

Effects of Vitamin D Supplementation on Healthy, Overweight, and Obese Adults: A Non-Blinded, Randomized Trial

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<https://dx.doi.org/10.13005/bpj/2627>

(Received: 21 December 2022; accepted: 17 January 2023)

A growing body of literature recognizes the role of vitamin D deficiency in various health-related problems such as obesity, cardiovascular diseases, and dyslipidemia. Hence, we design a small non-blinded randomized clinical study to explore some of these effects. The primary outcome was to investigate whether supplementation with vitamin D could reduce body mass index (BMI), while the secondary outcome was to see its effects on blood pressure (BP), serum total cholesterol (TC), and HDL-cholesterol over 12 weeks period in overweight otherwise healthy individuals. Twenty-two subjects were randomized into two groups, group A was given vitamin D supplementation of 200 IU/day and group B was assigned to 2000 IU/day. A baseline assessment of body mass index (BMI), blood pressure (BP), serum total cholesterol (TC), and serum HDL-cholesterol was performed at baseline, 4, 8, and 12 weeks. Repeated measure ANOVA was used to determine the effect of supplements within subjects and between the groups of our study. The study was unable to demonstrate any statistically significant effects of these supplemental doses of vitamin D on both primary and secondary outcomes over the study period. The scope of this study was limited by a small sample size and a large randomized double-blinded clinical study could provide more definitive evidence.

Keywords: BMI; Blood Pressure; Cholesterol; HDL-Cholestrol; Vitamin D.

It has been commonly assumed that vitamin D plays a fundamental role in growth, development, and general health, especially for bone maintenance as well as calcium and phosphorus hemostasis. However, recent scientific research has shown the implications of vitamin D on multiorgan systems, and serum level fluctuations have been seen in a variety of diseases. Notable examples of these diseases are cardiovascular diseases, diabetes, dyslipidemia, and obesity^{1,2,3}.

According to the last update of WHO, obesity worldwide has increased 3-fold since 1975, and “In 2016, more than 1.9 billion adults, 18 years and older, were overweight. Of these over 650 million were obese” as well as “39 million children under the age of 5 were overweight or obese in 2020”⁴. A large number of published papers have described the role of vitamin D on obesity and its complications such as alteration of blood pressure, serum lipid panel, and other

cardiovascular and metabolic diseases. Early meta-analysis has identified that vitamin D deficiency prevalence was 24% more in overweight subjects in comparison to placebo (PR: 1.24; 95% CI: 1.14-1.34)⁵. The above-mentioned study concluded that obese and overweight subjects are prone to vitamin D deficiency and its complications⁵. This view is supported by a previous study that has seen the same findings on Asians and European-Americans⁶. Another publication stated that patients could have lower body mass index (BMI) when they have desirable serum vitamin D levels and found the inverse relationship between blood pressure and serum vitamin D level⁷. Other meta-analysis studies including 12 RCTs have identified that vitamin D would benefit blood pressure in elderly and vitamin D-deficient patients⁸. Whereas, other meta-analysis research papers identified 11 cohort studies and 27 RCTs (43,320 and 3,810 participants respectively) that have not found such effects⁹.

In the case of dyslipidemia, some literature has shown a beneficial effect on lipid panels in those who are supplemented with vitamin D in comparison to controls^{10,11,12}. In contrast to these findings, several studies have shown negative consequence sees of supplemental vitamin D on HDL^{13,11,14}. To date, there has been little agreement on the impacts of vitamin D supplementation on serum lipid profile.

According to the World Health Organization Iraq Office website, an estimated 30% of the population have high blood pressure levels and more than 30% suffer from obesity. Additionally, more than 25% of total deaths are attributed to cardiovascular diseases¹⁵. In this study, we have tried to shed some light on the effect of two different affordable supplements of vitamin D3 (200 IU and 2000 IU) on body mass index (BMI), blood pressure (systolic and diastolic), serum total cholesterol (TC) and High-density lipoprotein cholesterol (HDL-C) on Iraqi people since these parameters have been recognized by WHO Iraq Office Website as the area where the actions should be acted to improve the public health outcome.

MATERIALS AND METHODS

Participants

This study was a non-blinded, randomized

trial which has been designed to discover the prevention role of supplemental doses of vitamin D. It has been approved and registered by an ethical committee in Al-Manara college of medical sciences/Ministry of Higher Education and Scientific research//Iraq with registration No: 317 Date:30-05-2021.

Inclusion criteria

All participants gave written informed consent and appeared healthy, men were 13 (59%) and women were 9 (41%), aged (20-41) years old with a body mass index (BMI) range between 27.1 and 32.36 kg.m⁻². A body mass index (BMI) above 25 kg.m⁻² is classified as overweight, and over 30 kg.m⁻² is considered obese.

Exclusion criteria

Individuals with any history of diabetes mellitus (DM), cardiovascular disease (CVD), malabsorption, renal disease, liver disease, difficulty in swallowing tablets or capsules, or who were taking medications or supplements (with or without vitamin D3) known to affect any dependent variable were excluded. Pregnant or lactating women and women who taking contraceptive medications were not included.

