Jufri, et.al.Amerta Nutr (2021). 180-195.
DOI: 10.20473/amnt.v5i2.2021. 180-195.

LITERATURE REVIEW Open Access

Pengaruh Suplementasi Vitamin D terhadap Kadar Serum 25(OH)D, Serum Kalsium, dan Densitas Massa Tulang pada Remaja: Tinjauan Pustaka

The Effects of Vitamin D Supplementation on Serum Levels of 25 (OH) D, Serum Calcium, and Bone Density in Adolescent: A Literature Review

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ABSTRAK

Latar Belakang: *Stunting dan densitas massa tulang rendah merupakan salah satu masalah gizi yang umum diderita oleh remaja. Hal ini terjadi akibat kurangnya asupan zat gizi yang adekuat terutama vitamin D yang berfungsi untuk pertumbuhan tulang dan mineralisasi jaringan. Jumlah yang terbatas dari makanan dan faktor pigmentasi kulit menjadi penyebab terjadinya defisiensi vitamin D sehingga dibutuhkan upaya suplementasi untuk memenuhi kebutuhan tersebut.*
Tujuan*: Menganalisis efek suplementasi vitamin D terhadap konsentrasi serum 25(OHD), serum kalsium, dan densitas massa tulang*
Ulasan*: Hasil skrining menemukan 12 artikel yang memenuhi kriteria inklusi dan diklasifikasikan berdasarkan luaran penelitian yaitu kadar serum 25(OH)D merupakan parameter biokimia yang merupakan luaran pada 10 artikel penelitian. Parameter biokimia serum kalsium sebanyak 6 artikel, dan densitas tulang sebanyak 8 artikel.*
Kesimpulan*: Suplementasi vitamin D yang diberikan pada remaja yang sehat maupun tidak sehat terbukti meningkatkan kadar serum 25(OH)D dan densitas massa tulang, namun tidak memberikan efek terhadap serum kalsium.*
Kata kunci*: Suplementasi vitamin D, serum 25(OH)D, serum kalsium, densitas massa tulang.*

ABSTRACT

Background: Stunting and low bone mass density are common nutritional problems suffered by adolescents. These problems occur due to insufficient intake of adequate nutrients, especially vitamin D, which functions in bone growth and tissue mineralization. Limited amounts of food and skin pigmentation lead to vitamin D deficiency. Thus, supplementation is needed to meet these needs.
Objective: Analyzed the effect of vitamin D supplementation on serum 25 (OH)D concentration, serum calcium and bone mass density.
Discussion: The search results through screening showed that 12 articles met the inclusion criteria and were classified based on the study outcome: 25 (OH) D serum biochemical parameters were found in 10 research articles, serum calcium biochemical parameters were found in 6 research articles, and bone density was found in 8 articles.
Conclusion: Vitamin D supplementation has been shown to increase serum 25 (OH) D levels and bone mass density in healthy and unhealthy adolescents, but it has no effect on serum calcium.
Keywords: Vitamin D supplementation, 25 (OH) D serum, calcium serum, bone mass density.

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Published by Universitas Airlangga and IAGIKMI

INTRODUCTION

Adolescence is a stage in the life cycle characterized by rapid growth and development physically, behavior and emotionally. At this stage it occurs*growth spurt*which is the peak growth in height (peak high velocity), bone mass (peak bone mass), and body weight (peak weight velocity). This causes the nutritional needs of adolescents to be very high compared to other phases of life[1].

Adolescent growth indicators can be measured from height and bone density. Height is an anthropometric measure that describes the state of bone

Received: 24-06-2020, Accepted: 08-02-2021, Published online: 21-06-2021.
doi: 10.20473/amnt.v5i2.2021. 180-195. **Joinly Published by IAGIKMI & Universitas Airlangga**

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/ skeletal growth. Bone as a living tissue consisting of a collagen protein matrix and absorbs mineral salts, especially phosphate and calcium. Bone supports the body and plays an important role in mineral homeostasis[2].

Suboptimal nutrient intake in adolescents can affect bone growth, changes in body composition, bone mineralization, and physical activity. Nutritional problems that can occur due to impaired growth are *stunting* and a decrease in density mass bone. The impact of stunting on adolescents is stunting, decreased health, obesity, decreased concentration and work capacity[3]. The impact of low bone density is osteopenia, a symptom or condition of bone transition from a healthy condition to an osteoporosis condition. Thus, bone density in adolescence can determine the risk of osteoporosis in old age.

