Journal of Health, Population and Nutrition

RESEARCH

Open Access

Effects of vitamin D supplementation on symptoms and clinical outcomes in adults with different baseline vitamin D levels: an interventional study

Osama Albasheer[1*], Siddig Ibrahim Abdelwahab[2], Ahmad Alqassim[1], Hatim Alessa[3], Afnan Madkhali[3], Afaf Hakami[3], Jamal Mohieddin[3], Anas E. Ahmed[1], Suhaila Ali[1], Amani Abdelmola[1], Omar Oraibi[4], Amal. H. Mohamed[4], Gassem Gohal[5], Ahmed Abdallah Altraifi[6] and Isameldin E. Medani[6]

Abstract

Background Hypovitaminosis D or vitamin D deficiency is a significant public health issue. Several vitamin D preparations are currently available. However, there is no consensus on the optimal dose and duration of vitamin D supplementation. This study aimed to evaluate the effects of vitamin D supplementation on symptoms and clinical outcomes in adults with insufficient or deficient baseline vitamin D levels.

Method A pre-post two-month intervention with 50,000 IU vitamin D3 supplementation for adults with documented insufficient or deficient baseline vitamin D levels, presented at Jazan University Hospital from August to December 2022.

Results Of the 204 participants, 65.1% had baseline vitamin D levels < 30 nmol/L. Vitamin D insufficiency is more prevalent among females, older adults, married individuals, and those with low income. However, these differences were not statistically significant ($p > 0.5$). The symptoms and clinical outcomes were significantly improved after 2 months of vitamin D3 supplementation for the participants who achieved vitamin D levels > 50 nmol/L ($p = 0.000$). After adjusting for multiple confounders, the significant determinants of symptom improvement and clinical outcomes post-supplementation included education level, income, smoking status, and baseline vitamin D level.

Conclusions Hypovitaminosis D or vitamin D deficiency was observed in study participants. The use of a 50,000 IU cholecalciferol (vitamin D3) orally once per week for two months is sufficient to improve the symptoms and clinical outcomes of vitamin D deficiency. However, long-term follow-up could better assess the sustainability of benefits and explore long-term outcomes, such as the risk of deficiency recurrence.

Clinical trial number Not applicable

Keywords Vitamin D, Sufficiency, Deficiency, Supplementation, Intervention, Clinical outcomes

*Correspondence:
Osama Albasheer
drosama802@gmail.com; oabasheer@jazanu.edu.sa

Full list of author information is available at the end of the article

Introduction

Vitamin D is endogenously produced during exposure to sunlight [1]. Additionally, vitamin D can be found naturally in some foods, added to other foods, and used as a nutritional supplement. It is crucial to regulate the metabolism of calcium and phosphate to maintain adequate bone mineralization and skeletal health [2, 3]. Deficient or insufficient levels of vitamin D can cause rickets in children, osteoporosis in older adults, and osteomalacia in the elderly [4]. Several large observational cohorts have shown a correlation between vitamin D insufficiency and an increased risk of fractures, fatigue symptoms, muscle pain, bone and lower back pain, and symptoms of depression [4–7]. There is controversy regarding the evaluation of vitamin D insufficiency by measuring serum 25-hydroxy vitamin D concentrations, specifically regarding the appropriate cut-off point(s) and the accurate levels that can be used to define low vitamin D status [8]. Currently, the most effective biomarker to determine vitamin D status is thought to be the sum of the 25-hydroxy vitamin D2 and 25-hydroxy vitamin D3 concentrations [9, 10]. Researchers have not definitively determined the serum levels linked to deficiency (as in rickets or osteomalacia) and sufficiency for overall health, particularly bone health. Nevertheless, there is consensus that individuals are generally considered to be at an increased risk of vitamin D insufficiency when their serum 25-hydroxy vitamin D concentration is less than 30 nmol/L (12 ng/mL), at risk of inadequacy when their concentration is 30–50 nmol/L (12–20 ng/mL), and not at risk when their concentration is 50 nmol/L (20 ng/mL) or above [11].

Saudi Arabia has a high prevalence of vitamin D insufficiency [12]. In addition, a significantly high prevalence of vitamin D insufficiency has been documented in children [13], adolescent girls [14] and the elderly [15]. This puts these groups at a higher risk of acquiring vitamin D insufficiency-related conditions, including musculoskeletal, cerebrovascular, and mental health disorders [14, 16]. Several previous studies have revealed that a variety of socio-demographic, clinical, and genetic predictors influence vitamin D status and impact vitamin D interventions [17–19]. Generally, it is documented that, to raise the serum levels of vitamin D by 25 nmol/L, supplements containing 1,000 IU vitamin D must be taken for three to four months [20]. However, there are no established recommendations for the amount or length of time vitamin D should be taken [21]. Hence, this study aimed to evaluate the effect of vitamin D supplementation on symptoms and clinical outcomes in adults whose baseline vitamin D levels are inadequate or deficient.

Methods

Study design; a pre-post interventional study

Study area: Family Medicine Clinics at Jazan University Hospital between August and December 2022.