Study designs

After the interview, the subjects went to a screening visit. If the inclusion criteria were achieved, the next visit and baseline assessment were performed in the fasting state within 1 week. Heights, weights, and blood pressure were measured as well as fasting blood samples were drawn. At this visit, all subjects were given a daily supplement of vitamin D3 throughout the 12 weeks. The participants were given oral information and written recommendation on a healthy diet. The subjects were randomized into two groups, group A takes one tablet of vitamin D 200 IU per day, and group B on 200 IU per day. The laboratory staff or the investigators had no contact with the study participants, and neither knew the group status of the participants. Fasting blood samples were drawn and blood pressure and weights were measured after 0, 4, 8, and 12 weeks of the study (Figure 1).

Adverse events

Five adverse events were reported, four from participants in group B and one from group A. Three participants in group B reported nausea, and joint pain, however, the events spontaneously disappeared within 1-2 days and all three remained

in the study. Tachycardia occurred in 2 subjects in group B and was excluded, and hypertension occurred in 1 subject in group A also excluded. None of them seem to be related to the study intervention.

Follow-up and measures

Anthropometric measurements at baseline 0, 4, 8, and 12 weeks were taken by trained staff at Almanara college of medical sciences/Iraq. Body weight was measured after an overnight fasting state without shoes and in minimal clothing using a digital scale (Rossmax BMI Body fat weighing scale WB220). Height was measured using a Seca tape measure (Seca, Hamburg, Germany). BMI was calculated by using MDCalc online Tools. Both systolic and diastolic blood pressure was measured with an automatic device at baseline (Rossmax CF155), and after every 4 weeks until the end of the study (12 weeks). The subjects were seated, rested for 5-10 min, and subsequently, two measurements of blood pressure were made at 2-min intervals in the morning and similarly two measurements in the evening. The mean value of the four measurements was used. Total cholesterol was measured using Free Cholesterol CHOD-POD Liquid (spinreact) and HDL- cholesterol was measured using HDL Cholesterol D Direct Enzymatic colorimetric (spinreact). All the work is performed according to the manufacturer's protocol.

Outcome

We evaluated the effects of vitamin D supplementation on BMI as a primary outcome over 12 weeks. In addition, both systolic and diastolic blood pressure, total serum cholesterol, and HDL cholesterol were also evaluated as secondary outcomes.

Statistical Analysis

Repeated measure ANOVA was performed to analyze our data using IBM® SPSS® Statistics (Statistical Package for the Social Sciences) version: 28.0.1.1 (15). Vitamin D groups and time are independent variables (IV) whereas BMI, systolic and diastolic blood pressure, TC, and HDL are dependent variables (DV). A P-value of $d > 0.05$ is considered significant. Within-subjects analyses were performed to see the effects of time on dependent variables, while between-subjects tests were performed to see the effect of vitamin D doses on the dependent variables across all time points.

Ethics statements

This study was conducted according to the principles of the Declaration of Helsinki, and the study design and protocols were approved by the ethics committee of Al-Manara college of medical sciences/ Ministry of Higher Education and Scientific research/Iraq with registration No: 317 Date:30-05-2021. All subjects were informed about the aims and protocol of our study. All participants gave written informed consent before conducting the study. However, we did not use a therapeutic dose of vitamin D and 200 and 2000 IU are considered supplemental and can be given without prescription (OTC).

RESULTS

Effect of two supplemental doses of vitamin D3 (200 IU and 2000 IU) on body mass index (BMI) at baseline, 4, 8, and 12 weeks of the study

The first aim of the current study is to investigate the impact of vitamin D supplementation on body mass index (BMI). Repeated measure ANOVA was conducted to see whether the body mass index of the subjects chosen would be affected by vitamin D3 supplements over 12 weeks of the study. Box's test for equivalence of covariance matrices indicates the assumption of homogeneity of covariances was met with a p-value larger than 0.001 (p-value=0.102). Mauchly's test of sphericity indicated the sphericity assumption was met (p-value=0.068). Hence, the multivariate test indicates that there were no statistically significant effects of vitamin D over time on BMI, Wilks' Lambda tests were 0.871 $F(3,18)=0.892$, p-value=0.464, Partial Eta Square=12.9%. In addition, it could not be seen significant effects of combined vitamin D*time interaction, Wilks' Lambda 0.847, $F(3,18)=1.081$, p-value=0.382, Partial Eta Square=15.3%. The pairwise comparison indicates that there was no obvious difference in BMI across all paired comparisons (p value>0.05) (Bonferroni adjusted paired t-test).

The test between subjects effects which means the main effects of grouping variables (200 IU and 2000 IU vitamin D) on BMI across all times has shown no statistically significant effects, $F(1,20)=0.137$, p-value=0.715, Partial Eta Square=7%. Finally, it could not be found any

significant difference neither within the subject body mass indexes nor between groups of vitamin D3 supplementation over all the time points. Figure 2 shows the effects of vitamin D over time and on BMI.

