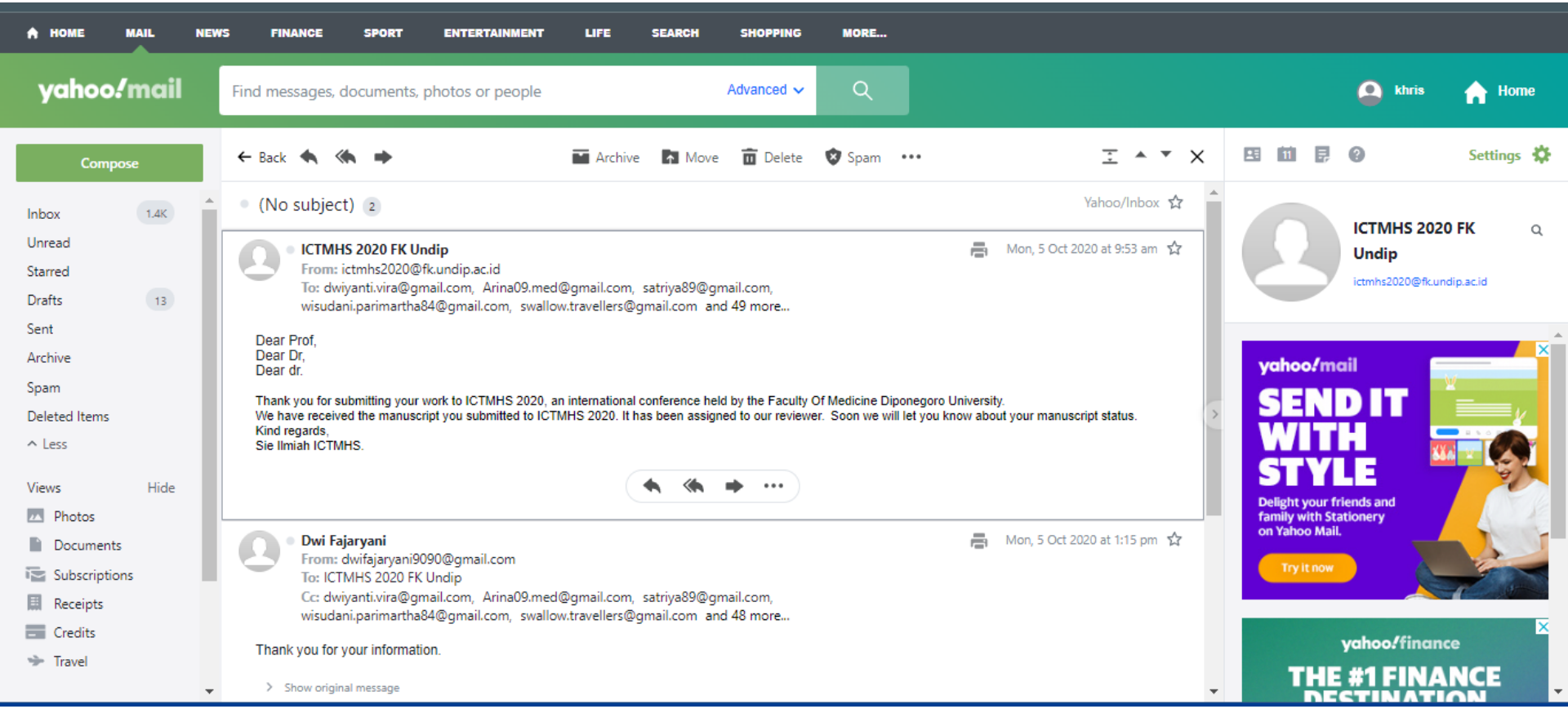
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Letter of Acceptance
6 February 2021

Dear: Heri Nugroho*, Tjokorda GDP, Tony Suhartono, Darmono
Endocrine-Metabolism Division, Department of Internal Medicine, Faculty of Medicine, Universitas Diponegoro, Dr. Kariadi Hospital, Semarang, Indonesia
*Corresponding author: khris_heri@yahoo.com

