were observed for 12 weeks, 3 subjects from the treatment group dropped out, 1 subject from the control group dropped out. Data analysis was performed on 54 subjects.

Table 1. Characteristics of the elderly at the Dharma Bakti Kasih Nursing Home, Surakarta, Central Java, based on gender in the treatment group and the control group

Characteristics	Respondent group		p-value
	Treatment	Control	
Gender			
Woman	17	20	0.379
Man	10	7	

Chi-square test; *) p-value is significant if ≤ 0.05

Table 2. Distribution of characteristics of the elderly at the Dharma Bakti Kasih Nursing Home in Surakarta, Central Java, before being given treatment

Characteristics	Treatment (n = 27)			Control (n = 27)			p-value
	n	%	Mean ± SD	n	%	Mean ± SD	
Age (Years)	27	100	71.7 ± 8.6	27	100	72.4 ± 8.1	0.91[a]
BMI (Kg/m2)							
Underweight (<18.5)	3	11.1	23.2 ± 3.6	3	11.1	23.1 ± 4.6	0.21[a]
Normal (18.5-22.9)	8	29.6		13	48.1		
Overweight (23-24,9)	9	33.3		2	7.4		
Obesity I (25 – 29.99)	5	18.5		7	25.9		
Obesity II (≥30)	2	7.4		2	7.4		
Physical Activity (MET)							

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Characteristics	Treatment (n = 27)			Control (n = 27)			p-value
	n	%	Mean ± SD	n	%	Mean ± SD	
Light intensity activities (<600)	6	22.2	1193.3 ± 1026.9*	12	44.4	978.9 ± 1003.2*	0.19[a]
Moderate intensity activities (600-2999)	19	70.3		14	51.8		
Vigorous intensity activities (>3000)	2	7.4		1	3.7		
Adequacy of daily vitamin D intake (µg/day)							
Less < 15	27	100	6.8 ± 4.412	27	100	7.2 ± 4.2*	0.85[b]
Enough ≥ 15	0	0		0	0		
Serum 25(OH)D level (ng/mL)							
Deficiency (0-20)	19	70.3	18.2 ± 8.5*	24	88.9	14.1 ± 6.3*	0.07[a]
Insufficiency (21-29)	5	18.6		1	3.7		
Normal (30-100)	3	11.1		2	7.4		
Toxic (>100)	0	0		0	0		
Handgrip strength (kgF)							
Less <20 kgf (female) or <40 kgf (male)							
Normal >20 kgf (female) or >40 kgf (male)							
Right							
< 20 or < 40	27	100	15.9 ± 8.9	27	100	14.1 ± 6.1	0.38[a]
> 20 or > 40	0	0		0	0		
Left							
< 20 or < 40	27	100	15.0 ± 7.8	27	100	12.5 ± 5.7	0.19[a]
> 20 or > 40	0	0		0	0		

[a]) Independent t-test; [b]) Mann-whitney test; *) data distribution is not normal; **) p-value is significant if ≤ 0.05; BMI (Body Mass Index); MET (Metabolic Equivalent of Task)

The results of BMI measurements based on Table 2 are known to have an average treatment group of 23.2 ± 3.6 kg/m2 with the highest percentage of 81.8% (n=9) having an overweight BMI. The control group had an average of 23.1 ± 4.6 kg/m^2, with the highest 41.4% (n=12) having normal BMI. The percentage of BMI in this study is similar to the 2018 Riskesdas data on the characteristics of the 60-64-year-old age group, where the majority have normal BMI[22].

The characteristics of physical activity in the treatment group had an average of 1193.3 ± 1026.9 MET, with the highest percentage being 70% (n=19) of subjects having moderate physical activity. The physical activity of the control group had an average of 978.9 ± 1003.2 MET, with the highest percentage of 51.8% (n=14) subjects having moderate physical activity. The elderly subject in this nursing home has an exercise schedule 3 times 1 hour a week, every 8 am sunbathing in an open area and additional activities such as sewing, cooking, gardening, and embroidery, helping caregivers take care of sick residents of the orphanage. The data of this study are under the results of the 2018 Riskesdas, the prevalence of which is 68.2% in the elderly group doing moderate physical activity[23].