Vitamin D is known as a vitamin that plays an important role in normal bone growth and tissue mineralization. This is because the active form of vitamin D which is 1,25 (OH) D2 together with parathyroid hormone and calcitonin maintains endocrine control of calcium and phosphorus concentrations.[4]. The specific role of active vitamin D includes increased intestinal calcium absorption[5], renal calcium reabsorption, and skeletal calcium absorption (in conjunction with parathyroid hormone)[6]. To assess the status of vitamin D in the body, the commonly used marker is serum 25 (OH) D levels, this is due to its longer half-life in the blood circulation compared to the active metabolite 1,25 (OH) D2.[7] .

Vitamin D can be obtained from food but in very limited quantities. Vitamin D can also be synthesized in the skin with the help of UV B rays. However, it cannot guarantee the availability of the amount of vitamin D in the body due to pigmentation in the skin and other factors. So that vitamin D supplementation is needed to support adolescent bone growth. The purpose of this literature review was to analyze the effects of vitamin D supplementation on serum 25 (OH) D levels, serum calcium and bone density were all influencing factors to growth in adolescents.

METHODS

This study used a systematic review design. The search for articles in this literature review was carried out using search engines through Medline, PubMed, EBSCO, ELSEVIER, Cambridge Core, and WILEY. Articles that meet the criteria for this literature review were articles that contain full text, in English and published years from 2010 to 2020. The search keywords entered were a combination of vitamin D supplementation, adolescent, teenagers, serum 25 (OH) D, *and Bone Mass Density* (BMD) using Boolean Operators "AND" and "OR".

The inclusion criteria for research articles were based on the PICOS principle (population, intervention, compare, outcome, study design). The population was adolescents aged 10-19 years according to the WHO definition, not limited to a healthy population but excluding those who experience concurrent acute / chronic disease or disease complications due to limited research articles on the effects of vitamin D supplementation on adolescents. The intervention given was vitamin D either D2 or D3 with low or high doses. Studies that had more than two test groups were eligible for inclusion in this review as long as the trial included comparing the vitamin D intervention groups. Studies that combined vitamin D and calcium supplementation were also included in the inclusion criteria. The output seen in this literature review was bone density and biochemical markers serum levels 25 (OH) D and serum calcium levels. The research design was a randomized controlled trial conducted on adolescents.

The quality of the articles was assessed using the Jadad score includes assessments randomization, blinding and dropout. If the study ddo it randomization given a value of 1, the randomization method described was given a value of 1, the described blinding method was given a score of 1. If the study did not explain the randomization method with the value minus 1, The blinding method was not described with the exact value minus 1. This literature review only uses systematic review or meta-synthesis techniques and did not synthesize the results statistically (meta-analysis).

RESULT AND DISCUSSION

General Characteristics

Article searches conducted via the search engines Medline, PubMed, EBSCO, ELSEVIER, Cambridge Core, and WILEY returned 468 articles after entering all keywords. After filtering articles based on articles that contain full text, 47 articles will be reviewed further. Further screening was carried out by looking at the established inclusion criteria, namely the subject population was adolescents aged 10-19 years according to the WHO definition. *Randomized Controlled Trial* (RCT), and the study outcome was bone density and biochemical markers levels serum 25 (OH) D and serum calcium. From the screening results, only 12 articles met the inclusion criteria. The characteristics of research types of intervention in an effort to increase growth in adolescents can be seen in table 1:

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Table 1. Characteristics of Vitamin D Intervention Research on Adolescent Growth

Author and Year	Country	n	Intervention Materials
Khadilkar et al, 2010[8]	India	49	1. Vitamin D + Calcium 2. Placebo + Calcium
Molgaard et al, 2010[9]	Denmark	221	1. Placebo 2. 5 ug of vit. D / d 3. 10 ug of vit. D / d
Ward et al, 2010[10]	United Kingdom	72	1. 150000 IU D2 2. Placebo
Dong et al, 2010[11]	USA	49	1. Vitamin D 200 IU / d 2. 2000 IU / d
Putman et al, 2012[12]	America	54	1. Vitamin D 200 IU 2. Vitamin D 1000 IU
Khadilkar et al, 2012[13]	India	210	1. Ca + Mz + Vit. D 2. Ca + vit. D 3. Placebo
Arpadi et al, 2012[14]	New York	53	1. Vitamin D (100000 IU) and calcium (500 mg) 2. Placebo
Al-shaar et al, 2013[15]	Beirut	338	1. Placebo 2. Low dose (vit. D 200 IU / d) 3. High dose (vit. D 2000 IU / d)
Plante et al, 2016[16]	North America	60	1. Vitamin D 400 IU / d 2. Vitamin D 2000 IU / d
Talib et al, 2016[17]	New York	183	1. Vitamin D 50,000 IU / w 2. 5000 IU / d 3. 1000 IU / d
Ghazal et al, 2016[18]	Lebanon	86	1. Vitamin D 1400/14000 / d 2. Placebo
Magge et al, 2018[19]	USA	22	1. Vitamin D 1000 IU / d 2. Vitamin D5000IU / d

Research Characteristics

The results of the study were classified based on the research outcome, namely from all articles that met the requirements for review, serum 25 (OH) D levels were biochemical parameters which were the outcomes contained in 10 research articles. The serum calcium biochemical parameters were 6 articles, and bone density as many as 8 articles.