Effect of two supplemental doses of vitamin D3 (200 IU and 2000 IU) on systolic and diastolic blood pressure at baseline, 4, 8, and 12 weeks of the study

In the case of systolic blood pressure, repeated measure ANOVA was conducted and have

shown that there were no significant effects of 2 supplemental doses of vitamin D on systolic blood pressure. Box’s test for equivalence of covariance matrices indicates the assumption of homogeneity of covariances was met with a p-value larger than 0.001 (p value=0.011). Mauchly’s test of sphericity indicated the sphericity assumption was not met (p value=0.001), however, it was adopted to evaluate the Greenhouse-Geisser and Huynh-Feldt (epsilon 0.413 and 0.448 respectively). Within-subject effects, the univariate repeated measure

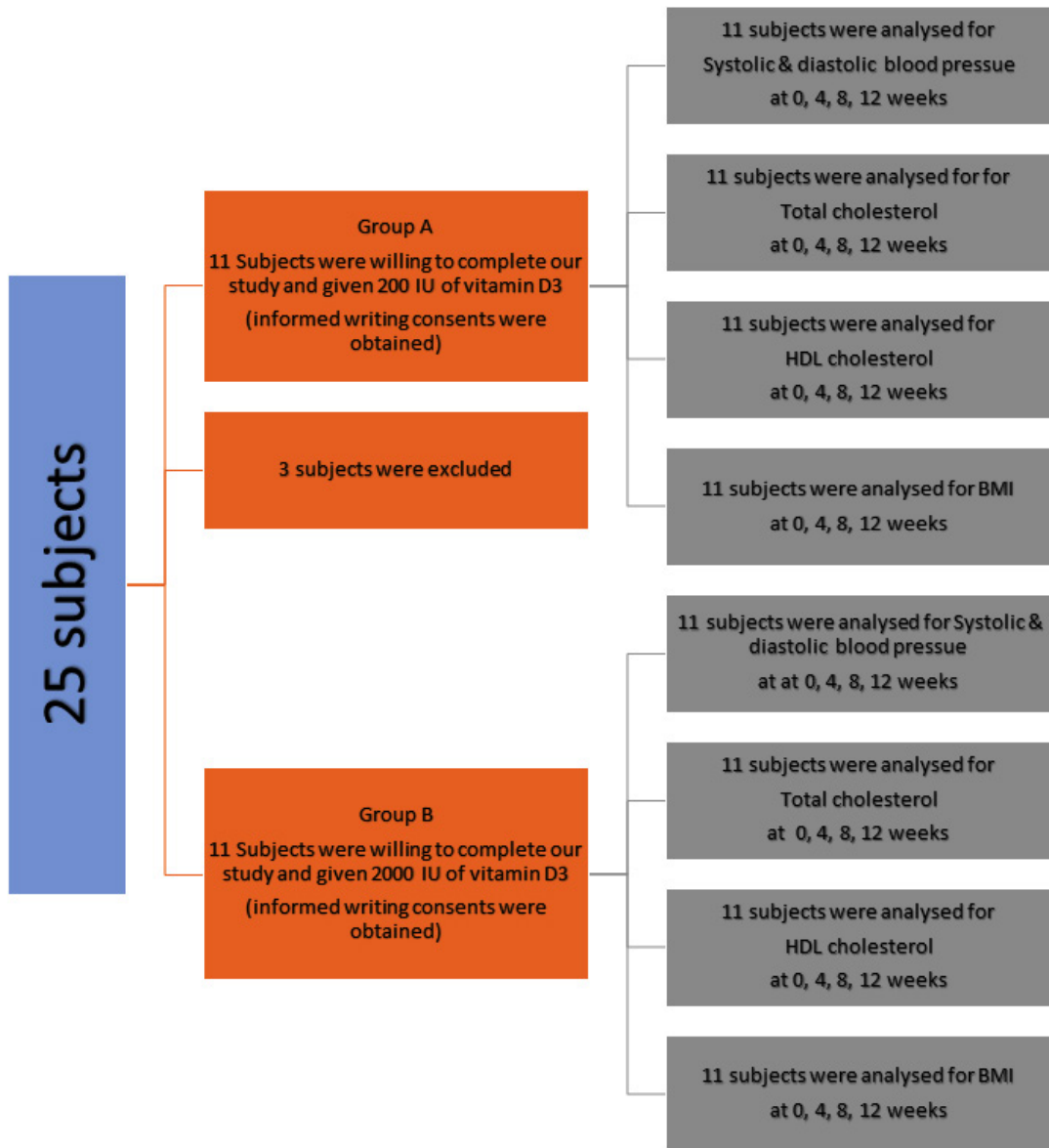


Fig. 1. Study Design

ANOVA with the Greenhouse-Geisser method of correction indicated there was no significant effect of time in both groups on systolic blood pressure, $F(1.238, 24.766)=0.647$, p value=0.461, Partial Eta Square=0.03. In addition, this was not qualified by supplements*time interaction, Greenhouse

Geisser $F(1.238,24.766)=0.864$, p -value=0.385, Partial Eta Square=0.041. The pairwise comparison indicates that there was no difference in systolic blood pressure across all paired comparisons (p value>0.05) (Bonferroni adjusted paired t-test).