I am very excited to accept your paper entitled:
"Vitamin-D supplementation in subjects with hypovitaminosis-D: a randomized double blind, placebo-controlled trial."
Your paper will be published in the issue of Vol. 10 Number 1, 2021.
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Vitamin D supplementation in subjects with hypovitaminosis D: a randomized double-blind, placebo-controlled trial

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ABSTRACT

Introduction: Despite having abundant sunshine all year long, hypovitaminosis D in Indonesia is still surprisingly prevalent. However, hypovitaminosis D in Indonesia has still been severely underdiagnosed and there were even fewer studies on its treatment. Thus, we aim to assess the effectiveness of daily vitamin D supplementation for subjects with hypovitaminosis D.
Method: A randomized double-blind, placebo-controlled trial conducted was conducted with a total of 76 healthy, non-obese, working-age participants with hypovitaminosis D. The intervention was daily 1,000 IU of vitamin D3 supplementation for 12 weeks, while the placebo group received a placebo pill. The serum 25(OH)D level was measured pre-intervention, after 4 weeks, and after 12 weeks of intervention. The data were analyzed using an unpaired t-test in SPSS version 24.0. Out of the 81 participants, a total of 76 participants (93.8%) have hypovitaminosis D.
Result: The serum 25(OH)D level in the treatment group was significantly higher than in the placebo group after 12 weeks of supplementation. The delta of serum 25(OH)D level after 12 weeks of supplementation was also significantly higher in the treatment group. Furthermore, the serum 25(OH)D level in the placebo group was found to be significantly reduced at the 12th week compared to the baseline. Participants who received daily supplementation of 1000 IU vitamin D3 for 12 consecutive weeks have significantly higher serum 25(OH)D levels than the participants in the placebo group. Same result was also observed when the changes of serum 25(OH)D after 12 weeks were analyzed.
Conclusion: Hypovitaminosis D was surprisingly very prevalent among the working-age group in Indonesia. Participants who received daily supplementation of 1000 IU vitamin D3 for 12 consecutive weeks have significantly higher serum 25(OH)D levels than the participants in the placebo group.

Keywords: vitamin D, vitamin D3, cholecalciferol, 25(OH)D level, hypovitaminosis D, dietary supplements.
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INTRODUCTION

Vitamin D is a steroid with hormone-like activity and properties. It regulates the function of over 200 genes and plays an important role in growth and development.[1] Vitamin D is essential for maintaining bone mineralization. An observational study revealed the association between poor 25-hydroxyvitamin-D level and the prevalence of fracture. Besides skeletal problems, vitamin D insufficiency is also associated with non-skeletal effects, such as cardiovascular disease, diabetes mellitus, cancer and immunological dysfunction.[2-5] Recent studies also support the association of vitamin D deficiency with several types of cancers (breast, prostate and colon cancers), autoimmune diseases, hypertension, obesity, diabetes, depression, fibromyalgia, chronic fatigue syndrome, infectious diseases, cardiovascular diseases, birth defects, periodontal disease, stroke, and neurodegenerative diseases (e.g. Alzheimer).[1,6]

The blood concentration of vitamin D heavily relies on the endogenous production of vitamin D3 in skin and vitamin D intake from foods or supplements. About 50-90% of the total vitamin D in the body is produced in the skin, which is stimulated by the ultraviolet light, and the rest is from food. Some known factors influence the serum concentration of vitamin D.1,7 The major causes of vitamin D deficiency are lifestyle and environmental factors. Sunlight is indispensable for the production of vitamin D in the skin. Very few foods that naturally contain vitamin D and fortified foods with vitamin D rarely meet both children's and adults' needs. Sunscreen usage, glass protectors in houses or cars, and clothing effectively inhibit ultraviolet B (UVB) radiation. Individuals working indoors wear fully covered clothings and routinely apply sunscreen, significantly reducing the UVB absorption to skin. The majority of dark-skinned, obese, and old individuals deliberately avoid sunlight, thus they are at risk of vitamin D3 deficiency.[8]