Of the 10 articles aimed at increasing serum 25 (OH) D levels, 8 articles used high doses of vitamin D ranging from 2000 IU / day to 150000 IU / 3 months within a year as an intervention material. Not a single article reported any side effects of vitamin D supplementation. The mean serum 25 (OH) D value before supplementation was <35 ng / ml, the standard for vitamin D deficiency varies according to the organization that makes the recommended vitamin D levels but the most commonly used was based on the Endocrine Society where it was said to be deficient when < 20 ng / ml and said to be sufficient if 30-100 ng / ml[20]. The mean increase after intervention was> 80 ng / ml, however there were several articles using a standard vitamin D deficiency <50 ng / ml. The characteristics of the studies that assessed serum 25 (OH) D as a study outcome of the effect of vitamin D supplementation in adolescents can be seen in Table 2.

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Table 2. Article Review Results yang Assessing Serum 25 (OH) D as An Effect Of Vitamin D Supplementation

Author / Year	Allocation of Interventions	n / group	Duration of Intervention	Intervention Results		Jadad Score	Conclusion
				25 (OH) early D	25 (OH) D final		
Khadilkar et al, 2010	1. Vitamin D + Calcium 2. Placebo + Calcium	1. 25 2. 24	12 months	1. 24.5 ± 12.7-33.2 2. 20.8 ± 12.7-30.4	1. 75.2 ± 64.2-85.5 2. 28.1 ± 16.7-34.0	4	1. There were differences in serum 25 (OH) D levels before and after the intervention both in the vitamin D + calcium group (P = <0.001) and in the placebo + calcium group (P = 0.001). 2. The mean percentage increase was higher in the supplementation group (68%) than in the placebo group (19%).
Molgaard et al, 2010	1. Placebo 2. 5 ug of vit. D / d 3. 10 ug of vit. D / d	1. 74 2. 73 3. 74	12 months	1. 43.4 ± 17.1 2. 41.9 ± 17.6 3. 44.4 ± 16.6	1. 39.7 ± 17.7 2. 52.9 ± 16.3 3. 57.9 ± 14.3	4	1. There was a difference in 25 (OH) D levels between groups after 12 months of intervention (p = <0.0001) 2. The results of regression analysis showed a significant increase in levels of 25 (OH) D between groups after 12 months of intervention (p = <0.0001).
Ward et al, 2010	1. 150000 IU D2 group 2. Placebo group	1. 36 2. 36	12 months	1. 18.1 ± 8.0 2. 17.9 ± 7.4	1. 56.0 ± 8.9 2. 15.7 ± 6.6	5	There was a significant increase in serum 25 (OH) D levels before and after the intervention in the intervention group (p = <0.001), while in the placebo group there was no significant increase or even decreased. There is no link between serum levels and bone density

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Author / Year	Allocation of Interventions	n / group	Duration of Intervention	Intervention Results		Jadad Score	Conclusion
				25 (OH) early D	25 (OH) D final		
Dong et al, 2010	1. Vitamin D control group 200 IU / d 2. Vitamin D experimental group 2000 IU / d	1. 24 2. 25	16 weeks	1. 34.0 ± 10.6 2. 33.1 ± 8.7	1. 59.8 ± 18.2 2. 85.7 ± 30.1	4	There was a significant increase in serum 25 (OI in the intervention group from week to weel examination (P = <0.001). The intervention group a higher significance at weeks 8 & 16 but not at w 4 and baseline of recruitment.
Putman et al, 2012	1. Vitamin D 200 IU 2. Vitamin D 1000 IU	1. 25 2. 29	11 weeks	1. 28.1 ± 6.2 2. 29.0 ± 7.3	1. 28.9 ± 7.0 2. 30.1 ± 6.6	4	1. Mean serum 25 (OH) D levels remained at both baseline and follow-up in both treatment groups. The mean change from base line to follow-up in the 200 IU group was 0.7-6.3 ng / mL and in the 1000 IU group 1.0-6.0 ng / mL 2. Change in mean serum 25 (OH) D level did not differ significantly between the two groups (p = 0.87).
Arpadi et al, 2012	1. Vitamin D (100000 IU) and calcium (500 mg) 2. Placebo	1. 25 2. 28	24 months	1. 24.1 ± 9.1 2. 23.6 ± 10.2	1. 38.6 ± 10.6 2. 26.2 ± 11.9	5	1. There was an increase in mean serum 25 (OH) D levels in the vitamin D and calcium supplementation group from 24 ng / mL to 35 ng / mL. 2. Although there was an increase in serum 25 (OH) D levels, it did not have a significant impact on the total bone density.