Additionally, the test between subjects effects which means the main effects of grouping variables (200 IU and 2000 IU vitamin D) on systolic blood pressure across all times has shown no statistically significant effects, $F(1,20)=2.244$, p -value=0.150, Partial Eta Square=10.1%. Figure 3 shows the estimated marginal means of systolic blood pressure across the time points.

In the case of diastolic blood pressure, repeated measure ANOVA was also conducted and has shown that there were no significant effects of 2 supplemental doses of vitamin D on diastolic blood pressure. Box's test for equivalence of covariance matrices indicates the assumption of homogeneity of covariances was met with a p -value larger than 0.001 (p -value=0.191). Mauchly's test of sphericity indicated the sphericity assumption was

Table 1. Relevant demographics of research participants

Sample Characteristics	Number	Percentage
Gender		
Women	9	40.90%
Men	13	59.10%
Age Group		
18-29	14	63.60%
30-39	6	27.3%
40-50	2	9.1%
Incidence of Obesity		
Overweight	18	81.80%
Obese	4	18.20%

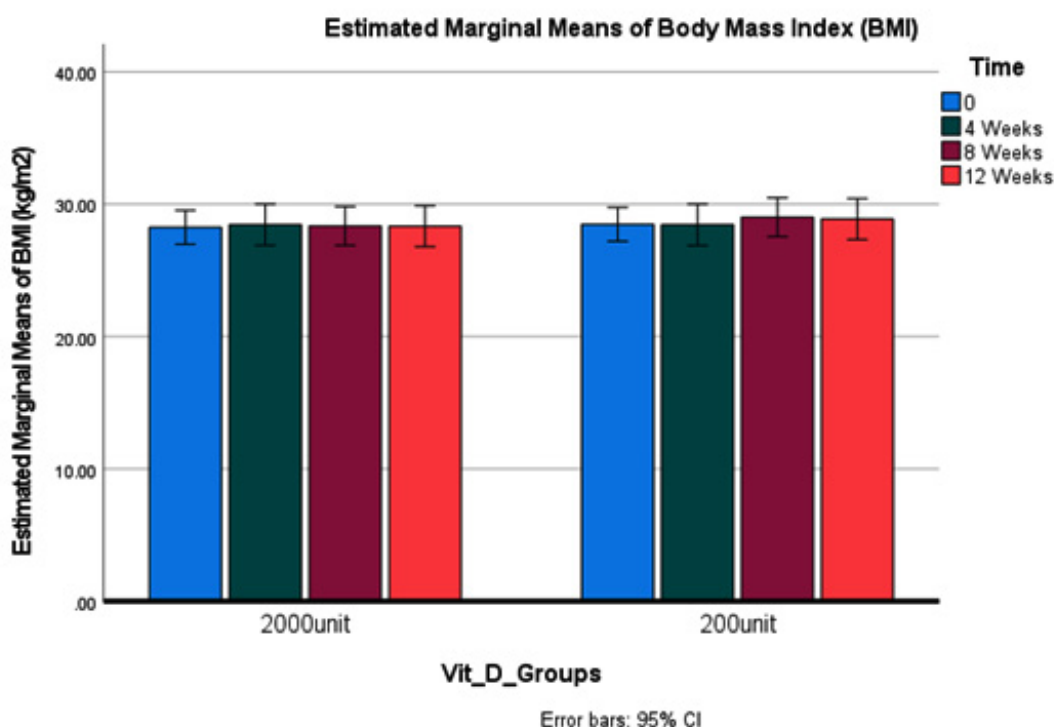


Fig. 2. The bar chart shows the effects of two different doses of vitamin D on body mass index (kg/m²) over multiple time points. 0 time means the baseline while other time points refer to 4, 8, and 12 weeks after induction of supplementations

met (p -value=0.731). Hence, the multivariate test indicates that there were no statistically significant effects of time on diastolic blood pressure, Wilks' Lambda tests were 0.990 $F(3,18)=0.060$, p -value=0.980, Partial Eta Square=10%. However, it could be seen significant effects of combined vitamin D*time interaction Wilks' Lambda 0.632, $F(3,18)=3.489$, p -value=0.037, Partial Eta Square=36.8%. The pairwise comparison indicates that there was no difference in diastolic

blood pressure across all paired comparisons (p value>0.05) (Bonferroni adjusted paired t -test).