Vitamin D deficiency is a global health problem. It is estimated that nearly 50% of the world's population of all ethnicities and age groups are vitamin

Table 1. Baseline characteristics of vitamin –D and placebo group (n=62)

Variables	Group				p-value
	Vit. D (n=32)		Placebo (n=30)		
	N	%	n	%	
Age					
≤ 30 years	16	50	12	40	0.337*
31 – 40 years	11	34.4	9	30	
41 – 50 years	4	12.5	4	13.3	
> 50 years	1	3.1	5	16.7	
Sex					
Male	9	30.6	10	33.3	0.866*
Female	23	69.4	20	66.7	
Education					
Junior High School	1	3.1	0	0	0.949*
Senior High School	12	37.5	11	36.7	
D3 (Academy)	13	40.6	13	43.3	
S1 (Bachelor)	6	18.8	6	20	
Consumption of frequency of vit.D food and drink/ week					
Insufficient (0-1 x)	12	37.5	12	40	0.969*
Sufficient (2-3 x)	14	43.8	13	43.3	
Good (> 3 x)	6	18.8	5	16.7	
The variety of vit. D food and drink/ week					
Insufficient (0-1 kind)	19	59.4	20	66.7	0.794*
Sufficient (2-3 kinds)	19	31.3	9	30.0	
Good (> 3 kinds)	4	9.4	1	3.3	
The use of protector					
Yes	29	90.6	24	80	0.409*
No	3	9.4	6	20	
Hijab Wearing					
Yes	18	56.3	10	33.3	0.120*
No	14	43.8	20	66.7	
Part of body exposure directly by sun					
Face	0	0	2	6.7	0.573*
Face, hand	23	71.9	17	56.7	
Face, hand, arm	6	18.8	8	26.7	
Face, hand, leg	1	3.1	1	3.3	
Face, hand, arm, leg	2	6.3	2	6.7	
Duration of sun direct exposure/ day					
Insufficient (< 10 minutes)	13	40.6	12	40	0.813*
Sufficient (10 – 30 minutes)	13	40.6	14	46.7	
Good (> 30 minutes)	6	18.8	4	13.3	
Frequency of direct sun exposure/ week					
Insufficient (0 – 1 x)	6	18.8	6	20	0.834*
Sufficient (2 – 3 x)	13	40.6	10	33.3	
Good (> 3 x)	13	40.6	14	46.7	
Means of initial 25(OH)D level of serum	14.42 ± 4.25		14.48 ± 4.28		0.955†

Legend: *Chi-square test, †unpaired t test

D deficient. Vitamin D deficiency or insufficiency is prevalent all across the globe, such as the United States (41.6%), Europe (40.4%), India (70%), Singapore (27%).[9–11] Although the associations of hypovitaminosis D and many diseases have been widely recognized, hypovitaminosis D in Indonesia is still underdiagnosed. Indonesia is a tropical country with abundant sunshine throughout the year, so there is a presumption that vitamin D deficiency will be scarce. Because of this assumption, the screening of the content of vitamin D serum in the subjects with high hypovitaminosis D risk in Indonesia is still sparse. In fact, based on a limited data, the prevalence of vitamin D deficiency in Indonesia was high: 50% in the female

Table 2. The comparison of 25(OH)D serum level between the vitamin D and placebo groups

Vit. D 25 (OH)	Group		*P*
	Vit. D	Placebo	
Initial	14.42 ± 4.25	14.48 ± 4.28	0.955*
4 weeks	15.11 ± 3.26	14.08 ± 3.13	0.210*
12 weeks	14.64 (9.13-22.30)	12.57 (9.60-19.48)	0.015†
Δ 4 weeks	0.69 ± 2.69	-0.40 ± 3.16	0.147*
Δ 12 weeks	0.69 ± 3.03	-1.30 ± 2.79	0.009*