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Author / Year	Allocation of Interventions	n / group	Duration of Intervention	Intervention Results		Jadad Score	Conclusion
				25 (OH) early D	25 (OH) D final		
Al-shaar et al, 2013	1. Placebo 2. Low dose (vit. D 200 IU / d) 3. High dose (vit. D 2000 IU / d)	Women (167) 1. 55 2. 58 3. 54 Male (171) 1. 56 2. 55 3. 60	12 months			4	The mean increase of 25 (OH) D was 3.2 ± 9.2 ng / ml (lov 30.3 ng / ml (high dose), versus 1.5 ± 5.4 ng / ml (placeb 3.7 ± 5.0 ng / ml, 18.6 ± 9.4 9 ng / ml, versus 0.9 ± respectively -Male
Plante et al, 2016	1. Vitamin D 400 IU / d 2. Vitamin D 2000 IU / d	1. 30 2. 30	12 months	1. 66.4 ± 21.9 64.7 ± 19.1	1. 15.2 ± 6.4: 24.1 2. 30.5 ± 21.3: 39.6	4	In all groups, the mean serum 25 (OH) D increase was 2x higher in the 2000 IU / d group
Talib et al, 2016	1. Vitamin D 50,000 IU / w 2. 5000 IU / d 3. 1000 IU / d	1. 59 2. 63 3. 61	8 weeks	1. 14.0 ± 3.7 2. 13.0 ± 3.9 3. 13.6 ± 4.1	1. 39.0 ± 15.1 2. 34.0 ± 14.3 3. 19.8 ± 5.3	2	1. The highest mean increase of 25 (OH) D was in the 50000 IU / w group and there was a significant difference between groups (p = <0.001) 2. The mean serum 25 (OH) D after supplementation in the high dose group was in the sufficient range while the low dose group was still below the range of deficiency values.

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Author / Year	Allocation of Interventions	n / group	Duration of Intervention	Intervention Results		Jadad Score	Conclusion
				25 (OH) early D	25 (OH) D final		
Magge et al, 2018	1. Vitamin D 1000 IU / d 2. Vitamin D5000IU / d	1. 10 2. 12	12 weeks	1. 11.7 (4.1) 2. 12.3 (3.5)	1. 18.8 (3.9) 2. 28.8 (11.4)	4	1. There is a difference in 25 (OH) D levels between the 1000 IU / day group and the 5000 IU / day group (p = <0.0001) 2. Post intervention, 25 (OH) D increased slightly in the 1000 IU group (5.6 ng / mL, p = 0.03) vs the 5000 IU group (15.6 ng / mL, p = 0.002). Post intervention 83% of the 5000 IU group and 30% of the 1000 IU group achieved ≥ 20 ng / mL 25 (OH) D (p = 0.01); 50% of the 5000 IU group, but no subjects in the 1000 IU group, achieved ≥ 30 ng / mL 25 (OH) D (p = 0.009).

The biochemical parameters of serum calcium can be seen from the 6 reviewed articles (Table 3). The serum calcium level was assessed as an outcome because of the function of calcium in bone formation. There were 2 research articles that combine vitamin D and calcium supplementation. Supplementation of vitamin D together with calcium led to an increase in serum calcium levels 68% higher than the placebo and calcium group which was only 19%[8]. The same thing happened to the percentage change in bone density where the vitamin D and calcium supplementation group had an average percentage change of 23.1% compared to the control group which was only 19.4%.[13].

