RESEARCH ARTICLES

EFFECT OF 12 WEEKS VITAMIN D SUPPLEMENTATION (*ALPHACALCIDOL*) ON BLOOD PRESSURE IN ELDERLY WOMEN PATIENTS

Achmad Zaki[1,*], Nida Nabila[1], M. Djauhari Widjajakusumah[1], Witri Ardini[1], Mery Nitalia[1]

[1]Departement of Internal Medicine, Faculty Of Medicine, Syarif Hidayatullah State Islamic University, Jakarta, Indonesia

*Corresponding Author: achmad.zaki@uinjkt.ac.id

ABSTRACT

Background: Cardiovascular disease have overtaken communicable disease for being the main killer worldwide. Hypertension or high blood pressure is one of the risk factors. Elderly women statistically have a high prevalence of hypertension. Vitamin D is known to affect blood pressure and many studies showed the association between vitamin D and blood pressure with varying result. This study aims to evaluate the effect of vitamin D supplementation (alphacalcidol) for 12 weeks and change in blood pressure of elderly women patients in community health service clinic (KPKM) Medical Faculty Syarif Hidayatullah State Islamic University of Jakarta (FK UIN Jakarta).

Methods : Analytical pre-post study design was conducted as a part of an RCT (Randomized Controlled Trial) studies with 90 subjects of elderly women (45 intervention group, 45 control group). The subjects were selected based on consecutive sampling and randomly allocated into two groups, intervention group with vitamin D supplementation (alphacalcidol 1 µg/day) and control group with placebo. Statistical analysis was performed with Mann Whitney test and Wilcoxon test started with normality test Kolmogorof Smirnov using IBM SPSS 23.0.

Results: Vitamin D deficiency in the intervention group significantly decreased post-supplementation from 22.2% to 8.9%. Subgroup analysis showed the decrease in blood pressure is greater in the subgroup middle-age elderly than young-age elderly category. Even though there was a significant change in the diastolic blood pressure in the subgroup of middle-age elderly post supplementation (p=0.03), Mann-Whitney statistical analysis showed that 12 weeks vitamin D supplementation (alphacalcidol) did not significantly effect the pre and post systolic nor diastolic blood pressure (p>0.05).

Conclusion: The study did not found significant effect of 12 weeks Vitamin D (alphacalcidol) supplementation on blood pressure in elderly women patients.

Keywords: Blood Pressure, Hypertension, Vitamin D, Alphacalcidol, Elderly Women.

INTRODUCTION

Hypertension as a major risk factor for cardiovascular disease is a condition of persistent pressure elevation on the blood vessels and often referred to as the silent killer for causing 7.5 million or about 12.8% deaths worldwide.[1-2] In 2015 alone prevalence of hypertension reached 1.13 billion worldwide and in Indonesia itself hypertension among people aged ≥18 years in 2018 was 34.1% which increased by 8.3% from 2013.[3]

The incidence of hypertension increase with age and it is known that at the age of >65 years the prevalence of hypertension in women is much higher than men.[4] Besides age and gender, Vitamin D deficiency is one the risk factor of hypertension which often occurs in elderly.[5] Previous study has shown a role for Vitamin D in influencing blood pressure (BP) through inhibition of renin gene transcription and prostaglandin production resulting the absence of renin.[6] Vitamin D can regulate BP through intra-cellular calcium homeostatis and acts as vascular protective agent by reducing the bad effect of AGEs (*Advanced Glycation End products*) on the endothelium, also increasing the activity of nitric oxide which can regulate blood vessel tone.[7-8]

This study aims to find the effect of Vitamin D supplementation (alphacalcidol) for 12 weeks and change in pre and post BP of high risk population to develop hypertension in the elderly women patients. Even though there have been several studies that carry out the effect of Vitamin D on blood pressure, but as far as the authors are aware of, there is no published study in Indonesia on the effect of Vitamin D supplementation on blood pressure especially in eldery woman in the community setting with pre-post study design.

In this study, alphacalcidol was used for the vitamin D supplementation. It is because alphacalcidol is considered to be more beneficial for the elderly who were the subjects of this study. Alphacalcidol has a longer half-life and a lower burden on the kidneys, so alphacalcidol is safer for elderly who have reduced kidney function.