Study population: All patients aged ≥ 18 years old, tested for Vitamin D status, regarded less of their presentation. The patients were grouped according to their initial vitamin D levels (deficient, insufficient, and sufficient). To lower the risk of falls and fractures in the elderly population, the "International Society for Clinical Densitometry" and the "International Osteoporosis Foundation" recommend minimum blood levels of 25-hydroxyvitamin D of 30 nmol/L [22]. In accordance with their advice, in the current investigation, we classified baseline vitamin D levels > 50 nmol/L (20 ng/mL) as sufficient, 30–50 nmol/L (12–20 ng/mL) as insufficient, and less than 30 nmol/L (12 ng/mL) as deficient. All those found to have inadequate or low vitamin D levels received 50,000 IU cholecalciferol (vitamin D3) orally once per week for two months.

Participant selection

Inclusion Criteria: Adults (aged 18 or older) with documented deficiency or insufficient baseline vitamin D levels, presence of symptoms or clinical concerns that could be related to vitamin D deficiency (e.g., fatigue, muscle pain, bone discomfort), and willingness to participate in the supplementation phase. Exclusion Criteria: Individuals with conditions affecting vitamin D metabolism (e.g., hyperparathyroidism), those with severe chronic illnesses, children (aged less than 18), pregnant women or women on breastfeeding (unless specified), and those already taking high-dose vitamin D supplements.

Sample size

We used the rule of thumb [23] for sample size calculation, as we planned to use multivariate analysis in this study. A common rule of thumb for the sample size in multivariate analysis is to have at least 10–15 observations per predictor variable. The minimum estimated sample size was 100 patients for the 10 variables. We had a sample size of 204 patients, which is well above the minimum and preferred numbers, to provide sufficient power to detect significant relationships and interactions between predictors and outcomes.

Intervention details

Participants received 50,000 IU of cholecalciferol (vitamin D3) tablets orally once per week for eight weeks (two months). Cholecalciferol (D3) was chosen over ergocalciferol (D2) due to its longer half-life and superior ability to maintain elevated 25(OH)D levels. Previous research has shown that 25(OH)D2 levels decline to baseline within 14 days, while 25(OH)D3 remains elevated at day

28. A two-month supplementation period was selected based on prior studies demonstrating that weekly 50,000 IU cholecalciferol for eight weeks effectively raises serum 25(OH)D levels. While some studies use a 12-week intervention, we acknowledge that a longer timeframe may provide additional insights into sustained outcomes.

Data collection and outcome measures

Symptom and clinical outcome assessment

Symptoms were assessed at baseline and after supplementation using a structured, physician-assessed questionnaire derived from standardized instruments after explaining the objectives and consent for participation. Socio-demographic information such as gender, age group, marital status, income, BMI (body mass index), and educational attainment were gathered, along with information on potential health outcomes such as cardiovascular disease, hypertension, diabetes, kidney diseases, cancer, and cognitive impairment, as well as symptoms related to vitamin D deficiency, such as fatigue, muscle soreness, lower back pain, fractures, and depressive symptoms. Self-reported smoking and height and weight measurements were included in the questionnaire. We used standardized procedures to measure body weight and height to the nearest 0.1 kg and 0.1 cm, respectively. Weight in (kg) divided by height squired in (m) is the formula for BMI. Obesity was defined as a BMI of 30 or above.

Vitamin D level measurement

Individuals were tested for vitamin D serum levels as requested by their family physicians. Serum 25-hydroxyvitamin D [25(OH)D] levels were measured before and after the intervention using a chemiluminescence immunoassay (CLIA). The tests were conducted in a hospital laboratory, and the results were recorded using an electronic system.

Outcome comparison

Post-intervention levels were categorized as deficient (< 30 nmol/L), insufficient (30–50 nmol/L), or sufficient (> 50 nmol/L), and then the outcomes were compared between participants who reached normal (sufficient) vitamin D levels and those who still had low levels after supplementation have been done.

Statistical analysis

Data analysis was performed using SPSS version 20. Categorical variables are expressed as frequencies and percentages. The mean ± standard deviation (SD) and median ± interquartile range (IQR) were used to express continuous variables. Univariate logistic regression analysis was used to evaluate the predictors of vitamin D insufficiency. Differences were considered significant at $p < 0.05$. Multivariate robust logistic regression was used to identify the independent determinants of serum 25-hydroxy vitamin D concentrations below 25 nmol/L and 50 nmol/L.

Results

Table 1 interprets the association between socio-demographic factors and vitamin D levels; In terms of baseline vitamin D levels, 24.8% of males have levels less than 30 nmol/L, 11.2% have levels between 30 and 50 nmol/L, and 1.9% have levels greater than 50 nmol/L. 40.3% of females have levels less than 30 nmol/L, 21.4% have levels between 30 and 50 nmol/L, and only 0.5% have levels greater than 50 nmol/L. However, the difference, based on the genders, lacks statistical significance (p -value = 0.127). When it comes to the age group, compared to participants over 45 (15.0%), a greater proportion of participants under 45 (50%) are vitamin D deficient (vitamin D < 30 nmol/L). Again, the difference lacks statistical significance (p-value = 0.565). A higher proportion of married participants and all income groups are vitamin D deficient. Still, these differences lack statistical significance (p-value = 0.951and 0.090 respectively). Most of the participants are in the "Higher education" category (44.2%). While more educated participants appear to have better vitamin D levels, the p-value (0.018) suggests a statistically significant association between education level and vitamin D status. The p-value of 0.723 suggests that there is no statistically significant variation in vitamin D levels between individuals who smoke and those who do not.