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Table 3. Results of Review of Articles Assessing Serum Calcium as the Effect of Vitamin D Supplementation

Author / Year	Allocation of Interventions	n / group	Duration of Intervention	Intervention Results		Jadad Score	Conclusion
				Initial calcium	Final calcium		
Khadilkar et al, 2010	1. Vitamin D + Calcium 2. Placebo + Calcium	1. 25 2. 24	12 months	1. 0.94 ± 0.89-1.01 2. 0.91 ± 0.84-0.94	1. 1.05 ± 1.0-1.09 2. 1.05 ± 1.03-1.10	4	1. There were differences in calcium ion levels before and after the intervention in the vitamin D + Ca group (p = <0.001). Likewise in the placebo + Ca group (p = <0.001 2. The average increase in the supplementation group was 68% compared to the placebo group which was only 19%
Ward et al, 2010	1. 150000 IU D2 group 2. Placebo group	1. 36 2. 36	12 months	1. 2.3 ± 0.1 2. 2.3 ± 0.1	1. 2.2 ± 0.1 2. 2.2 ± 0.1	5	1. The corrected serum calcium concentration decreased in both groups. 2. The mean change in serum calcium before and after the intervention in both the intervention group and the placebo group was -0.1 (0.1) with P <0, 0001 and 0.02, respectively.

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Author / Year	Allocation of Interventions	n / group	Duration of Intervention	Intervention Results		Jadad Score	Conclusion
				Initial calcium	Final Calcium		
Dong et al, 2010	1. Vitamin D control group 200 IU / d 2. Vitamin D experimental group 2000 IU / d	1. 24 2. 25	16 weeks	1. 7.95 ± 1.76 2. 7.55 ± 1.54	1. 7.95 ± 1.76 2. 7.55 ± 1.54	4	There was no change in serum calcium before and after intervention (P = 0.29)
Putman et al, 2012	1. Vitamin D 200 IU 2. Vitamin D 1000 IU	1. 25 2. 29	11 weeks	1. 9.4 ± 0.4 2. 9.5 ± 0.5	1. 9.5 ± 0.3 2. 9.5 ± 0.4	4	The mean change in serum calcium levels did not differ significantly between the two groups (p = 0.20). Mean change from base line to follow-up in the 200 IU group was 0.1-0.4 mg / dL and in the 1000 IU group 0.0-0.5 mg / dL
Khadilkar et al, 2012	1. Ca + Mz + Vit. D 2. Ca + vit. D 3. Placebo	1. 71 2. 70 3. 69	12 months	1. 1.00 ± 0.08 2. 1.03 ± 0.10 3. 1.14 ± 0.07	1. 1.10 ± 0.08 2. 1.16 ± 0.07 3. 1.15 ± 0.06	5	Significant increase in ionized calcium concentration of all three groups after intervention (Ca + MZ (10.5%), Ca (14.1%), C (0.55%). was higher in the two augmented groups (Ca and Ca + MZ) than in the control group (p <0.05).
Plante et al, 2016	1. Vitamin D 400 IU / d 2. Vitamin D 2000 IU / d	1. 30 2. 30	12 months	1. 2.38 ± 0.08 2. 2.42 ± 0.08	1. 0.00 ± -0.03: 0.03 2. 0.01 ± -0.02: 0.04	4	The mean changes in calcium levels before and after the intervention in the low dose vitamin D group (0.00 ± -0.03: 0.03) and the high dose group (0.01 ± -0.02: 0.04). There was no significant difference before and after intervention (P = 0.84)

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An investigation of the effect of cholecalciferol on bone density as an outcome of the study resulted in 8 articles showing varying results for changes in total bone density (Table 4). There was no significant effect on the percentage change in TBBA (Total Body Bone Area) and TBBMC (Total Body Bone Mineral Content) and the median of LS BMAD (Lumbar Spine Bone Mineral Apparent Density) did not differ between the intervention group and the control group.[8]. While the research was conducted in different years show There was a significant percentage change in TBBA (Total Body Bone Area), TBBMC (Total Body Bone Mineral Content) and TBBMD (Total Body Bone Mineral Density)[13]. A significant increase occurred in the percentage of BMD NN (Bone Mineral Density Narrow Neck)[15]. The results of other studies indicate that vitamin D supplementation did not have a significant effect on changes in bone density in adolescents[9,10,14,16]. One study showed that vitamin D supplementation only had a significant effect on hip bone mass density but not on lumbar bone density[18].

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Table 4. Results of Review of Articles Assessing Bone Density as an Effect of Vitamin D Supplementation