METHODS

This study was conducted with an analytical pre-post study design as a part of a main double-blind RCTs about Vitamin D supplementation.

The subjects were women aged ≥60 years who went to the community clinic. They had examination of pre and post supplementation BP, and had examination of Vitamin D serum level. Those with Vitamin D level <125 nmol/L before supplementation were eligible for the study. The exclusion criteria are subjects with incomplete data sets and drugs consumption that may interact with Vitamin D supplements. The subjects were selected based on consecutive sampling and randomly allocated permutation-block randomization, using computer program random number generator (http://stattrek.com/statistics/random-numbergenera-toraspx) for the random sequencing and divided into two groups, intervention group with Vitamin D supplementation and control group with placebo.

The subjects were randomly assigned to take Vitamin D supplements or placebo 1 mcg/day with the same capsule appearance without smell and flavor for 12 weeks every morning after meals. Each subject was equipped with a supplement taking control card and were explained directly regarding the benefits and possible side effects for monitoring the subject's compliance to taking the capsule. Statistical analysis was performed with Mann Whitney test and Wilcoxon test started with normality test Kolmogorof Smirnov using IBM SPSS 23.0.

The ethical approval was given by the Ethics Committee of the Faculty of Medicine, Syarif Hidayatullah State Islamic University Jakarta with protocol number 3674022P211132020022700007.

RESULTS AND DISCUSSION

Characteristics of Subjects

Table1 shows the characteristic distribution of 90 subjects. All the subjects fulfilled the inclusion criteria and eligible for the study. After 12 weeks of Vitamin D supplementation and placebo, there was no side effects nor complaints from the subjects. The intervention and the control group have the same characteristics such as age, 25(OH)D serum level, systolic blood pressure (SBP) and diastolic blood pressure (DBP) at the beginning of the study (p>0.05).

Table 1. Distribution of Subjects Characteristics

Characteristics of Subjects	Category	Intervention Group		Control Group		P value
		Frequency (n)	Percentage (%)	Frequency (n)	Percentage (%)	
Age	Young Elderly (60-69 years old)	36	80	39	86.7	0.96
	Middle-aged Elderly (70-79 years old))	9	20	6	13.3	
	Total	45	100	45	100	
25(OH)D Serum Level	Sufficient (>50-125 nmol/L)	11	24.4	9	20	0.75
	Insufficient (25-50 nmol/L)	24	53.3	29	64.4	
	Defficient (<25 nmol/L)	10	22.2	7	15.6	
	Total	45	100	45	100	
Blood Pressure (*baseline*)	Normal (SBP <120 and DBP <80)	17	37.8	15	33.3	S: 0.41 D: 0.95
	Pre-hypertension (SBP 120-139 or DBP 80-89)	6	13.3	7	15.6	
	Hypertension grade 1 (SBP 140-159 or DBP 90-99)	14	31.1	13	28.9	
	Hypertension grade 2 (SBP >160 or DBP >100)	8	17.8	10	22.2	
	Total	45	100	45	100	

*a : Mann Whitney test
S : P value of Systolic Blood Pressure
D : P value of Diastolic Blood Pressure

Post-Supplementation 25(OH)D Serum Level

The 25(OH)D serum levels pre and post Vitamin D supplementation can be observe in the table 2. Interestingly in the control group, the number of subjects with sufficient Vitamin D increased from 10% to 14.4%. Vitamin D insufficiency also decreased from 32.2% to 24.6%, also subjects with Vitamin D deficiency decreased from 13.1% to 10%. The mean serum levels of 25(OH)D in the control group increased from 39.02 (± 14.23) to 39.64 (± 14.73).

In the intervention group, the percentage of subjects with Vitamin D deficiency significantly decreased from 22.2% to 8.9%. The percentage of sufficient levels increased to 28.9% from 24.4%, and the mean levels of serum 25(OH)D in the intervention group increased from 39.03 (± 15.01) nmol/L to 41.62 (± 15.11) nmol/L.