Data on the adequacy of vitamin D intake was obtained from the SQ-FFQ, where each subject received the same menu from the caregiver in the form of 3 main meals and 2 snacks, fruit, and snacks. Caregiver ensures and records the amount of portion spent by each subject. Based on data on the adequacy of daily vitamin D intake, the treatment and control groups were still below 15 µg/day. This finding is in line with the study by Amrein et al. that the Asian population's daily consumption of vitamin D intake is lower than the recommended nutritional adequacy rate[22].

A 2018 literature study with 1139 subjects in Singapore, Malaysia, and India, found a prevalence of vitamin D deficiency of 47.8%[24]. Similar to this study, the mean serum 25(OH)D level in the treatment group was 18.2 ± 8.5 ng/mL with 70% (n=19), while the mean in the control group was 14.1 ± 6.3 ng /mL with 88.9% (n=24) so that the majority of research subjects experienced deficiency in the serum level category of 0 - 20 ng/mL. Supports the Scientific Advisory Committee on Nutrition 2016 statement that vitamin D deficiency is influenced by many factors, including the ability to synthesize vitamin D, which will decrease with age and lack of intake of foods high in vitamin D[25].

Handgrip strength is used to measure muscle strength and is positively related to the lower extremity and upper body muscle strength, with the dominant hand having a greater value[19]. The mean grip strength of the right hand in the treatment group was 15.9 ± 8.9 kgF, and in the control group, 14.0 ± 6.1 kgF. The mean on the left hand of the treatment group was 15.0 ± 7.8 kgF, and the control group was 12.5 ± 5.7 kgF. The results of the handgrip strength of all subjects in the two groups were below normal values, with the dominant hand, namely the right hand, having higher results.

The effect of giving cholecalciferol 1000 IU in the treatment group compared to the control group can be seen in Table 3. The results of the analysis showed that there was a significant increase in serum 25(OH)D levels in the treatment group (p<0.05) with a mean change of 8.2 ± 7.6, whereas in the control group, there was a decrease in 25(OH)D levels with an average change of -0.5 ± 5.4 but not statistically significant. The results of the two groups' unpaired tests were significant (p<0.05), indicating a significant difference between the treatment and control groups. Serum levels in the intervention group increased by 77%, which aligns with recent recommendations that vitamin D3 supplementation of 600 IU – 800 IU can increase serum 25(OH)D levels up to 20 ng/mL[10]. The results of this study indicate that vitamin

D supplementation can increase serum 25(OH)D levels in the elderly. Whereas in the control group that was only given a placebo, the results followed the literature that vitamin D deficiency occurs in the elderly due to physiological and pathological factors. Decreased production of vitamin D in the skin, decreased digestion and metabolism function of vitamin D[10,26,27].

Table 3. Comparison of the effects of supplementation in the form of 25(OH)D serum levels and handgrip strength in the treatment group compared to the control group

Variable	Treatment Group				Control Group				p^b
	Before	After	Average change (95% CI)	p^a	Before	After	Average change (95% CI)	p^a	
Serum levels 25(OH)D (ng/mL)	18.2 ± 8.5	26.5 ± 7.1	8.2 ± 7.6	<0.001*	14.1 ± 6.3	13.5 ± 5.6	-0.5 ± 5.4	0.65	<0.001*
Handgrip strength (kgF)									
Right	15.9 ± 8.9	16.9 ± 9.2	1.0 ± 5.1	0.29	14.0 ± 6.1	14.0 ± 7.1	-0.05 ± 4.8	0.95	0.748
Left	15.0 ± 8.1	16.0 ± 8.0	0.9 ± 3.4	0.15	12.5 ± 5.7	12.8 ± 7.5	0.3 ± 4.4	0.71	0.323

[a]) Paired t-test; [b]) Independent t-test; *) p-value is significant if ≤0.05; kgF (kilogram Force); p (p-value)