The test between subjects effects which means the main effects of 200 IU and 2000 IU vitamin D groups on diastolic blood pressure across all time has shown no statistically significant effects, $F(1,20)=1.071$, p -value=0.313, Partial Eta Square=5.1%. Figure 4 shows the effects of time and vitamin D on diastolic blood pressure.

Table 2. Baseline characteristic of study participants

Baseline	VIT_D_200 IU		VIT_D_2000 IU	
	Group A Mean	N=11 SD	Group B Mean	N=11 SD
Age	27.27	8.101	26.09	7.79
BMI kg/m ²	28.49	2.13	28.25	1.93
BP (Systolic)	115.91	13.103	123.91	12.15
BP (Diastolic)	74.09	10.719	81.45	8.66
Cholesterol (mg/dl)	173	30.29	187.45	28.79
HDL (mg/dl)	43.55	10.15	37	7.67

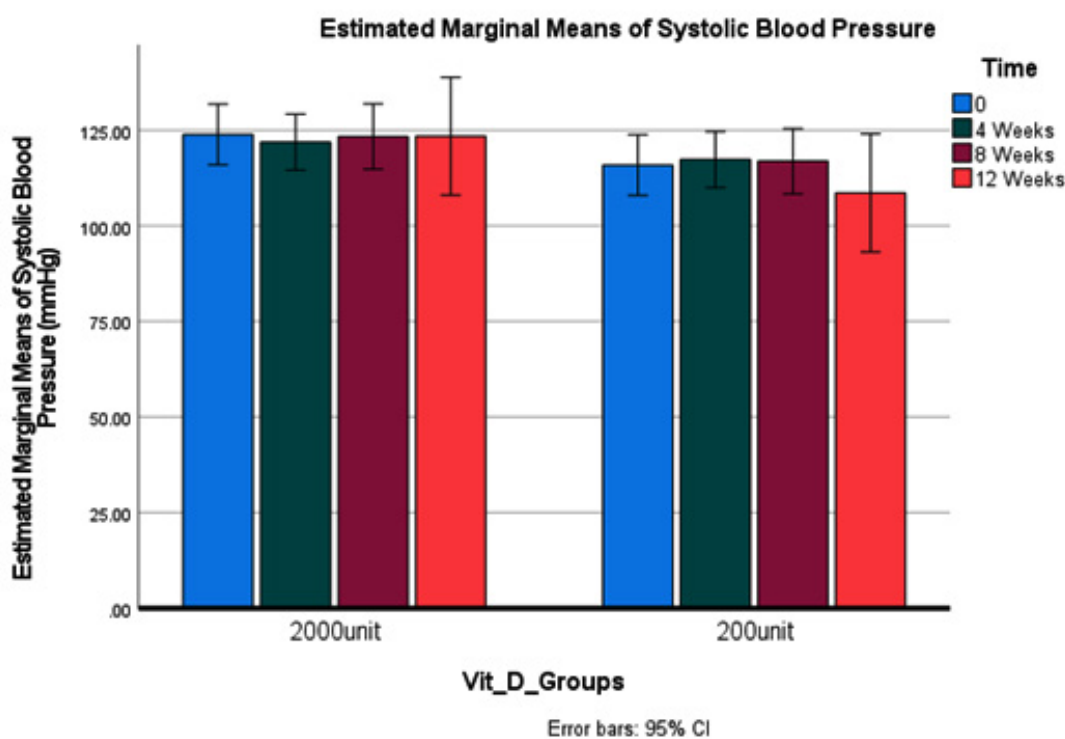


Fig. 3. The bar chart shows the effects of two different doses of vitamin D on systolic blood pressure over multiple time points. 0 time means the baseline while other time points refer to 4, 8, and 12 weeks after induction of supplementations.

In conclusion, A clear benefit of vitamin D on systolic and diastolic blood pressure could not be identified in this analysis.

Effect of two supplemental doses of vitamin D3 (200 IU and 2000 IU) on serum total cholesterol level at baseline, 4, 8, and 12 weeks of the study

Repeated measure ANOVA was also conducted to investigate whether the two doses of vitamin D have an effect on serum total

cholesterol over 12 weeks period. It has shown that there were no significant effects. Box's test for equivalence of covariance matrices indicates the assumption of homogeneity of covariances was met with a p-value larger than 0.001 (p value= 0.372911). Mauchly's test of sphericity indicated the sphericity assumption was not met (p value= 0.001), however, it was adopted to evaluate the Greenhouse Geisser and Huynh Feldt (epsilon

Table 3. Characteristics of study participants after 12 weeks of vitamin D supplements

Vit_D_3 months	VIT_D_200 IU		VIT_D_2000 IU	
	Group A Mean	N=11 SD	Group B Mean	N=11 SD
Age	27.27	8.101	26.09	7.79
BMI kg\m2	28.88	2.64	28.34	2.26
BP (Systolic)	108.64	33.09	123.45	10.54
BP (Diastolic)	75.36	6.313	79.09	9.803
Cholesterol (mg/dl)	177.27	33.45	185.18	30.64
HDL (mg/dl)	44.52	10.76	40.45	9.06