Author / Year	Allocation of Interventions	n / group	Duration of Intervention	Intervention Results		Jadad Score	Conclusion
				Initial bone density	End bone density		
Khadilkar et al, 2010	1. Vitamin D + Calcium 2. Placebo + Calcium	1. 25 2. 24	12 months	- -	1. 4.2 ± 0.6-9.3 2. 3.7 ± 1.0-7.7	4	There was no significant effect on the percentage change in LSBA, TBBA, and TBBMC. The median of LSBMAD was not both in the two groups
Molgaard et al, 2010	1. Placebo 2. 5 ug of vit. D / d 3. 10 ug of vit. D / d	1. 74 2. 73 3. 74	12 months	1. 0.863 ± 0.064 2. 0.866 ± 0.066 3. 0.872 ± 0.070	1. 0.909 ± 0.075 2. 0.915 ± 0.075 3. 0.917 ± 0.080	4	There was an increase in bone mineral density (p = 0.007) and bone mineral content (p = 0.048) but there was no increase in body height (p = 0.93)
Ward et al, 2010	1. 150000 IU D2 group 2. Placebo group	1. 36 2. 36	12 months	1. 308.86 ± 34.72 2. 302.57 ± 36.85	1. 10.51 ± 14.17 2. 9.79 ± 11.07	5	1. There was no significant difference in BMD between before and after the intervention 2. There is no link between serum levels and bone density
Khadilkar et al, 2012	1. Ca + Mz + Vit. D 2. Ca + vit. D 3. Placebo	1. 71 2. 70 3. 69	12 months	1. -1.1 ± 0.9 2. -1.2 ± 0.8 3. -1.1 ± 0.9	1. -0.9 ± 0.9 2. -0.9 ± 0.7 3. -1.1 ± 0.8	5	1. TBBA, TBBMC and TBBMD significantly increased in the three groups before and after the intervention (p = <0.05 2. The percentage of changes in TBBMC and TBBMD was significantly higher in the Ca + MZ + vit.D group (21.5%, 5.7%) and the Ca + vit.D group (23.1%, 6.1%) than the control group (19.4%, 4.2%)

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								3. The percentage change in TBBA increase in percentage was significantly higher in the Ca group (15.7%) compared to the C group (13.8%) but not much different from the Ca + MZ group (14.4%) (p> 0.1) . 4. There was a significant difference between the Ca + Mz + vit.D group and the Ca + vit.D group on the increase in the mean percentage of TBBMC (p = <0.05) 5. There was no significant difference between the Ca + Mz + vit.D group and the Ca + vit.D group on the increase in the mean percentage of TBBMD (p => 0.1)
Arpadi et al, 2012	1. 2. 3.	Vitamin D (100000 IU / 2 months) and calcium (500 mg / d) Placebo	1. 25 2. 28	24 months	1. 0.814 ± 0.123 2. 0.826 ± 0.100	1. 0.835 ± 0.123 2. 0.863 ± 0.123	5	Although there was an increase in serum 25 (OH) D levels, it did not have a significant impact on the total bone density.

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DOI: 10.20473/amnt.v5i2.2021. 180-195.

Author / Year	Allocation of Interventions	n / group	Duration of Intervention	Intervention Results		Jadad Score	Conclusion
				Initial Bone Density	End Bone Density		
Al-shaar et al, 2013	1. Placebo 2. Low dose (vit. D 200 IU / d) 3. High dose (vit. D 2000 IU / d)	Women (167) 1. 55 2. 58 3. 54 Male (171) 1. 56 2. 55 3. 60	12 months	BMD NN: 1. 0.99 ± 0.2 2. 0.99 ± 0.2 3. 0.97 ± 0.2 BMD S 1. 1.38 ± 0.24 2. 1.34 ± 0.24 3. 1.35 ± 0.24 BMD IT 1. 0.94 ± 0.20 2. 0.91 ± 0.15 3. 1.35 ± 0.24	BMD NN 1. 5.25 ± 0.96 2. 7.50 ± 0.92 3. 6.12 ± 0.98 BMD S 1. 8.32 ± 0.84 2. 9.10 ± 0.85 3. 8.15 ± 0.84 BMD IT 1. 5.18 ± 0.91 2. 8.10 ± 0.88 3. 5.84 ± 0.92	4	1. There was a significant correlation between baseline serum 25 (OH) D levels and BMD NN and S (r = 0.16, p = 0.04 and r = 0.17, p = 0.03) 2. Vit supplements. D significantly increased the percentage of BMD NN + 7.85% (low dose), + 6.79% (high dose), + 4.23% in placebo (p = 0.049).
Plante et al, 2016	1. 2. Vitamin D 400 IU / d 3. Vitamin D 2000 IU / d	1. 30 2. 30	12 months	1. -2.0 (1,1) 2. -2.1 (1,2)	1. 0.0 (-0.1; 0.2) 2. 0.1 (-0.1: 0.2)	4	There were no changes in TB / U and BMD before and after the intervention
Ghazal et al, 2016	1. 2. Vitamin D 1400/14000 / d 3. Placebo	1. 54 2. 32	24 months	Lumbar Spine BMD 1. 0.819 ± 0.43 2. 0.836 ± 0.140 Hip BMD 1. 0.815 ± 0.134 2. 0.820 ± 0.124	Lumbar Spine BMD 1. 0.819 ± 0.43 2. 0.836 ± 0.140 Hip BMD 1. 0.815 ± 0.134 2. 0.820 ± 0.124	4	1. There was an increase in the average hip BMD before and after the intervention and there was a significant difference between the intervention and placebo groups after the intervention with p = 0.02 2. There was no significant difference in LSBMD between placebo and the intervention group after the intervention (p = 0.09)