The mean levels of 25(OH)D serum in the intervention group pre and post Vitamin D supplementation is still insufficient. This condition may be influenced by the different of nutritional intake of each subject which we didn't identify further and/or the doses and duration of supplementation were not adequate to increase the level of 25(OH)D serum to the sufficient level.

The aging metabolism process will reduce the absorption of Vitamin D in the intestine, therefore the increase in serum Vitamin D levels is not sufficient and may affect the results the effect of Vitamin D supplementation on the blood pressure of the subjects.[9-10]

Table 2. Serum Vitamin D (25(OH)D) Levels Before and After Vitamin D Supplementation in Elderly Women

		Before Vitamin D Supplementation		After Vitamin D Supplementation	
		Frequency (n)	Percentage (%)	Frequency (n)	Percentage (%)
Serum 25(OH)D Levels (Intervention Group)	Sufficient (>50-125 nmol/L)	11	24.4	13	28.9
	Insufficient (25-50 nmol/L)	24	53.3	28	62.2
	Defficient (<25 nmol/L)	10	22.2	4	8.9
	Total	45	100	45	100
Mean (±SD)		39.03 (±15.01)		41.62 (±15.11)	
Serum 25(OH)D Levels (Control Group)	Sufficient (>50-125 nmol/L)	9	10	13	14.4
	Insufficient (25-50 nmol/L)	29	32.2	23	24.6
	Defficient (<25 nmol/L)	7	13.1	9	10
	Total	45	7.8	45	100
Mean (±SD)		39.02 (±14.95)		39.64 (±15.53)	

Vitamin D Supplementation and Blood Pressure

Statistically, there was no significant association found between Vitamin D supplementation for 12 weeks and the pre and post SBP (p=0.17) nor DBP (p=0.6) in the elderly women patients. The results obtained in this study are not in line with Lind L et al. (1988) that stated the administration of 1 mcg alphacalcidol for 6 months significantly reduced BP (p <0.05) .[11] This difference may be due to the duration of supplementation given. Vitamin D can affect the BP through the renin-angiotensin-aldosterone system (RAAS). Vitamin D which binds to the Vitamin D receptor (VDR) will inhibit the transcription of the renin gene causing renin level to decrease and nothing converts angiotensinogen to angiotensin I. Angiotensin II is also not formed causing inhibition of aldosterone secretion and BP will decreased.