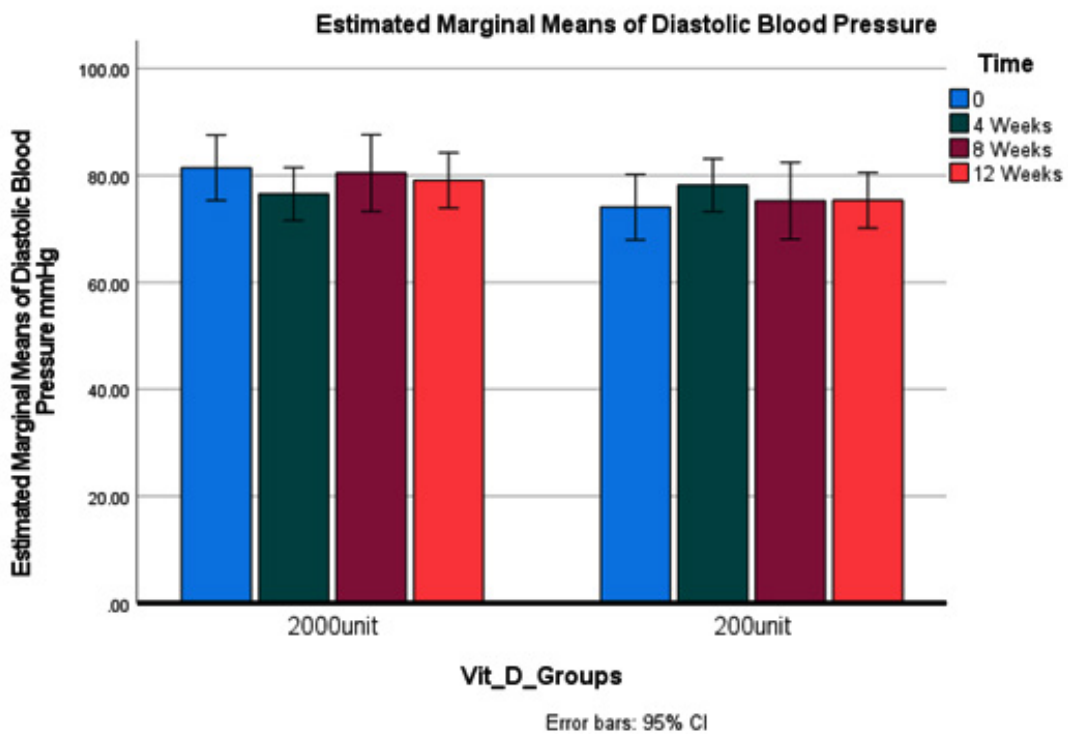


Fig. 4. The bar chart shows the effects of two different doses of vitamin D on systolic blood pressure (mmHg) over multiple time points. 0 time means the baseline while other time points refer to 4, 8, and 12 weeks after induction of supplementations.

.641 and 0.743 respectively). Within-subject effects, the univariate repeated measure ANOVA with Greenhouse Geisser method of correction indicated there was no significant effect of time in both groups of the study on serum total cholesterol, $F(1.924, 38.473)=1.616$, p value=0.212, Partial Eta Square=7.5%. In addition, this was not qualified by vitamin D3 group*time interaction, Greenhouse Geisser $F(1.924, 38.473)=0.413$, p -value=0.657, Partial Eta Square=2%. The pairwise comparison indicates that there was no difference in serum total cholesterol across all paired comparisons (p value>0.05) (Bonferroni adjusted paired t-test).

Additionally, the test between subjects effects which means the main effects of grouping variables (200 IU and 2000 IU vitamin D) on total cholesterol across all time has shown no statistically significant effects, $F(1,20)=0.556$, p -value=0.465, Partial Eta Square=2.7%. Figure 5 shows the estimated marginal means of TC across the time points.

Effect of two supplemental doses of vitamin D3 (200 IU and 2000 IU) on serum HDL-cholesterol level at baseline, 4, 8, and 12 weeks of the study

As described earlier, repeated measure ANOVA was also conducted to see any effects of vitamin D3 supplements on HDL-cholesterol over 12 weeks of study and we could not see any significant difference in serum HDL-cholesterol levels in both groups of vitamin D over the time of the study. Box's test for equivalence of covariance matrices indicates the assumption of homogeneity of covariances was met with a p -value larger than 0.001 (p -value=0.551). Mauchly's test of sphericity indicated the sphericity assumption was met (p -value=0.452). Hence, the multivariate test indicates that there were no statistically significant effects of vitamin D over time on HDL-cholesterol, Wilks' Lambda tests were 0.863 $F(3,18)=0.950$, p -value=0.438, Partial Eta Square=12.8%. In addition, it could not be seen significant effects of combined vitamin D*time