Table 2 shows the distribution and correlation of the symptoms across several vitamin D levels. The majority of participants with fatigue (63.6%) were vitamin D-deficient (vitamin D < 30 nmol/L, $p = 0.623$). Muscle pain was more common in the participants with low vitamin D levels (63.6%). Bone pain appeared to be more common among those with low vitamin D levels (61.7%), but the p-value (0.854) suggested no significant association. No statistically significant association was found between vitamin D levels and joint pain ($p = 0.890$), low back pain ($p = 0.680$), history of fractures ($p = 0.353$), depressive symptoms ($p = 0.623$), stress ($p = 0.392$), or sleep disturbances ($p = 0.202$).

Table 3 presents the distribution of various comorbidities (bronchial asthma, hypertension, diabetes, and cardiovascular disease (CVD)) across different vitamin D levels. Most participants without bronchial asthma (62.6%) had vitamin D levels < 30 nmol/L. Only a small percentage of participants with asthma (2.4%) were included, making it difficult to draw strong conclusions. The p value (0.880) indicated no statistically significant association between vitamin D levels and bronchial asthma. Participants with hypertension tended to have

Table 1 The association between socio-demographic factors and vitamin D levels

	Vitamin D level			*P* Value
	< 30	30–50	> 50	
Gender				
Male	51 (24.8%)	23 (11.2%)	4 (1.9%)	0.127
Female	83 (40.3%)	44 (21.4%)	1 (0.5%)	
Age				
Less than 45	103 (50.0%)	47 (22.8%)	4 (1.9%)	0.565
More than 45	31 (15.0%)	20 (9.7%)	1 (0.5%)	
Marital Status				
Single	42 (20.4%)	25 (12.1%)	1 (0.5%)	0.951
Married	89 (43.2%)	40 (19.4%)	4 (1.9%)	
Divorced	1 (0.5%)	1 (0.5%)	0 (0.0%)	
Widow	2 (1.0%)	1 (0.5%)	0 (0.0%)	
Income				
Low	36 (17.5%)	14 (6.8%)	1 (0.5%)	0.090
Medium	61 (29.6%)	28 (13.6%)	0 (0.0%)	
High	37 (18.0%)	25 (12.1%)	4 (1.9%)	
Education				
Illiterate	12 (5.8%)	8 (3.9%)	0 (0.0%)	0.018
Primary	1 (0.5%)	0 (0.0%)	0 (0.0%)	
Secondary	30 (14.6%)	2 (1.0%)	0 (0.0%)	
Higher	91 (44.2%)	57 (27.7%)	5 (2.4%)	
Smoking				
Non-Smoker	121 (58.7%)	61 (29.6%)	4 (1.9%)	0.723
Smoker	13 (6.3%)	6 (2.9%)	1 (0.5%)	
Exercise				
Less than one hour	36 (17.5%)	13 (6.3%)	0 (0.0%)	0.400
One to three	81 (39.3%)	42 (20.4%)	3 (1.5%)	
Four to Six	16 (7.8%)	12 (5.8%)	2 (1.0%)	
Seven and more	1 (0.5%)	0 (0.0%)	0 (0.0%)	
BMI				
Underweight	2 (1.0%)	1 (0.5%)	0 (0.0%)	0.150
Normal	93 (45.1%)	43 (20.9%)	1 (0.5%)	
Overweight	32 (15.5%)	22 (10.7%)	3 (1.5%)	
Obese	7 (3.4%)	1 (0.5%)	1 (0.5%)	

lower vitamin D levels (11.2%); however, the majority of hypertensive individuals were still in the deficient range (7.3%). The p-value (0.831) suggested no significant association between vitamin D status and hypertension. Participants with diabetes showed a distribution similar to that of non-diabetic participants, predominantly within the vitamin D-deficient range. The p-value (0.154) was higher than 0.05, indicating no significant association between vitamin D levels and the presence of diabetes. The majority of participants with CVD had vitamin D deficiency or insufficiency, similar to those without CVD. The p-value (0.405) suggested no statistically significant association between vitamin D status and CVD.

Table 4 cross-tabulates the improvement in symptoms after 2 months of vitamin D3 supplementation against the post-intervention vitamin D levels (< 30, 30–50, and > 50 nmol/L). In the category of vitamin D level < 30 nmol/L; 4 participants (1.9% of the total sample) with vitamin D levels still below 30 nmol/L showed no improvement in symptoms and none of the participants in this category showed slight improvement or complete improvement. The p-value of 0.000 suggests this observation is statistically significant. In the next category where vitamin D level 30–50 nmol/L; A majority (23.8%) of participants with vitamin D levels between 30 and 50 nmol/L experienced slight symptom improvement, and a small proportion (2.4%) showed complete improvement. Only 8 participants (3.9% of the total) showed no improvement. This indicates some benefit in achieving vitamin D levels within this range, though optimal symptom relief may require even higher levels. In the last category where vitamin D level > 50 nmol/L: The majority of participants showed either slight improvement (22.3%) or complete improvement (44.2%) in symptoms. This suggests that achieving higher vitamin D levels (> 50

Table 2 The distribution and correlation of the symptoms across several vitamin D levels