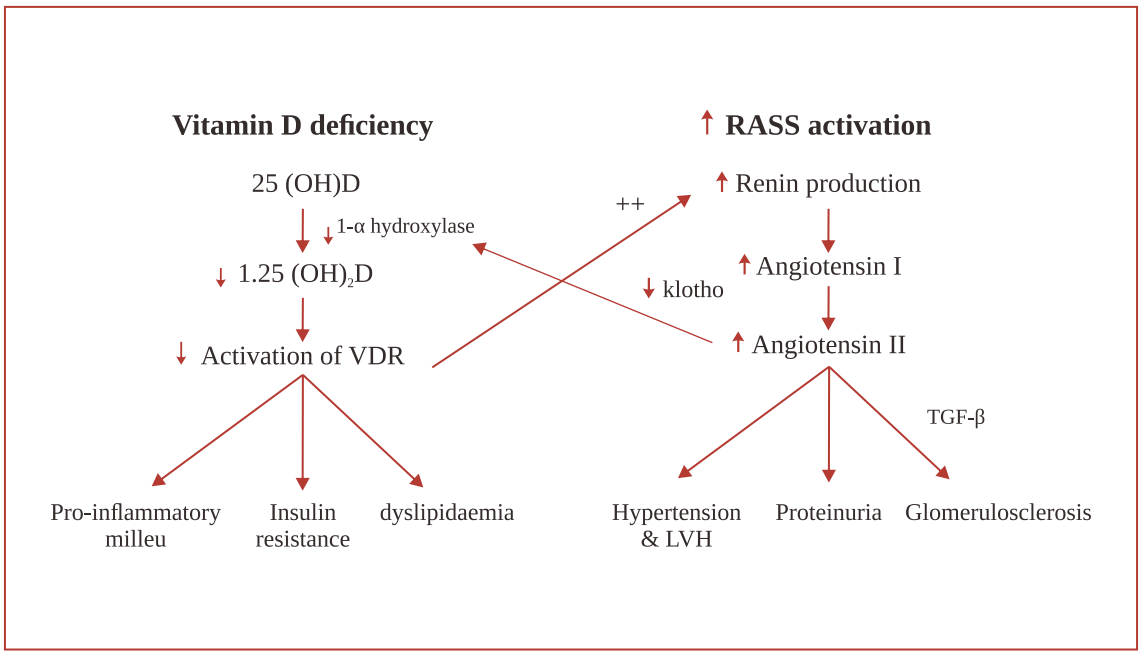

Figure 1. Vitamin D axis and the renin-angiotensin system (modified from Shroff, R et al. Can Vitamin D slow down the progression of chronic kidney disease? Pediatr Nephrol (2012) 27:2167-2173.)[12]

Vitamin D can also inhibit cyclooxygenase-2 (COX-2) and arachidonic acid so it does not turn into prostaglandins in the macula dens of the kidneys. Due to the absence of prostaglandins, activation of protein kinase-A (PKA) by cyclic adenosine monophosphate (cAMP) also does not occur resulting in no renin production.[6] Besides affecting renin gene expression, Vitamin D can regulate BP through intracellular calcium homeostasis. It affects blood vessel tone by regulating calcium concentration in vascular smooth muscle cells which leads to vasodilatation and acts as a protective agent for blood vessels by reducing the adverse effects of AGEs (Advanced Glycation End products) on the endothelium and increasing nitric oxide activity which can regulate blood vessel tone.[7-8]

Table 3. Association between Vitamin D Supplementation and BP

Blood Pressure		Intervention Group (n=45)		Control Group (n=45)	
		Frequency (n)	Mean (±SD)	Frequency (n)	Mean (±SD)
SBP	Before Supplementation	45	131.11 (±23.44)	45	135.33 (±22.94)
	After Supplementation	45	130 (±18.94)	45	132.44 (±17.85)
	Mean Difference		-1.11 (±21.26)		-2.88 (±20.98)
	P Value		0.84*b 0.7*a		0.59*b
DBP	Before Supplementation	45	81.33 (±10.35)	45	82.22(±11.70)
	After Supplementation	45	80.22 (±9.41)	45	80.44 (±9.52)
	Mean Difference		-1.11 (±13.35)		-1.77 (±9.66)
	P Value		0.62*b 0.82*a		0.21*b

*a : Mann Whitney test
*b : Wilcoxon test

There was a decrease in SBP and DBP both in the intervention and control group (see table 3). The results can be influenced by many factors, such as differences in the amount of Vitamin D consumed from daily food in both group that would become confounding factors, differences in exposure to sunlight, physical activity, sodium intake, and other cardiometabolic disease.

Wei Zheng et al. (2017) reported that Vitamin D3 supplementation can reduce both SBP and DBP only in subjects with primary hypertension and does not have an effect on patients without hypertension.[13] He, S (2019) also reported that the effect of hypotension is only in patients with hypertension.[14] This result can also influenced by 25(OH)D serum levels after supplementation (table 2) that still insufficient, so that the results of changes in BP are not significant.

Furthermore, we analyze the effect of Vitamin D supplementation and changes in BP according to the subgroup analysis of elderly people, the young-age elderly (60-69 years old) and middle-age elderly (70-79 years old) subgroup.

Table 4. Vitamin D Supplementation and BP in Subgroup Young-age Elderly and Middle-Age Elderly

