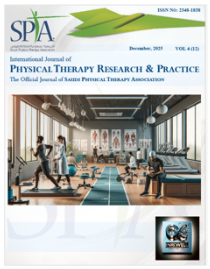

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Systematic Review

The Effect of Vitamin D Supplementation on Pediatric Skeletal Muscle Strength: A Systematic Review

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Abstract

Background. Vitamin D plays a key role in calcium absorption and contributes to several physiological functions. While serum vitamin D levels are positively associated with skeletal muscle strength, the effect of supplementation on pediatric skeletal muscle strength remains unclear. **Purpose.** To systematically review the literature on the effect of vitamin D supplementation on muscle strength in the pediatric population. **Method.** This systematic review included only randomized controlled trials (RCTs) that investigated vitamin D supplementation and assessed muscle strength in healthy children or adolescents before and after the intervention. Non-experimental studies and trials involving additional supplementation were excluded. **Results.** This review was registered in PROSPERO (CRD42022314030). Five RCTs studies met the inclusion criteria, with excellent methodological quality on the PEDro scale. A total of 747 participants (mean age 12.6 years; two-thirds female) were included. VitD insufficiency was common at baseline but improved in most participants after supplementation. Only handgrip strength was measured in all studies, except one that assessed knee muscle strength. Overall, VitD supplementation did not significantly improve muscle strength, except in one trial involving premenarchal girls with VitD deficiency, where handgrip strength improved. **Conclusion.** Vitamin D supplementation may be beneficial in improving muscle strength among premenarchal girls with vitamin D deficiency, possibly through suppression of parathyroid hormone (PTH).

Keywords: Vitamin D, Supplementation, Pediatric, Children, Muscle, Strength

Introduction

Vitamin D (VitD) is a molecule with different forms; inactive forms and one active form. Inactive forms of VitD include Cholecalciferol (D_3) in the skin and Calcifediol (25(OH)D) in the blood, while the active

form of VitD is a Calcitriol ($1,25(OH)_2D$) which is produced in the kidney(1). VitD can be obtained from diet or manufactured in the skin under the effect of solar radiation. From the diet, VitD present in many kinds of food as either D_3 like in oily fish, and egg yolk or Ergocalciferol (D_2) in mushrooms; however, food can only cover up to 10% of the daily need, hence the body primarily relies on the skin for providing VitD(1–3) (Figure 1).