	Vitamin D level			*P* Value
	< 30	30–50	> 50	
Fatigue				
No	3 (1.5%)	3 (1.5%)	0 (0.0%)	0.623
Yes	131 (63.6%)	64 (31.1%)	5 (2.4%)	
Muscle Pain				
No	3 (1.5%)	1 (0.5%)	0 (0.0%)	0.890
Yes	131 (63.6%)	66 (32.0%)	5 (2.4%)	
Bone Pain				
No	7 (3.4%)	3 (1.5%)	0 (0.0%)	0.854
Yes	127 (61.7%)	64 (31.1%)	5 (2.4%)	
Joint Pain				
No	6 (2.9%)	3 (1.5%)	0 (0.0%)	0.890
Yes	128 (62.1%)	64 (31.1%)	5 (2.4%)	
Low Back Pain				
No	5 (2.4%)	4 (1.9%)	0 (0.0%)	0.680
Yes	30.6	63 (0.0%)	5 (2.4%)	
Fractures				
No	134 (65.0%)	66 (32.0%)	5 (2.4%)	0.353
Yes	0 (0.0%)	1(0.5%)	0 (0.0%)	
Depression				
No	129 (62.6%)	66 (32.0%)	5 (2.4%)	0.623
Yes	5 (2.4%)	1 (0.5%)	0 (0.0%)	
Stress				
No	127 (61.7%)	66 (32.0%)	5 (2.4%)	0.392
Yes	7 (3.4%)	1 (0.5%)	0 (0.0%)	
Sleep Disturbances				
No	65 (31.6%)	41(19.9%)	2 (0.1%)	0.202
Yes	69 (33.5%)	26(12.6%)	3 (1.5%)	

Table 3 The distribution of various comorbidities across different vitamin D levels

	Vitamin D level			*P* Value
	< 30	30–50	> 50	
Bronchial Asthma				
No	129 (62.6%)	65 (31.6%)	5 (2.4%)	0.880
Yes	5 (2.4%)	2 (1.0%)	0 (0.0%)	
Hypertension				
No	119 (57.8%)	59 (28.6%)	4 (1.9%)	0.831
Yes	15 (7.3%)	8 (3.9%)	1(0.5%)	
Diabetes				
No	126 (61.2%)	58 (28.2%)	5 (2.4%)	0.154
Yes	8 (3.9%)	9 (4.4%)	0 (0.0%)	
CVD				
No	132 (64.1%)	64 (31.1%)	5 (2.4%)	0.405
Yes	2 (1.0%)	3 (1.5%)	0 (0.0%)	

nmol/L) is strongly associated with significant symptom improvement.

Table 5 presents the results of both crude and adjusted logistic regression analyses, examining the association between various independent variables (such as sex, age, marital status, levels of education, income, smoking, exercise, BMI, and baseline vitamin D levels) and a specific outcome (likely related to vitamin D levels or symptom improvement after supplementation). Females had lower odds of the outcome than males before adjusting for other variables (Crude OR 0.520, $p = 0.032$). After adjusting for other factors, the odds ratio for females was 0.623 ($p = 0.212$). This indicates that the association was no longer statistically significant after adjustment. The odds of the outcome were 1.641 times higher in individuals older than 45 years than in those aged

Table 4 Cross-tabulation of the improvement in symptoms after 2 months of vitamin D supplementation against the post-intervention vitamin D levels

			Symptoms after management			Total	*P* Value
			No improvement	Slight improvement	Improved		
Vitamin D	Less than 30	Count	4	0	0	4	0.000
		% of Total	1.9%	0.0%	0.0%	1.9%	
	30–50	Count	8	49	5	62	
		% of Total	3.9%	23.8%	2.4%	30.1%	
	More than 50	Count	3	46	91	140	
		% of Total	1.5%	22.3%	44.2%	68.0%	
Total		Count	15	95	96	206	
		% of Total	7.3%	46.1%	46.6%	100.0%	

Table 5 Logistic regression analyses of the association between various independent variables and related outcomes

Independent variables	*P*-value	Crude OR	95% C.I. for Crude OR		*P*-value	Adjusted OR	95% C.I. for Adjusted OR	
			Lower	Lower			Lower	Upper
Gender								
Male (Reference)								
Female	0.032	0.520	0.286	0.945	0.212	0.626	0.300	1.307
Age								
18–44 (Reference)								
more than 45	0.138	1.641	0.853	3.155	0.967	0.982	0.418	2.306
Marital Status								
Single (Reference)								
Married	0.138	1.640	0.853	3.153	0.706	0.835	0.326	2.138
Divorced	0.446	3.000	0.178	50.615	0.824	1.408	0.069	28.922
Widow	0.747	1.500	0.128	17.600	0.852	0.745	0.034	16.379
Income					0.083			
Low (SAR 1–3 K) (Reference)								
Medium (SAR 4–8 K)	0.479	1.343	0.594	3.034	0.049	2.945	1.004	8.643
More than SAR8K	0.005	3.221	1.413	7.342	0.003	6.864	1.900	24.793
Smoking								
Non-Smoker (Reference)								
Smoker	0.002	4.660	1.762	12.324	0.023	4.048	1.217	13.464
Exercise					0.477			
Less than one hour (Reference)								
One to three	0.193	0.632	0.316	1.262	0.420	0.698	0.292	1.670
Four to Six	0.851	0.914	0.357	2.338	0.855	1.111	0.360	3.424
Seven and more	1.000	0.000	0.000	.	1.000	0.000	0.000	.
BMI								
Underweight (Reference)								
Normal	0.899	0.854	0.075	9.684	0.520	2.637	0.137	50.664
Overweight	0.902	1.167	0.100	13.656	0.550	2.475	0.127	48.334
Obese	1.000	1.000	0.063	15.988	0.868	1.325	0.048	36.541
Education								
Illiterate (Reference)								
Primary	1.000	0.000	0.000	.	1.000	0.000	0.000	.
Secondary	0.180	0.455	0.144	1.438	0.399	0.527	0.119	2.337
University and above	0.079	0.430	0.168	1.103	0.005	0.148	0.039	0.569
Baseline vitamin D level								
Less than 30 (Reference)					0.008	2.710	1.295	5.671
30–50	0.008	2.293	1.238	4.250	0.631	0.558	0.052	6.031
More than 50	0.760	0.707	0.076	6.543	0.008	2.710	1.295	5.671