Age	BP		Intervention Group		Control Group	
			Frequency (n)	Mean (±SD)	Frequency (n)	Mean (±SD)
Young-age Elderly (60-69 years old)	SBP	Before Supplementation	36	130.28 (±22.65)	39	132.05 (±21.32)
		After Supplementation	36	132.85 (±20.08)	39	130 (±14.86)
		Mean Difference		2.57 (±17.07)		-2.05 (±20.18)
		P Value		0.41*b 0.26*a		0.88*b
	DBP	Before Supplementation	36	81.14 (±10.78)	39	81.28 (±11.10)
		After Supplementation	36	81.14 (±9.93)	39	79.48 (± 9.44)
		Mean Difference		0.0 (±13.71)		-1.79 (±10.03)
		P Value		1.00*b 0.44*a		0.25*b
Middle-Age Elderly (70-79 years old)	SBP	Before Supplementation	9	136.66 (±27.38)	6	156.66 (±23.38)
		After Supplementation	9	117.77 (±6.66)	6	148.33 (±27.86)
		Mean Difference		-18.88 (±26.66)		-8.33 (±27.14)
		P Value		0.07*b 0.47*a		0.45*b
	DBP	Before Supplementation	9	83.33 (±8.66)	6	88.33 (±14.71)
		After Supplementation	9	75.55 (±5.27)	6	86.66 (±8.14)
		Mean Difference		-7.77 (±8.33)		-1.66 (±7.52)
		P Value		0.03*b 0.84*a		0.56*b

*a : Mann Whitney test,
*b :Wilcoxon test.

In the subgroup analysis of middle-age elderly (table 4), there was a decrease in the mean SBP of intervention group from 136.66±27.38 mmHg which was classified as pre-hypertension, to 117.77±6.66 mmHg which classified in the normal. Although the change was not statistically significant (p=0.07), but clinically there was a change in blood pressure from pre-hypertension into normal category based on the JNC 7 hypertension classification. There was a statistically significant change in the DBP pre and post supplementation in the intervention group (p=0.03). Blood pressure was seen to have decreased from 83.33±8.66 mmHg to 75.55±5.27 mmHg post-supplementation, which indicates a decrease in BP classification from pre-hypertension to normal.

In the Table 4, can also be seen that the mean difference of pre and post Vitamin D supplementation in the intervention group. The SBP of the subgroup middle-age elderly decreased by 18.88±26.66 mmHg, while in the young-age elderly increased by 2.57±17.07 mmHg. The same thing also happened to the DBP, the middle-age elderly decreased by 7.77 ± 8.33 mmHg, while the young-age elderly was 0.0 ± 13.71 mmHg. These data indicate that the decrease in BP is greater in the subgroup analysis of middle-age elderly than young-age elderly category.

These results indicate the effect of Vitamin D supplementation is more significant with older age, this may happen because the mean BP of the subgroup middle-age elderly before the supplementation, both SBP and DBP is higher than the young elderly. Higher BP in the middle-age elderly occurs due to aging process, the walls of the blood vessels will thicken and the elasticity of the blood vessels will decrease, resulting in arteriosclerosis which can affect peripheral resistance and BP will increase.[15]

In addition, aging also causes the level of Vitamin D in the body to decrease because the ability of the intestines to absorb Vitamin D decreases, sun exposure also decreases due to infrequent activities outside the home, and last but not least, the production of 7-dehydrocholesterol in the skin decreased twice compared to young people which causes the decrease of Vitamin D synthesis through a photochemical process.[16] With an aging factor that resulting the condition of Vitamin D deficiency in older subjects, it also can increase their BP. Higher blood pressure in the subgroup middle-age elderly will increase the effect of Vitamin D supplementation on lowering BP, according to a study that reported that the effect of Vitamin D on BP only occurs in patients with hypertension.[13,14]

Vitamin D reduce the synthesis of angiotensin II, which is a strong vasoconstrictor resulting decreases in BP. This is in accordance with the results of the study by Zhang D et al. (2020) that the beneficial effects of Vitamin D on BP may occur in older people.[17] This is consistent with our results that indicate the effect of Vitamin D supplementation is more significant with older age.

There are several factors that can affect blood pressure, for example salt intake, history of metabolic diseases such as diabetes mellitus, lifestyle such as smoking and physical activity that possibly exist in the subjects that are not identified further and those became the limitations of this study. Therefore in future studies all the factors that can affect blood pressure should be identify to minimize the bias.