Legend: *Unpaired t test, †Mann-Whitney Test

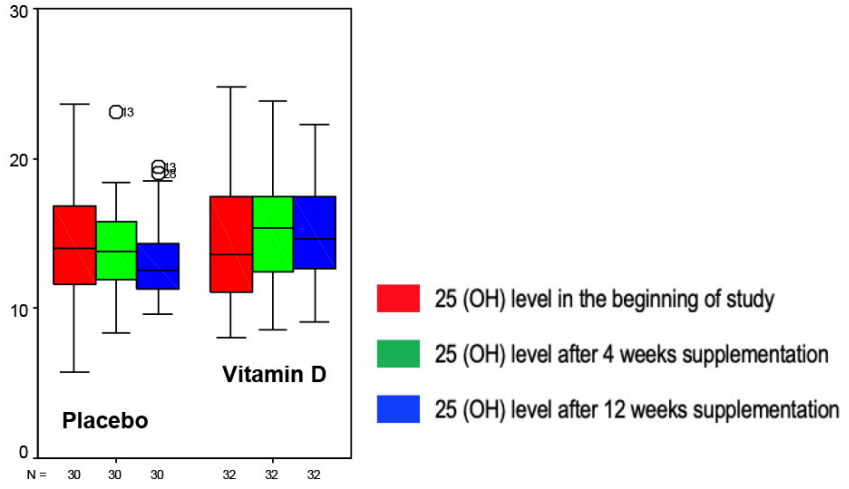

Figure 1. Comparison of 25(OH)D levels of serum, 4 and 12 weeks, in vitamin D and placebo groups.

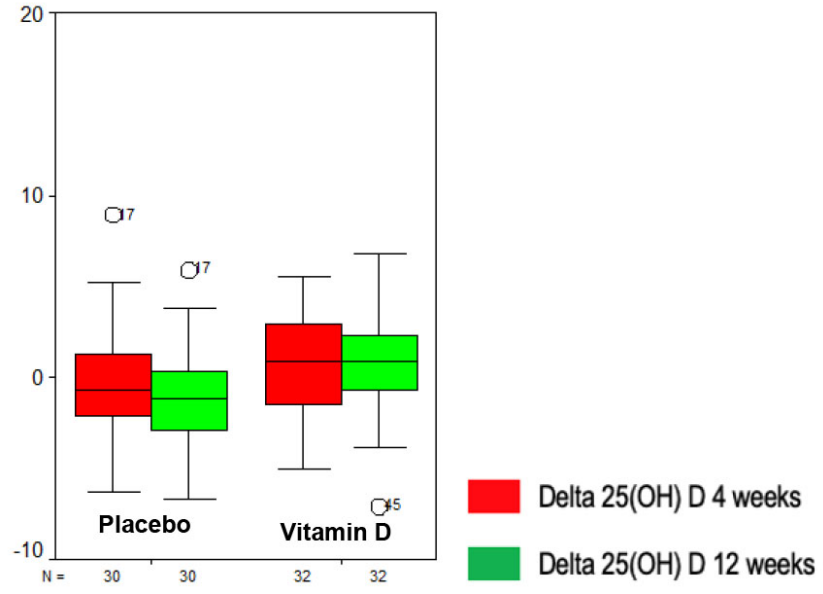

Figure 2. Comparison of 25(OH)D delta, 4 and 12 weeks, in vitamin D and placebo groups.

population aged 45-55 years, 35.1% in the subjects aged 60-75 years, and 63% in the women aged 18-40 years in Jakarta.[12–14]

Due to the lack of awareness of hypovitaminosis D in Indonesia, few studies have only been done on this topic. Vitamin D supplementation has never been considered as a routine essential supplementation. The subjects at risk for vitamin D deficiency, especially in the urban residents working as office workers in buildings from morning to evening, may only be minimally exposed to sunlight, so they need to rely on vitamin D-rich foods and supplements.[15] Vitamin D supplementation is hypothesized to improve blood levels, particularly for hypovitaminosis D cases. This study aimed to assess the effectiveness of vitamin D supplementation for subjects with hypovitaminosis D.