Received: 24-06-2020, Accepted: 08-02-2021, Published online: 21-06-2021.
doi: 10.20473/amnt.v5i2.2021. 180-195. **Joinly Published by IAGIKMI & Universitas Airlangga**

Jufri, et.al.Amerta Nutr (2021). 180-195.
DOI: 10.20473/amnt.v5i2.2021. 180-195.

Effects of Vitamin D Supplementation on Biochemical Results Concentration of Serum 25 (OH) D and Serum Calcium

Vitamin D was known as a unique vitamin because it can be synthesized by the body, especially in the skin. Ultra Violet radiation (UVB) with a wavelength of 290-315 nm was able to mediate the conversion of 7-dehydrocholesterol, which was a precursor of cholesterol contained in the skin to vitamin D3. Vitamin D3 and D2 undergoes a two-step hydroxylation process: 1) to form 25-hydroxyvitamin D (25 (OH)D) in the heart which was not biologically active[21.22]; 2) meform an active metabolite 1,25-dihydroxy-vitamin D (1,25 (OH) 2D in the kidneys that assisted and strictly controlled by parathyroid hormone (PTH), PTH levels will increase when 25 (OH) D levels were at the threshold of 75 nmol / L or lower[23].

Mbiologically active etabolite 1,25 (OH) 2D function to maintenance of calcium and phosphorus homeostasis via endocrine mechanisms that target the intestines, kidneys and bones[24.25]. This was important for bone health throughout the life cycle, from bone gain and growth in infancy, childhood and adolescence, to maintaining healthy bones and preventing bone loss in adulthood.In adolescence Vitamin D and calcium very necessary because bone accruals occur most rapidly[26]. About 80-90% of the peak bone mass was achievedat the time late adolescence so by maximizing this condition can help reduce bone loss in old age[27].

Serum 25 (OH) D level was the best indicator for assessing vitamin D status because it has a long half-life in circulation (15 days), was relatively stable, has high concentrations in the blood and iresponsive to good vitamin D production from endogenous (skin) and exogenous (food and supplements)[28]. Meanwhile, 1,25 (OH) D has a very short half-life (4 hours) and its concentration in blood is three times lower than that of 25 (OH) D[29]. Determination of the limit value for vitamin D deficiency is still a matter of debate because of the different approaches used by each organization tasked with developing recommendations, strengths and interpretation of the evidence linking vitamin D status to specific health outcomes in a target population. The serum level value that is often used to determine the limit of vitamin D deficiency is around 25-30 nmol / L[20].

The difference in dosage and duration of vitamin D supplementation intervention had an effect on levels serum 25 (OH) D in study subjects. Duration of intervention minimum 12 months and a high dose of at least 2000 IU / d is shown to indicate an increase in serum 25 (OH)D once done vitamin D supplementation alone or in combination with calcium supplements, as has been seen in studies Khadilkar et al[8], MolgaArd et al[9], Ward et al[10], Arpadi et al[14], Al-shaar et al[15], Plante et al[16] (Table 2). Conversely, a low dose of a maximum of 1000 IU / d and a short duration of intervention showed no increase in mean serum 25 (OH) D after supplementation. vitamin D (Putman et al[12] in table 2). However, different results were obtained in the study Talib et al[17] and Magge et al[19] which showed that the duration of vitamin D supplementation intervention which was carried out was very short, each 8 weeks at a dose of 5000 IU / d and 12 weeks at a dose of 50,000 IU / d giving the effect of an increase in serum 25 (OH) D. Based on of this, the dose of vitamin D given is the most influential thing tagainst an increase in serum 25 (OH) D levels, another factor which also matters among them health status, ethnicity and race as well gender.

Calcium as a mineral that functions in bone formation is closely related to vitamin D because of the physiological function of vitamin D to help the absorption of calcium in the intestine, helps reabsorption of calcium in the proximal tubule of the kidney and regulates the release of calcium from bones into the blood. So that the effectiveness of calcium in the body was very dependent on vitamin D.[30]. However, from the results of a systematic review conducted in several studies, it was found that vitamin D supplementation had no effect on calcium levels in the blood, especially studies with single vitamin D supplementation without additional calcium. as shown in table 3. This can be caused by the regulation of parathyroid hormone in balancing calcium levels in the blood. When the calcium level in the blood was low, the thyroid gland immediately stimulates the release of parathyroid hormone which helps release calcium from the bones into the blood. While vitamin D will function to help balance calcium in the blood when parathyroid hormone has converted vitamin D into a hormonal form of vitamin D in the kidneys.[31.32].