18–44 (reference); however, this association was not statistically significant ($p = 0.138$). After adjustment, the odds ratio decreased to 0.982, with a p-value of 0.967, indicating that age was not a significant predictor of the outcome after controlling for other variables. Regarding marital status, the crude OR for married individuals compared with single individuals (reference) was 1.640, with a p-value of 0.138, but it became non-significant after adjustment (Adjusted OR 0.835, p-value = 0.706). There was no strong association with the outcome for both divorced and widowed categories, as the Adjusted OR odds ratios were not statistically significant (adjusted OR = 1.408, and 0.745 respectively). Higher income (> SAR 8 K) was significantly associated with a higher odds of the outcome (Crude OR 3.221, $p = 0.005$). This association remained significant even after adjusting for other variables (Adjusted OR 6.864, $p = 0.003$), suggesting that higher income is a significant predictor of the outcome. Smokers had significantly higher odds of the outcome than non-smokers (Crude OR 4.660, $p = 0.002$). This association remained significant after adjustment (Adjusted OR 4.048, $p = 0.023$), indicating that smoking is a strong predictor of the outcome. Even after adjusting for other factors, exercise level and BMI were not significantly associated with the outcome, as indicated by the non-significant p-values ($p > 0.5$). Educational level had a significant impact on improvement ($p = 0.005$). Those with a university education or above were less likely to show improvement than the illiterate group (Adjusted OR 0.148). This suggests that other factors tied to education influence how individuals respond to interventions. Baseline vitamin D levels less than 30 were significant for the outcome, with a p-value of 0.008 and adjusted OR of 2.710, indicating that patients with baseline vitamin D levels of less than 30 nmol/L were 2.71 times more likely to improve compared to those with levels above 50 nmol/L, confirming the importance of initial deficiency in predicting response to supplementation. These nuanced changes in effect sizes underscore the complex interplay of independent variables in predicting the outcome and provide valuable insights for further analysis and decision-making processes.

Discussion

Vitamin D insufficiency is common worldwide. Currently, there are no clear guidelines for the amount and duration of vitamin D administration [21]. This study aimed to evaluate the symptoms and clinical outcomes of two months intervention with 50,000 IU vitamin D supplementation in adults with documented deficient or insufficient baseline vitamin D levels. The majority of individuals in this study reported low levels of vitamin D (less than 30 nmol/L), with certain groups (e.g., females, younger individuals, married participants) appearing more affected, although most of these differences were not statistically significant. A higher prevalence of low levels of vitamin D among females and younger populations could be related to spending more time indoors (e.g., due to school, work, or technology use) or using sunscreen extensively. Considering our findings, half of the world's population was reported to have vitamin D insufficiency, and approximately one billion individuals were vitamin D deficient [24]. In contrast, other studies report higher vitamin D insufficiency in the elderly because of reduced outdoor activity, mobility limitations, or time spent indoors in care facilities [15, 25]. In our study, variances in vitamin D levels were not significantly correlated with participants' BMI categories, indicating that BMI categories may not be strongly linked to variations in vitamin D levels. In contrast, a previous meta-analysis reported a significant association between obesity and vitamin D deficiency or insufficiency [26]. The variation in reported vitamin D deficiency or insufficiency among sex, age groups, and BMI categories can be explained by lifestyle factors, biological differences, and geographic location. Education level was significantly associated with vitamin D levels ($p = 0.018$), suggesting that higher education may be linked to better vitamin D status. This could be due to better awareness and better health practices among those with higher education.

It is well documented that individuals with vitamin D deficiency are more likely to experience multiple non-specific symptoms such as fatigue, joint pain, muscle pain, depression, and sleep disturbances [24]. In the current study, the majority of participants reporting symptoms such as fatigue, muscle pain, bone pain, joint pain, and lower back pain had vitamin D levels below 30 nmol/L, indicating a trend toward more symptoms in those with vitamin D deficiency. However, these trends did not reach statistical significance in this sample, as indicated by p-values being greater than 0.05. Supporting our findings, a large cohort of adults in the UK found that musculoskeletal pain was not significantly correlated with vitamin D levels, although individuals with severe deficiency often reported multiple symptoms [27]. While a clear, significant relationship between vitamin D levels and specific symptoms is not always observed, those with a deficiency tend to have a greater overall burden of non-specific, overlapping symptoms, which supports the broader role of vitamin D in general health.