RESEARCH DESIGN AND METHODS

Study Design and Study Participants

This research design is a randomized double-blind, placebo-controlled trial with a pre and post-test design. A consecutive sampling selected the research subjects. The study population was workers in Kariadi General Hospital, i.e. nurses, administrative staff, and cleaning service personnel. Inclusion criteria were men or women aged 18-60 years with a body mass index of <25 kg/m^2, normal SGOT and SGPT level, and gave written consent to participate in this research by filling the informed-consent form. The exclusion criteria had a history of malabsorption disorders, acute/chronic liver disease, taking any kind of multivitamin/ supplement within the past 2 months, pregnant, breastfeeding, and taking anti-seizure medication, rifampicin, antiretroviral or steroid which can hinder the vitamin D absorption. All subjects who met the criteria were checked for their serum 25 (OH)D level as the baseline data. Only subjects with serum 25(OH)D level <30 ng/dl were included.

Based on the minimal sample size formula, the minimal sample was 48 subjects (24 subjects per group).

Table 3. Mean difference of 25(OH)D serum level at initial, after 4 weeks, and after 12 week-intervention in the vitamin D and placebo group

Group	Mean Serum Concentration of 25(OH)D (ng/ml)			p-value between initial and 4 weeks*	p-value between initial and 12 weeks*	p-value between 4 and 12 week*
	Initial	4 week-intervention	12 week-intervention			
Vitamin D group	14.42 ± 4.25	15.11 ± 3.26	15.11 ± 3.34	0.154	0.204	0.999
Placebo group	14.48 ± 4.28	14.08 ± 3.13	13.18 ± 2.70	0.496	0.017	0.022

Legend: *paired t-test

Table 4. Analysis of the Factors Affecting the Serum 25(OH)D Level in the Vitamin D and Placebo Group

Variable	Vitamin D (n=32)			Placebo (n=30)		
	n	ΔVit D	p	n	Δ Vit D	p
Gender						
Male	9	-0.89 ± 3.24	0.063*	10	-2.39 ± 2.11	0.135†
Women	23	1.31 ± 2.77		20	-0.75 ± 2.98	
Compliance to supplement						
Poor (<80%)	10	-0.22 ± 2,65	0.248‡	9	-2.00 ± 2.73	0.101§
Fair (80-90%)	8	2.39 ± 3.81		8	0.08(-1.21-5.89)	
Good (91-95%)	7	-0.25 ± 3.41		2	-1.34 ± 1.28	
Very good (96-100%)	7	1.01 ± 1.37		11	-2.31 ± 2.54	
Wearing hijab						
Yes	18	1.75 ± 2.53	**0.023***	10	0.35 ± 2.70	**0.019***
No	14	-0.66 ± 3.16		20	-2.12 ± 2.51	
Wearing protector						
Yes	29	0.82 ± 3.11	0.487*	24	-1.24 ± 2.98	0.822*
No	3	-0.49 ± 2.12		6	-1.51 ± 2.07	
Daily direct sun exposure duration						
Poor (< 10 minutes)	13	1.56 ± 3.19	0.375‡	12	-0.05 ± 3.39	0.105§
Fair (10 – 30 minutes)	13	0.33 ± 2.25		14	-1.97 ± 1.72	
Good (> 30 minutes)	6	-0.39 ± 4.07		4	-2.68 ± 3.11	
The frequency of direct sunlight exposure per week						
Poor (0 – 1 x)	14	1.63 ± 3.51	0.387§	11	-1.20 ± 2.86	0.981‡
Fair (2–3 x)	15	0.04 ± 2.51		13	-1.29 ± 3.01	
Good (> 3 x)	3	-0.37 ± 2.59		6	-1.49 ± 2.66	
The frequency of foods or drinks consumption per week						
Poor (0-1 x)	2	1.23 ± 7.11	0.216§	3	-0.27 ± 5.49	0.944§
Fair (2-3 x)	25	1.12 ± 2.57		24	-1.41 ± 2.49	
Good (>3 x)	5	-1.64 ± 3.28		3	0.35(-5.06-0.49)	
The number of food or drink variations per week						
Poor (0-1 type)	3	2.09 ± 2.49	0.108§	2	0.64 ± 7.43	0.936§
Fair (2-3 types)	17	1.58 ± 3.01		13	-1.64 ± 2.52	
Good (> 3 types)	12	-1.91 ± 2.64		15	-1.24 ± 2.47	