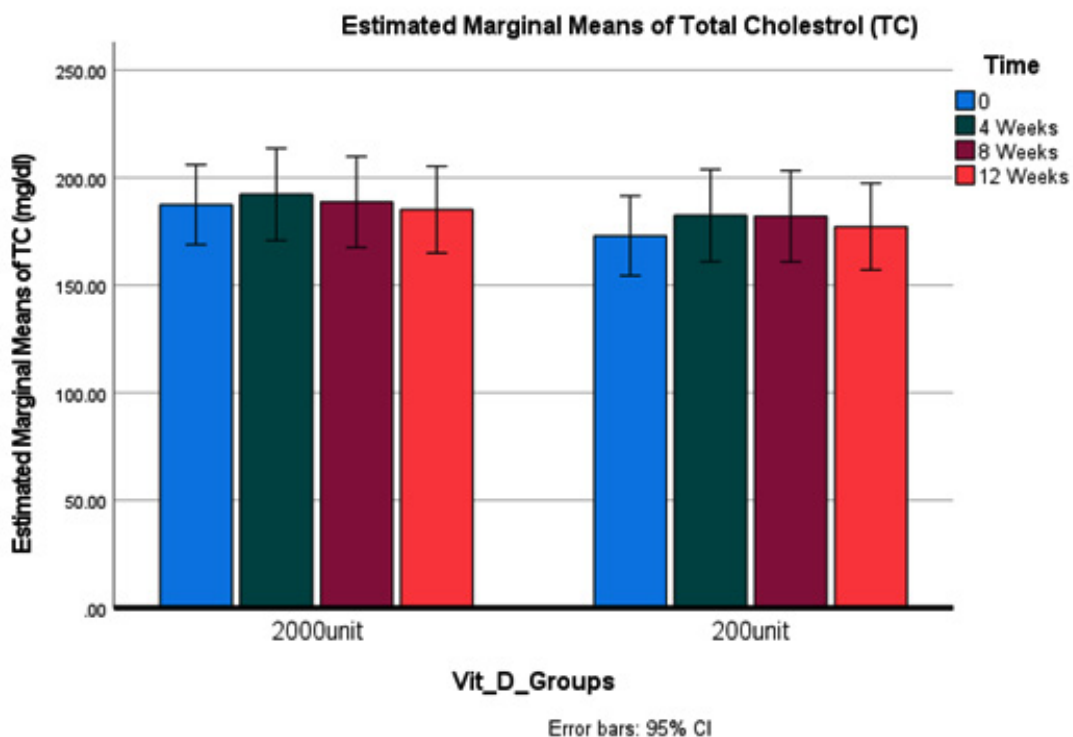


Fig. 5. The bar chart shows the effects of two different doses of vitamin D on serum total cholesterol (mg/dl) over multiple time points. 0 time means the baseline while other time points refer to 4, 8, and 12 weeks after induction of supplementations

interaction, Wilks' Lambda 0.872, $F(3,18)=0.881$, $p\text{-value}=0.469$, Partial Eta Square=36.8%. The pairwise comparison indicates that there was no difference in serum HDL-Cholesterol across all paired comparisons ($p\text{ value}>0.05$) (Bonferroni adjusted paired t-test).

The test between-subjects effects of grouping variables (200 IU and 2000 IU vitamin D) on serum HDL-cholesterol across all times has shown no statistically significant effects, $F(1,20)=1.100$, $p\text{-value}=0.307$, Partial Eta Square=5.2%. Figure 6 shows the effects of vitamin D and time on serum HDL cholesterol.

DISCUSSION

Being overweight and obese have been considered risk factors for several chronic and metabolic diseases, including cardiovascular diseases and diabetes which are the leading causes of death worldwide. Many risk factors for overweight and obesity are preventable and

modifiable ⁴. The association between vitamin D deficiency and body mass index is debatable. In 2018, a meta-analysis and systematic review of 55 observational studies were carried out and concluded that "the vitamin D deficiency could be associated with an increased BMI of both diabetic and non-diabetic subjects, however, they recommended more robust randomized, double-blinded future study to overcome the limitation of the observational studies ¹⁶. Our study could not detect any evidence of that effects at both 200 and 2000 IU on BMI across multiple time points.

Hypertension could be caused by being overweight and obese and is a major health burden and a fundamental risk factor for coronary artery disease, stroke, renal diseases, peripheral vascular diseases, etc ¹⁷. The previous literature investigated the role of vitamin D in many different doses on blood pressure and has observed inconsistent results on whether it has positive or negative consequences. It has been reported in a different experimental study that VDR (vitamin D receptor)