Accumulating epidemiological and laboratory evidence are now showing an association between vitamin D deficiency and the onset and progression of many chronic diseases such as CVD, bronchial asthma, hypertension, diabetes, depression and cancer [24, 28]. In the current study, a trend was observed where the majority of participants with different comorbidities, such as bronchial asthma, hypertension, diabetes, and CVD, had low levels

of vitamin D (< 30 nmol/L). However, these trends did not reach statistical significance, as indicated by p-values all being greater than 0.05. The lack of statistically significant associations suggests that although lower vitamin D levels are prevalent among individuals with various comorbidities, this study does not provide strong evidence that vitamin D deficiency is directly associated with the presence of these comorbidities.

Existing evidence demonstrates a lack of consensus regarding the ideal and adequate duration of vitamin D administration [29–32]. The current study targeted only those with deficient or insufficient vitamin D levels and administered them 50,000 IU vitamin D3 supplement for two-months, in order to assess the effects of correcting vitamin D insufficiency, which is the primary population of interest for vitamin D supplementation. This approach avoids unnecessary supplementation in individuals who already have sufficient vitamin D levels, minimizes the risk of potential toxicity, and focuses resources on those who might benefit the most. The majority of participants who achieved vitamin D levels > 50 nmol/L experienced complete improvement in their symptoms; when levels were below 30 nmol/L, there was no improvement at all, and most participants in the intermediate range (30–50 nmol/L) experienced only slight improvement. Many studies have reported similar results. For instance, a systematic review showed that weekly administration of 50,000 IU vitamin D supplement is effective in raising serum vitamin D levels and improving related symptoms, especially in individuals with severe deficiency [33]. Saeidlou et al. discovered that when subjects with low and deficient levels of vitamin D were given a monthly supplement of 50,000 IU vitamin D for a year, their serum vitamin D level increased to a suitable level (> 30 nmol/L); however, the level did not increase above 50 ng/mL in the adequate group [21]. Another randomized clinical trial reported that a monthly supplement of 80,000 IU of vitamin D for 6 months was effective in correcting insufficient vitamin D levels [34]. Reactions to vitamin D administration can vary according to absorption rates, baseline vitamin D levels, and individual metabolic factors. Further studies are needed to optimize dosing based on specific patient characteristics and long-term outcomes.

In the current study, after adjusting for confounders, the significant determinants of symptom improvement and clinical outcomes post-supplementation included education level, income, smoking status, and baseline vitamin D level. Sex, age, marital status, exercise, and BMI did not show significant associations with the outcome after adjustment, indicating that these factors may not be strong predictors when considered alongside other variables. The associations between higher income and education and better clinical outcomes have been well documented in health research [35]. Higher-income groups often have better access to health care, nutrition, and preventive care, potentially leading to more consistent vitamin D supplementation or healthier diets that include vitamin D-rich foods. Interestingly, while higher education is typically associated with better health outcomes, our study's findings negatively impact vitamin D-related improvements. Higher education often correlates with better health outcomes due to increased awareness of health practices, but it can also result in more sedentary lifestyles, having more sedentary office jobs, or spending more time engaged in technology-based activities, hence reducing outdoor activities, or higher use of sunscreens that block UV exposure. This paradox could explain why those with higher education may not experience the same level of improvement as vitamin D supplementation. Highlighting this contrast more explicitly can clarify why a typical protective factor such as education shows a negative association in this context. In line with our findings, many studies have indicated that individuals with lower baseline levels of vitamin D respond more robustly to supplementation, showing significant improvements in symptoms such as depression, fatigue, muscle pain, and bone pain [36, 37]. The finding that smokers have higher odds of improvement could be related to the fact that smokers tend to report lower baseline vitamin D levels due to the negative impact of smoking on vitamin D metabolism [38, 39]. Consequently, these individuals might exhibit a greater response when supplemented.

Strengths and limitations of the study

The study targeted individuals with documented deficient or insufficient vitamin D levels, which enabled a precise evaluation of the impact of vitamin D supplementation. Excluding those with sufficient levels maximizes the focus on those who can benefit the most. The use of a 50,000 IU vitamin D3 dosage over two months aligns with established therapeutic strategies for correcting deficiency, providing a strong framework for assessing improvement in symptoms and clinical outcomes. The study was adjusted for multiple confounders (e.g., education level, income, smoking, and baseline vitamin D levels), which strengthens the validity of the conclusions by addressing potential biases. Furthermore, the study population and intervention aligned well with real-world clinical practices, making the findings potentially more generalizable to clinical settings dealing with vitamin D deficiency. However, while two months of supplementation is sufficient for some improvements, longer-term follow-up could better assess the sustainability of benefits and explore long-term outcomes, such as the risk of recurrence of deficiency. Despite adjusting for several variables, other unmeasured factors, such as

dietary habits, genetic differences in vitamin D metabolism, and adherence to supplementation protocols, could still affect the outcomes. Symptoms were assessed using a structured, physician-assessed questionnaire derived from standardized instruments. However, fully validated symptom assessment tools were not employed. This may introduce some degree of subjectivity in symptom reporting and limit the comparability of findings with studies using fully standardized instruments. The study employed a rule-of-thumb approach for determining sample size, ensuring at least 10–15 participants per predictor variable in multivariate analysis. While this method provided a sufficiently powered study, a formal power calculation was not conducted. Future studies should incorporate precise power calculations to optimize sample size and strengthen the robustness of statistical findings. The study primarily showed associations between vitamin D levels and symptoms or outcomes but did not explore the causal mechanisms or pathways by which vitamin D supplementation exerts its effects. The study noted that the response to supplementation may vary based on factors such as baseline vitamin D levels, smoking status, and education level, but did not explore why certain groups (e.g., smokers) responded better than others.