Legend: *T-test; †Mann-Whitney test; ‡One-way Anova test; §Kruskal-Wallis test

Intervention Protocol

The participants were randomized into two groups; vitamin D and placebo group. The intervention was a daily 1000 IU vitamin D oral supplementation for 12 consecutive weeks. During the intervention, the importance of obediently taking the supplement daily was highly emphasized to every participant. Each subject was given a logbook to record their daily adherence, adverse event(s), consumption of foods/ beverages containing vitamin D, direct sunlight exposure, and painful events during the intervention. At the end of the treatment (supplementation

Table 5. Adverse Events

Adverse Events	Frequency	%
Sprue	1	1.6
Throat pain	2	3.1
Abdominal discomfort	1	1.6
Diarrhea	1	1.6
No complaint	59	92.1

with vitamin D3 or placebo), the serum 25(OH)D level was measured again for treatment evaluation.

Statistical Analysis

The numeric data with normal distribution were presented as mean (standard deviations), and data with abnormal distribution were presented as median (min-max). The baseline characteristics between the vitamin D and placebo groups were compared using chi-square tests. The normality of the data was tested using the Kolmogorov-Smirnov test. For normally distributed data, the hypothesis test used was unpaired t-test. Meanwhile, for the abnormally distributed data, the hypothesis was tested using Mann-Whitney test. Comparison of the mean serum 25(OH)D levels at baseline, after 4 weeks of supplementation, and after 12 weeks of supplementation, both in the vitamin D and placebo group.

RESULTS

There were 86 respondents who met the inclusion criteria. Five of whom were excluded because they had abnormal levels of SGOT and/or SGPT. The remaining 81 respondents were examined for their serum 25(OH)D level, a total of 76 respondents (93.8%) have 25-(OH)D level of serum below 30 ng/dl and thus included as the study sample. During the study, there were four dropout subjects, either due to pregnancy, moved to another workplace, experienced sore throat (side effect), or were absent during post-intervention blood sampling.

As seen from Table 1, there was no statistically significant difference between the participant's characteristics' in the vitamin D and placebo groups. Therefore, the participants in the treatment and placebo group were distributed homogeneously.

At the initial stage, the serum 25(OH) D level in the treatment group was lower than in the placebo group. Both after 4 and 12 weeks of intervention, the serum 25(OH)D level in the treatment group is higher than the placebo group. After 12 weeks of intervention, the mean serum 25(OH)D level in the treatment group was higher than the initial level. In contrast, the serum 25(OH)D level in the placebo group was lower than the initial level. The comparison of the serum 25(OH)D level at the initial stage, after 4 and 12 weeks of intervention was shown in figure 1. This result is consistent with the delta of serum 25(OH)D level after 4 and 12 weeks of intervention in the treatment group, which is higher than in the placebo group (Figure 2).

The Effect of Vitamin D3 Supplementation on Serum 25(OH)D Level

The data distribution of the serum vitamin D level at baseline and after the 4 weeks of intervention was normal (Kolmogorov-Smirnov test, $p>0.05$). Meanwhile, the data distribution of the serum vitamin D levels after 12 weeks intervention was abnormal (Kolmogorov-Smirnov test, $p<0.05$). The comparison of serum 25(OH)D levels between the treatment and placebo group can be seen in Table 2 and 3.