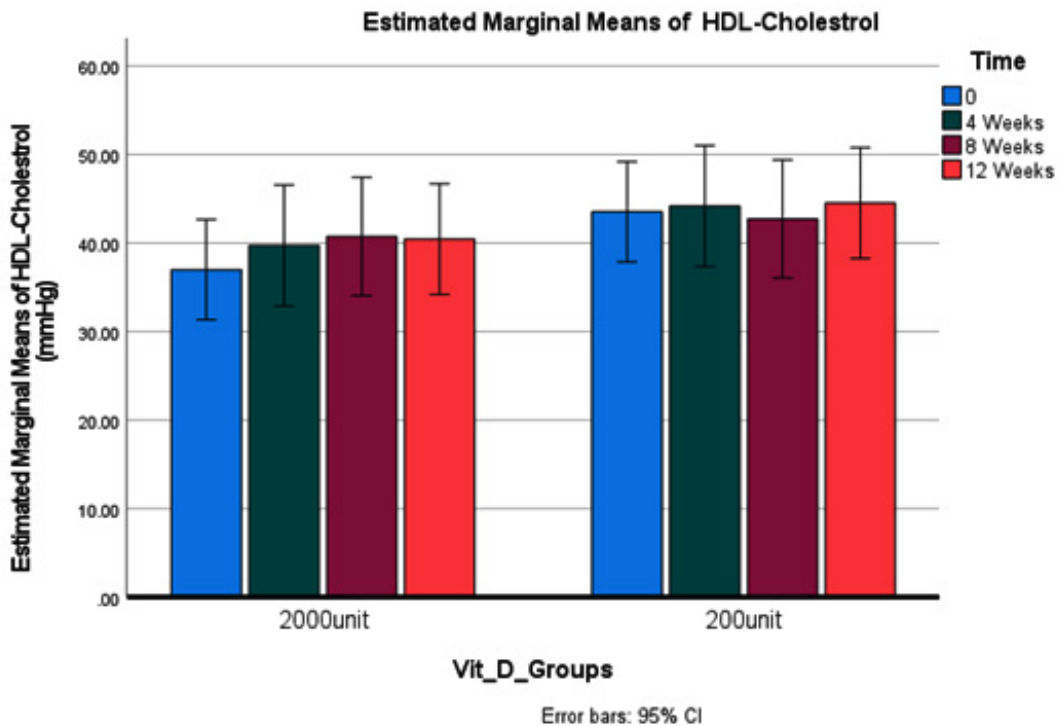


Fig. 6. The bar chart shows the effects of two different doses of vitamin D on serum HDL-cholesterol (mg/dl) over multiple time points. 0 time means the baseline while other time points refer to 4, 8, and 12 weeks after induction of supplementations

deficiency is associated with increases in both systolic and diastolic blood pressure^{18,19}. A group of researchers investigated a total of 491 healthy subjects without any chronic diseases, ages 21 to 67 at baseline and followed up over 8 year period. Accordingly, they have concluded “vitamin D deficiency is a potential risk for blood pressure elevation and the development of hypertension” in an 8-year follow-up²⁰. Another clinical study has shown that vitamin D3 could affect both mean arterial pressure and systolic pressure but not diastolic one after 8 weeks of study²¹. In contrast to the above findings, our study has been unable to identify a statistically significant effect of vitamin D (200 and 2000 IU tablets) on both systolic and diastolic blood pressure. Our set of results is consistent with those that have been seen by^{22,23}.

The results of previous research which examined the effects of vitamin D on serum lipids are conflicting. Positive effects have been reported in some of them^{11,10}. The debate about whether vitamin D has effects gained fresh prominence over decades. The two main meta-analysis studies have shown contradictory findings on lipid profiles. A meta-analysis of 12 randomized controlled trials (1346 participants) has indicated that “No statistically significant effects for vitamin D supplementation were observed for TC, HDL-C and TG (differences in means were 1.52 mg/dl (-1.42 to 4.46 mg/dl), -0.14 mg/dl (-0.99 to 0.71 mg/dl) and -1.92 mg/dl (-7.72 to 3.88 mg/dl) respectively)”²⁴. However, in 2019 meta-analysis of a total of 41 randomized control clinical trials (RCTs) comprising 3434 participants found a beneficial effect on total cholesterol, LDL-cholesterol, and triglyceride but no effects on HDL cholesterol²⁵. In our research, a clear benefit of supplemental doses of vitamin D (200 and 2000 IU tablets) on serum total cholesterol, and HDL-cholesterol could not be identified in this study.

CONCLUSION

The current research aimed to examine the effect of supplemental doses of vitamin D3 on BMI, blood pressure, serum total cholesterol, and HDL-cholesterol across multiple time points (0, 4, 8, and 12 weeks). The results of the current research have not detected statistically significant effects on the above-mentioned parameters.

Limitation

The scope of this research was limited in terms of sample size, study period, and exposure to sunlight. Further researches need to investigate in depth the effect of multiple doses of vitamin D3 on all cardiovascular risk parameter including subjects with metabolic syndrome with a large sample size in good design randomized, double-blinded, clinical trial. Finally, it can be said that our evidence was considered to be of mild to moderate quality depending on all the strengths and weaknesses of the study.

ACKNOWLEDGMENT

Special thanks to Al-Manara college for medical sciences and to the people who took part in the study as study subjects and investigators who did the laboratory assessment.

Conflict of Interest

There is no conflict of interest.

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