Conclusion

Baseline Vitamin D deficiency is a strong predictor of better outcomes after supplementation. Education showed a significant relationship, potentially highlighting the role of awareness and lifestyle choices in maintaining adequate vitamin D levels. These findings can inform targeted interventions to maintain adequate vitamin D levels in high-risk patients. Although vitamin D insufficiency is more commonly observed among those with various symptoms (e.g., fatigue and muscle pain), the lack of statistically significant associations suggests that other factors may also contribute to these symptoms. Further research with larger sample sizes or controlled trials is needed to explore these relationships more conclusively. In the current study, a trend was observed where most participants with various comorbidities were deficient or insufficient in vitamin D. However, due to the lack of statistically significant associations, it cannot be conclusively stated that vitamin D deficiency is directly related to these conditions. Larger studies or more controlled research might be necessary to further explore these relationships and understand the potential underlying mechanisms. These results strongly support the effectiveness of vitamin D supplementation in improving symptoms, especially when post-intervention levels exceed 50 nmol/L. This finding highlights the importance of achieving and maintaining sufficient vitamin D levels in the management of related symptoms. Future interventions should aim to elevate vitamin D levels above 50 nmol/L to achieve optimal symptom relief.

Acknowledgements
We acknowledge the participation of the patients. We extend our thanks for the laboratory staff for their help and support in vitamin D testing among the study participants.

Author contributions
"Conceptualization, O.A., A.A.,S.A., and S.I.A.; methodology, S.I.A.; soft-ware, H.E., A.M., A.H., J.M. and A.E.A.; validation, O.A., A.A.,S.A., and S.I.A.; formal analysis, O.A., A.H.M.; investigation, A.A.A.; resources, H.E., A.M., A.H., J.M., G.G., and A.E.A.; data curation, O.A., A.A.,S.A., and S.I.A.; writing—original draft preparation, O.A., A.A.,S.A.,A.A.A., I.M., G.G., and S.I.A.; writing—review and editing, O.A. and G.G.; visualization, S.I.A.; supervision, O.A.; project administration, O.A., A.A.,S.A., G.G., and S.I.A.; funding acquisition, O.A. All authors have read and agreed to the published version of the manuscript."

Funding
"This research received no external funding."

Data availability
No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate
The study was conducted in accordance with the Declaration of Helsinki, and approved by the Standing Committee for Scientific Research, Jazan University (HAPO-10-Z-001), Saudi Arabia (Reference No.: REC-44/06/463 on 2/1/2022). Informed consent was obtained from all subjects involved in the study.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

Author details
[1]Department of Family and Community Medicine, College of Medicine, Jazan University, Jazan 45142, Saudi Arabia
[2]Health Research Centre, Jazan University, Jazan, Saudi Arabia
[3]Department of Family Medicine, Jazan University Hospital, Jazan, Saudi Arabia
[4]Department of Internal Medicine, College of Medicine, Jazan University, Jazan, Saudi Arabia
[5]Department of Pediatric Medicine, Faculty of Medicine, Jazan University, Jazan, Kingdom of Saudi Arabia
[6]Department of Obstetrics and Gynecology, Obstetrics and Gynecology, Faculty of Medicine, Jazan University, Jazan, Saudi Arabia

Received: 17 September 2024 / Accepted: 12 April 2025
Published online: 29 May 2025

References

1. Xenos K, et al. Vitamin D supplementation and genetic polymorphisms impact on weight loss diet outcomes in Caucasians: a randomized double-blind placebo-controlled clinical study. Front Med. 2022;9:811326.
2. Erdman JW Jr, Macdonald IA, Zeisel SH. Present knowledge in nutrition. Wiley; 2012.
3. Ross AC, et al. Modern nutrition in health and disease. Jones & Bartlett Learning; 2020.
4. Aspray TJ, Hill TR. Osteoporosis and the ageing skeleton. Biochemistry and cell biology of ageing: Part II clinical science, 2019;453–476.
5. Pennisi M, et al. Decrease in serum vitamin D level of older patients with fatigue. Nutrients. 2019;11(10):2531.
6. Bansal D, et al. High prevalence of hypovitaminosis D in patients with low back pain: evidence from meta-analysis. Pain Physician. 2018;21(4):E389.