Effects of Vitamin D Supplementation on Skeletal

Bone density or bone mineral density was influenced by achieving peak optimal bone mass growth and loss of bone mass with age. Achieving peak optimal bone mass growth since adolescence plays an important role in preventing osteoporosis and fractures later in the life cycle. Many factors can affect bone mineral density, one of which was the consumption of foods containing calcium, phosphorus and vitamin D. Vitamin D deficiency which was associated with calcium deficiency can cause bones to become soft (*osteomalacia*), decreased bone mass and risk of fractures in old age [33].

Bone tissue was a netan which was very dynamic because it undergoes a life-long regeneration process. After resorption occurs, new bone will be formed through the mineralization process by steroid-producing osteoblasts (extracellular matrix (ECM)), this process was tightly controlled by endocrine factors, namely 1α, 25-dihydroxyvitamin D3 (1α, 25 (OH) 2D3 which was very important for bone mineralization either directly or indirectly[34]. The direct effect (1α, 25 (OH) 2D3 on osteoblasts involves the control of extracellular matrix protein production (collagen type 1, osteopontin, osteocalcin, gla matrix protein) and the effect on the activity of the alkaline phosphatase enzyme as a provider of phosphate for mineral deposition.[35].

Bone mineralization consists of several stages, in which osteoblasts, chondrocytes and odontoblasts

Received: 24-06-2020, Accepted: 08-02-2021, Published online: 21-06-2021.
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carry out extracellular mineralization. The initial stage begins with the formation of hydroxyapatite (HA) crystals which take place in a nano-vesicle-sized cellular matrix (EVS). The second stage of HA spreads beyond the vesicles causing mineral build-up in the extracellular matrix. Each stage of mineralization depends on balanced regulation, in the first stage calcium was taken up by extracellular vesicles that sprout on the cell membrane. This process occurs through acid-binding phospholipids and calcium-binding proteins. The phosphate concentration in the vesicles was regulated by phosphohydrolases such as alkaline phosphatase which use inorganic pyrophosphate as a substrate. If the solubility products of calcium and phosphate were exceededu then mineral deposits were formed in the extracellular vesicles and in the second stage of mineralization begins with the release of previously formed HA crystals [36] The immediate effects of vitamin D occur in the period before mineralization begins and involve an accelerated maturation of the extracellular matrix[37], so that if the mineralization process has passed, the vitamin D will no longer have an effect. So it can be concluded that the direct effect of (1α, 25 (OH) 2D3 on human osteoblast activity depends on the phase of osteoblast differentiation.[38].

Sex difference was one of the factors that influence bone mass density. In table 4, the study conducted by Al-shaar et al[15] find that girls gave a positive response to giving vitamin D supplements in dibandingright in boys. This matter influenced by the time of puberty where puberty delays in males and hormones estrogen that was owned by women has an impact on the geometric structure of the bones.

CONCLUSION

Vitamin D supplementation given to healthy and unhealthy adolescents has been shown to increase serum vitamin D levels in the body, serum 25 (OH) D levels were a marker of the availability of vitamin D in a person's body. The effect of vitamin D supplementation on serum calcium did not show any significant difference before and after administration. There was an increase in bone mass density after vitamin D supplementation. There were several things that must be considered when giving supplements vitamin D in increased bone mass density so that growth can take place optimallynamely: 1) The use of threshold values for the category of deficiency, insufficiency and deficiency of vitamin D should follow the appropriate guidelines according to the geographic location of an area; 2) The use of dosage for healthy and unhealthy subjects needs to be differentiated; 3) The duration of the intervention; and 4) Combination of intervention ingredients with other nutrients that support linear growth and increase in bone mass density.

ACKNOWLEDGEMENT

The authors would like to thank the Nutrition of Science of Public Health, Faculty of Public Health, Halu Oleo University, Southeast Sulawesi, Kendari, Indonesia

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Received: 24-06-2020, Accepted: 08-02-2021, Published online: 21-06-2021.
doi: 10.20473/amnt.v5i2.2021. 180-195. **Joinly Published by IAGIKMI & Universitas Airlangga**

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Received: 24-06-2020, Accepted: 08-02-2021, Published online: 21-06-2021.
doi: 10.20473/amnt.v5i2.2021. 180-195. **Joinly Published by IAGIKMI & Universitas Airlangga**