CONCLUSION

This study findings that there was no significant statistical effect between Vitamin D supplementation (alphacalcidol) for 12 weeks and BP in elderly women. We found that Vitamin D supplementation (alphacalcidol) for 12 weeks can affect the reduction of DBP in the intervention group of subgroup analysis of middle-age elderly women. To determine the effectiveness of Vitamin D supplementation on BP, the future study can be carried out by giving different doses and duration. Also using subjects with deficiency serum of 25(OH)D, and includes all participants with pre-hypertension and hypertension grade 3, combine with anti-hypertension drugs compare with drugs only to see the effect of Vitamin D on BP.

CONFLICTS OF INTEREST
We declare that there is no conflicts of interest in this study

FUNDING SOURCES
The source of funding in this study is self-funded.

REFERENCES

1. World Health Organization (WHO). Hypertension [Internet]. [cited 2020 Sep 23]. Available from: https://www.who.int/health-topics/hypertension/
2. Jeong HY, Park KM, Lee MJ, Yang DH, Kim SH, Lee SY. Vitamin D and hypertension. Electrolyte Blood Press. 2017;15(1):1–11.
3. Kementrian Kesehatan RI. HASIL UTAMA RISKESDAS 2018 [Internet]. kemenkes.go.id. 2018. Accesed from: https://www.kemkes.go.id/resources/download/info-terkini/hasil-riskesdas-2018.pdf
4. Go AS, Mozaffarian D, Roger VL, Benjamin EJ, Berry JD, Borden WB, et al. Heart disease and stroke statistics-2013 update: A Report from the American Heart Association. Circulation. 2013;127.
5. Martins D, Wolf M, Pan D, Zadshir A, Tareen N, Thadhani R, et al. Prevalence of cardiovascular risk factors and the serum levels of 25-hydroxyvitamin D in the United States: Data from the Third National Health and Nutrition Examination Survey. Arch Intern Med. 2007;167(11):1159–65.
6. Hermawan D, Kadarsih S, Sunarti, Astuti I, Agus ZAN. Efek asupan vitamin D terhadap tekanan darah sistolik tikus putih (Rattus norvegicus). J Gizi Klin Indones. 2012;9(1):10.
7. Gröber U, Kisters K. Influence of drugs on vitamin D and calcium metabolism. Dermatoendocrinol. 2012;4(2):158–66.
8. Vaidya A, Forman JP. Vitamin D and hypertension: Current evidence and future directions. Hypertension. 2010;56(5):774–9.
9. Boucher BJ. The problems of vitamin d insufficiency in older people. *Aging Dis*. 2012;3(4):313-329.
10. Maurya VK, Aggarwal M. Factors influencing the

absorption of vitamin D in GIT: an overview. J Food Sci Technol. 2017;54(12):3753–65.

11. Lind L, Wengle B, Wide L, Sorensen OH, Ljunghall S. Hypertension in primary hyperparathyroid-ismreduction of blood pressure by long-term treatment with vitamin d (Alphacalcidol) a double-blind, placebo-controlled study. Am J Hypertens. 1988;1(4):397–402.
12. Shroff, R et al. Can Vitamin D slow down the progression of chronic kidney disease ? Pediatr Nephrol (2012) 27:2167-2173
13. Wei Zhen, Li Nanfang, Zhou Ling, et al. Effect of vitamin D3 supplement on blood pressure: a meta-analysis. Chin J Hypertension. 2017;25:636–642.
14. He S, Hao X. The effect of vitamin D3 on blood pressure in people with vitamin D deficiency: A system review and meta-analysis. Medicine (Baltimore). 2019;98(19):e15284.
15. Singh JN, Nguyen T, Dhamoon AS. Physiology, Blood Pressure Age Related Changes. StatPearls Publishing. 2019.
16. MacLaughlin J, Holick MF. Aging decreases the capacity of human skin to produce vitamin D3. J Clin Invest. 1985;76(4):1536–8.
17. Zhang D, Cheng C, Wang Y, Sun H, Yu S, Xue Y, dkk. Effect of Vitamin D on Blood Pressure and Hypertension in the General Population: An Update Meta-Analysis of Cohort Studies and Randomized Controlled Trials. Prev Chronic Dis. 2020 Jan 9;17:E03–E03

Print ISSN: 2716-3628, Online ISSN: 2720-9563