7. Menon V, et al. Vitamin D and depression: a critical appraisal of the evidence and future directions. Indian J Psychol Med. 2020;42(1):11–21.
8. Sempos CT et al. Vitamin D assays and the definition of hypovitaminosis D: results from the First International Conference on Controversies in Vitamin D. British journal of clinical pharmacology, 2018;84(10):2194–2207.
9. Dai Z, et al. Assessment of the methods used to develop vitamin D and calcium recommendations—a systematic review of bone health guidelines. Nutrients. 2021;13(7):2423.
10. Holick MF, et al. Evaluation, treatment, and prevention of vitamin D deficiency: an endocrine society clinical practice guideline. J Clin Endocrinol Metabolism. 2011;96(7):1911–30.
11. Cashman KD, Kiely M. EURRECA—Estimating vitamin D requirements for deriving dietary reference values. Crit Rev Food Sci Nutr. 2013;53(10):1097–109.
12. Al-Daghri NM. Vitamin D in Saudi Arabia: prevalence, distribution and disease associations. J Steroid Biochem Mol Biol. 2018;175:102–7.
13. Al Shaikh AM, et al. Prevalence of vitamin D deficiency and calcium homeostasis in Saudi children. J Clin Res Pediatr Endocrinol. 2016;8(4):461.
14. Al-Raddadi R, et al. Prevalence of lifestyle practices that might affect bone health in relation to vitamin D status among female Saudi adolescents. Nutrition. 2018;45:108–13.
15. Al-Daghri NM, et al. Decreasing prevalence of vitamin D deficiency in the central region of Saudi Arabia (2008–2017). J Steroid Biochem Mol Biol. 2021;212:105920.
16. Głąbska D, et al. The influence of vitamin D intake and status on mental health in children: a systematic review. Nutrients. 2021;13(3):952.
17. Whiting SJ, et al. Moderate amounts of vitamin D3 in supplements are effective in Raising serum 25-hydroxyvitamin D from low baseline levels in adults: a systematic review. Nutrients. 2015;7(4):2311–23.
18. Sollid S, et al. Large individual differences in serum 25-hydroxyvitamin D response to vitamin D supplementation: effects of genetic factors, body mass index, and baseline concentration. Results from a randomized controlled trial. Horm Metab Res. 2016;48(01):27–34.
19. Rees JR, et al. Lifestyle and other factors explain one-half of the variability in the serum 25-hydroxyvitamin D response to cholecalciferol supplementation in healthy adults. J Nutr. 2016;146(11):2312–24.
20. Cannell JJ, Hollis BW. Use of vitamin D in clinical practice. Altern Med Rev. 2008;13(1):6.
21. Saeidlou SN, et al. Determining the vitamin D supplementation duration to reach an adequate or optimal vitamin D status and its effect on blood lipid profiles: a longitudinal study. J Health Popul Nutr. 2024;43(1):81.
22. Dawson-Hughes B, et al. IOF position statement: vitamin D recommendations for older adults. Osteoporos Int. 2010;21(7):1151–4.
23. Cohen J. Statistical Power Analysis for the Behavioral Sciences, 2nd Edn. Hillsdale, NJ: Erlbaum. 1988.
24. Sizar O, et al. Vitamin D Deficiency.[Updated 2021 Jul 21]. StatPearls. Treasure Island (FL): StatPearls Publishing; 2021.
25. Palacios C, Gonzalez L. Is vitamin D deficiency a major global public health problem? J Steroid Biochem Mol Biol. 2014;144:138–45.
26. Pereira-Santos M, et al. Obesity and vitamin D deficiency: a systematic review and meta-analysis. Obes Rev. 2015;16(4):341–9.
27. Xie Y et al. Serum vitamin D and chronic musculoskeletal pain: A Cross-Sectional study of 349,221 adults in the UK. J Pain. 2024;(9):104557. https://doi.org/10.1016/j.jpain.2024.104557
28. Wang H, et al. Vitamin D and chronic diseases. Aging Disease. 2017;8(3):346.
29. Bader DA, et al. The effect of weekly 50,000 IU vitamin D3 supplements on the serum levels of selected cytokines involved in cytokine storm: a randomized clinical trial in adults with vitamin D deficiency. Nutrients. 2023;15(5):1188.
30. Hashemipour S, et al. Association of weekly or biweekly use of 50 000 IU vitamin D3 with hypervitaminosis D. Br J Clin Pharmacol. 2022;88(7):3506–9.
31. Apaydin M, et al. The effects of single high-dose or daily low-dosage oral colecalciferol treatment on vitamin D levels and muscle strength in postmenopausal women. BMC Endocr Disorders. 2018;18:1–8.
32. Mueangpaisarn P, Chaiamnuay S. A randomized double-blinded placebo controlled trial of ergocalciferol 40,000 versus 100,000 IU per week for vitamin D inadequacy in institutionalized postmenopausal women. Aging Clin Exp Res. 2020;32:41–8.
33. Mavar M, et al. The power of vitamin D: is the future in precision nutrition through personalized supplementation plans?? Nutrients. 2024;16(8):1176.
34. Penckofer S, et al. Vitamin D supplementation for the treatment of depressive symptoms in women with type 2 diabetes: a randomized clinical trial. J Diabetes Res. 2022;2022(1):4090807.
35. Lai ET, Yu R, Woo J. The associations of income, education and income inequality and subjective well-being among elderly in Hong Kong—A multilevel analysis. Int J Environ Res Public Health. 2020;17(4):1271.
36. Ju S-Y, Lee Y-J, Jeong S-N. Serum 25-hydroxyvitamin D levels and the risk of depression: a systematic review and meta-analysis. J Nutr Health Aging. 2013;17(5):447–55.
37. Autier P, et al. Vitamin D status and ill health: a systematic review. Lancet Diabetes Endocrinol. 2014;2(1):76–89.
38. Lorensia A, Suryadinata RV, Rahmawati RK. The effect of smoking habit on vitamin D status of adults in Indonesia. KEMAS: Jurnal Kesehatan Masyarakat. 2024;19(3):410–21.
39. Yang L, et al. Smoking behavior and Circulating vitamin D levels in adults: A meta-analysis. Volume 9. Food Science & Nutrition; 2021. pp. 5820–32. 10.

Publisher's note