The results of the analysis on the value of handgrip strength before and after the intervention showed that the treatment group experienced an average increase in handgrip strength of 1.0 ± 5.1 kgF in the right hand, but not statistically significant (p=0.29), whereas in the control group, there was a decrease in handgrip strength with an average of -0.05 ± 4.8 (p=0.95). The results of the different unpaired tests on both the right and left-handgrip strength were insignificant (suitable=075, left=0.32). There was no significant variation in handgrip strength after supplementation with vitamin D. Vitamin D can affect skeletal muscle through genomic pathways, increasing protein expression in electron transport and the tricarboxylic acid cycle in metabolism in the mitochondria of skeletal muscle cells. Genes related to electron transport activity and the conversion of acetyl-CoA to CO_2 are regulated by vitamin D[28]. This process will initiate muscle strength, and this theory is supported by research by Cavalcante et al., 2015 explaining that vitamin D3 supplementation of 942 IU/day can significantly increase handgrip strength[7,12,18,19]. Whereas the study of Pirrota et al. 2015 showed that giving vitamin D3 2000 IU for ten weeks increased muscle strength by 8-11% but not significantly, and the results were in line with this study[29].

The factors that are thought to cause handgrip strength in this study are not significant compared to the Cavalcante et al., 2015 study, including the subject's age average of 62.16 years, younger age than in this study, and the average serum level of 25(OH)D is 22.4 ± 3.9 ng/mL higher than the mean serum level in this study. Another aspect suspected of causing a difference in results with previous studies is that 50% of the subjects are overweight, associated with decreased bioavailability of low vitamin D and expression of vitamin D receptors (VDR), resulting in excessive absorption in adipose tissue[13,30]. Differences in subject demographics and the chemical form of vitamin D are also factors in the results. Vitamin D deficiency is only one of the conditions that can alter muscle function in the elderly. Previous studies have shown that even in healthy elderly, vitamin D treatment cannot prevent decreased muscle strength with age. In addition, comorbidities combined with physical activity levels can cause muscle weakness and functional impairment and cannot be improved by treating vitamin D deficiency[19]. So, vitamin D is a small part of the factors that affect handgrip strength[7].

Table 4. Relationship between changes in serum 25(OH)D levels and changes in handgrip strength treatment

Variable	Serum levels of 25(OH)D	
	r	p-value
Handgrip strength		
Right	0.02	0.87^a
Left	0.07	0.60^b

r (correlation coefficient -1 ≤ r ≤ 1); p (significant p-value ≤0.05); [a]) Spearman's rho test; [b]) Pearson test

Table 4 shows that changes in serum 25(OH)D levels after supplementation had a fragile relationship to changes in handgrip strength in both the right hand (r=0.02 and p=0.87) while in the left hand (r=0.07 and p=0.60). This result is in line with research from Silva et al., which states that modulation of muscle strength is a complex process, vitamin D being one of several other factors involved, such as diet, hormonal response, and physical activity or exercise. Although many researchers have investigated the effect of vitamin D supplements on muscle function, the results are controversial[8]. Most of the physiological mechanisms of muscle fiber in the elderly group have experienced a decrease in their ability to respond to both contractile and metabolic stimuli, which also affect the effect of vitamin D supplementation on muscle strength[11]. Another study by el Hajj et al., 2019 with cholecalciferol supplementation of 10,000 IU for six months in 128 elderly pre-sarcopenic subjects, showed

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significant results in increasing Appendicular Skeletal Muscle Mass (ASMM) but not in muscle strength[19].

The advantage of this study is that the method used (RCT) in research on the elderly population in Indonesia has never been used besides the minimum of participants dropping out. However, this study also has limitations in determining the efficacy of vitamin D supplementation. The intervention period was relatively short, the number of samples was small, and the time and dose of vitamin D supplementation. If the study time was longer, the number of samples suspected was more significant. The higher dose of cholecalciferol, namely 5,000-10,000 IU/week, is expected to show more significant results.

CONCLUSIONS

In summary, the supplementation of cholecalciferol 1000 IU did not affect changes in handgrip strength, while the serum 25(OH)D level showed a significantly increasing effect. Further research is needed to assess the effect of potential confounders such as BMI, waist circumference, fat mass, muscle mass, kidney function, and other comorbid diseases on handgrip strength.

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Conflict of Interest and Funding Disclosure

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