After 4 weeks of intervention, there was no significant difference between the serum 25(OH)D level in the treatment and placebo group (Table 2). However, there was a significant difference of the serum level post 12 weeks of supplementation between the treatment and placebo group ($p=0.015$). The same result was found when the delta of the serum level was being analyzed. After 4 weeks of intervention, the delta of serum 25(OH)D level between the intervention and placebo group was not significant (Table 2). Nonetheless, the delta of serum 25(OH)D level after 12 weeks of supplementation was substantial between the two groups ($p=0.009$).

As seen from Table 3, in the treatment group, the serum 25(OH)D level after 4 and 12 weeks of supplementation was increased from the baseline, but it was not statistically different ($p=>0.05$). In the placebo group, the serum 25(OH)D level decreased after 4 and 12 weeks compared to the baseline level, and the decrease was statistically significant at 12th week ($p=0.01$).

Factors Affecting the Change of Serum 25(OH)D Level

We analyzed several factors that were predicted to influence the serum 25(OH) D level. There were sex, adherence to daily supplement consumption, hijab usage, direct sunlight exposure duration per day, frequency of direct sunlight exposure per week, the variety of vitamin D-rich foods and drinks per week, and frequency of vitamin-D-rich foods and drinks consumption per week. We found a significant association between the use of hijab and the changes of serum 25(OH)D level after 12 weeks of intervention (Δ 12-week vitamin D) (Table 4).

Adverse Events

Several subjects reported some complaints during this study, which we considered as the side effects or adverse events, as presented in table 5. The adverse events reported were mild and did not cause any interference to their daily activities, except for one subject who felt discomfort and stopped consuming supplements (dropped out).

DISCUSSION

Vitamin D supplementation is a cost-effective and efficient method to treat vitamin D deficiency and to maintain adequate 25(OH)D level in the blood. According to the RDA (Recommended Daily Allowance), the recommended daily vitamin D dose of 600-800 IU is needed to optimize bone health. However, in the majority of the population, higher vitamin D intake (1000 -2000 IU) is required to achieve and maintain 25(OH)D level to be more than 30 ng/ ml.[1,15,16] This is the main consideration of choosing 1000 IU supplementation in this study, instead of

other doses.

The increase of serum 25(OH)D level is slightly different compared to previous studies with a wide variety of vitamin D dosage (400-10.000 IU). In addition, the duration of vitamin D administration also varied greatly.[17] One study in Norway identified a significant increase in the mean serum 25(OH)D level (p<0.001) in healthy subjects receiving a 400 IU vitamin D3 supplementation for 4 weeks.[18] Similar significant result has been shown in subjects who received daily 600 IU vitamin D3 supplementation for 8 weeks compared to the placebo group.[19] Two other studies using the same dose of supplementation as this study (1000 IU vitamin D3) for 11 consecutive weeks in healthy subjects showed a significant increase of serum 25(OH)D level (12.28 ng/ml and 9.8 ng/ml, respectively).[20,21]

In this study, daily 1000 IU vitamin D3 supplementation resulted in an increase of serum 25(OH)D level, but it was not statistically significant compared to the placebo group (p=0.2). One possible explanation was that subjects in the treatment group have considerably lower baseline 25(OH)D levels compared to those in the placebo group, even though it was not statistically significant. In contrast, there was a trend of decreased serum 25(OH)D level after 4 and 12 weeks compared to the initial 25(OH)D level in the placebo group.

It might take longer than 12 weeks to observe the effect of vitamin D3 supplementation. Another factor that may contribute to the fewer increase of serum 25(OH)D level than expected might be a higher dose of supplementation needed to correct the very low initial 25(OH)D level (<20 ng/ml in 85% of the participants). A greater dose of vitamin D supplementation might be required to achieve the desired 25(OH)D level. Other studies stated that, in most populations, especially in Europe and the United States, a high vitamin D intake (1000-2000 IU) is required to achieve and maintain the level of 25(OH) D over 30 ng/ml.[16,22] Other researchers estimated that to maintain a serum 25(OH) D level >25, 30, and 50 nmol/L in 97.5% of the population, the daily vitamin D3 doses needed were 10, 13, and 26 μg (1200 IU), respectively.[17,23] A study by Zittermann et al. even used a larger dose of vitamin D, up to 4000 IU of vitamin D3 per day.[24] Lukaszuk and Luebbers conducted a study among overweight or obese individuals. Following daily supplementation of 5,000 IU of vitamin D3, all subjects' 25(OH)D levels rose to an adequate level (≥30 ng/ml). This finding concurred with the Institute of Medicine and Endocrine Society recommendations that two to three times the daily requirement of vitamin D is required to improve serum vitamin D levels in individuals who are overweight or obese.[25]

The strength of this study was the study design which was a randomized double-blind, placebo-controlled trial, the best study design for interventional research with minimal risk of bias. Furthermore, there was an analysis of potential factors that might affect the serum 25(OH)D level. The use of clothing that largely covered the body surface, such as hijab, was the most critical factor affecting the serum 25(OH)D level, even with an adequate direct sun exposure time. The efforts to improve hypovitaminosis D's condition can be performed with oral vitamin D supplementation along with lifestyle changes, such as increasing daily direct sun exposure duration and consumption of rich vitamin D-foods and/or drinks.

The limitation in this study is the lack of quality control of the reported daily adherence via logbook and the wide range of adherence rates across participants. This might be caused by participants generally still feeling healthy even without routine supplementation, which made them easily forget or bored in taking supplements.

Other than the compliance measurement, this study might also need a longer observation time (more than 12 weeks) to observe the effect of daily oral vitamin D3 supplementation. Another factor that might need to be adjusted is the dose, a greater dose of vitamin D supplementation might be required to correct the very low initial 25(OH)D level (<20 ng/ml in 85% of the participants) among participants. The daily tolerable upper intake level of vitamin D is 4,000 IU, while we only used 1,000 IU of vitamin D. Further researches with higher dose are needed.

Few participants also blamed the daily supplementation for their complaints, i.e. sore throat, sprue, nausea or abdominal pain, and diarrhea, so they took the supplementation less frequently. Vitamin D3 is widely recognized to be safe as daily supplementation. Adverse events were rarely observed, unless the doses were extremely high. In few rare cases, vitamin D may cause undesirable effects, such as allergic reactions/hypersensitivity, weakness, easy drowsiness, headache, loss of appetite, nausea and vomiting. There was also recall bias for the history taking for the participants' diet and direct sun exposure.

CONCLUSIONS

Hypovitaminosis D was surprisingly very prevalent among the working-age group in Indonesia. Participants that received daily supplementation of 1000 IU vitamin D3 for 12 consecutive weeks have significantly higher serum 25(OH)D levels compared to the participants in the placebo group. Moreover, the delta of serum 25(OH) D level between baseline and after 12 weeks was also significantly higher in the treatment group compared to the placebo group. There is a significant association between the use of hijab and the changes of serum 25(OH)D level after 12 weeks of intervention (Δ 12-week vitamin D).

CONFLICT OF INTEREST

The authors declare no conflict of interest regarding the publication of this article.

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This study received a non-APBN grant year 2017.

ETHICAL CONSIDERATION

The Ethical Committee had approved this study protocol of Faculty of Medicine Universitas Diponegoro and Dr. Kariadi General Hospital, Semarang, Central Java, Indonesia (No.15/EC/FK-RSDK/1/2017). The study was conducted in accordance with the Good Clinical Practice.

AUTHOR CONTRIBUTION

All authors had contributed equally in writing the original draft and agreed for

the final version of the manuscript for publication.

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