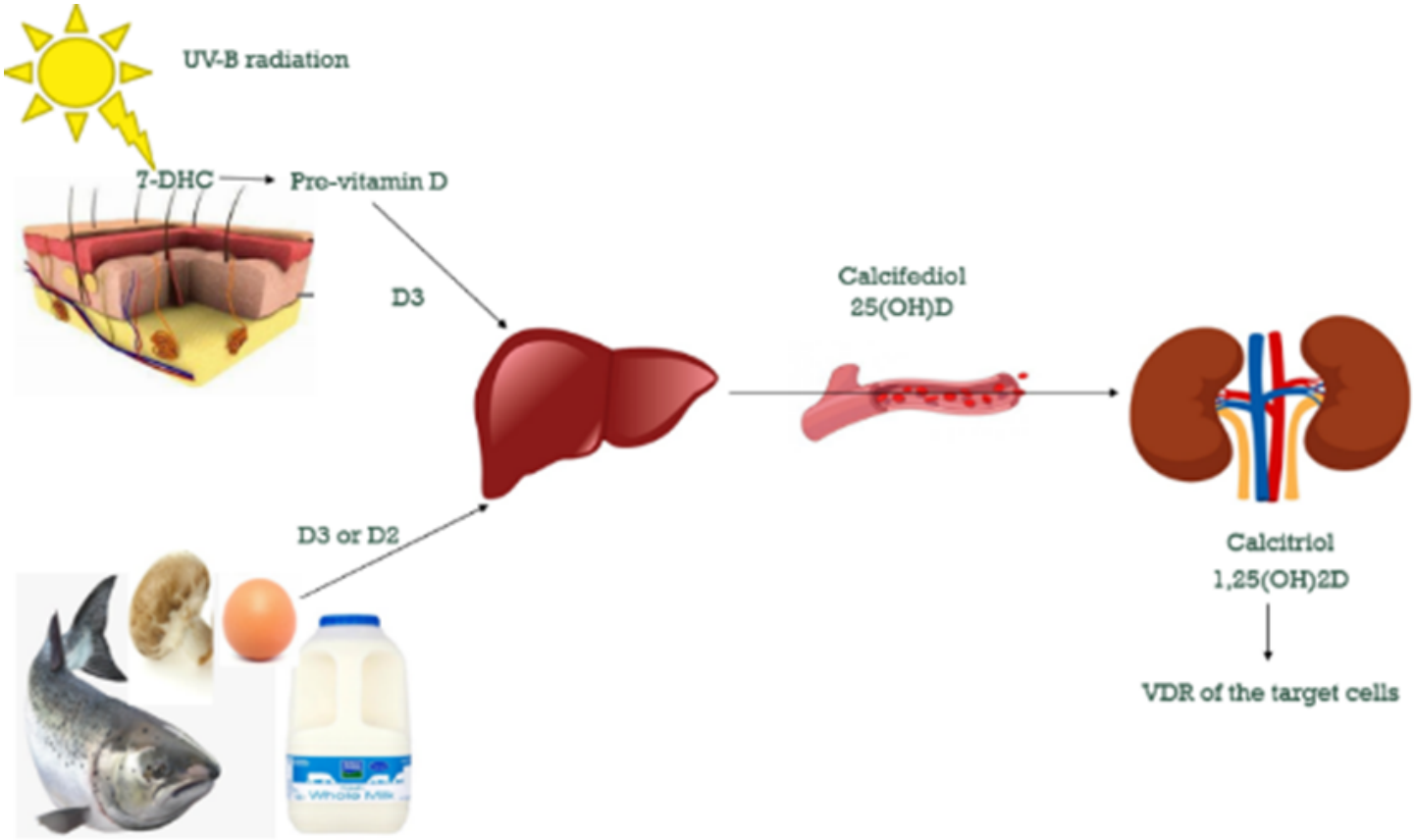

Figure 1: Vitamin D Sources and Synthesis

Physiological Roles of Vitamin D

Calcitriol ($1,25(OH)_2D$) is a hormonal form of VitD, which can be activated or inhibited depending on the desired functions in the target cells(4). The essential function of calcitriol is to regulate calcium ions (Ca^{+2}) and phosphate homeostasis(1). Additionally, calcitriol contributes to a multitude of non-calcemic functions in the immune(1,5), endocrine(6), cardiovascular(1,7), and musculoskeletal systems. It has a stimulatory effect on the satellite cells of skeletal muscle by activation of mitogenic factors for muscle repair, regulates mitochondrial genes expression, increases oxygen consumption rates in myocytes, and counteracts sarcopenia by regulating myocytes aging factors(8,9).

Vitamin D Levels Definition

VitD definition is a diagnostic classification for VitD level in the blood in which Calcifediol (25(OH)D) assay represents the level of VitD in the blood serum that is commonly diagnosed as deficient, insufficient/inadequate, sufficient/adequate, normal, or toxic. However, 25(OH)D levels definition is a controversial issue in which there is no international consensus for one definition(5,10).

Several studies defined VitD deficiency across

secondary hyperparathyroidism(3,10–16). Consequently, VitD has a regulatory effect on PTH at ≥50 *nano mol per liter* (nmol/L) = ≥20 *nano gram per milliliter* (ng/ml)(17). However, 25(OH)D >75 nmol/L is adequate for optimum PTH supression(10,13,14,17–19), while the definitions of deficiency <50 nmol/L, insufficiency 50–75 nmol/L, and sufficiency >75 nmol/L were proposed by the US Endocrine Society, International Osteoporosis Foundation, US Natural Osteoporosis Foundation and American Geriatric Society. In contrast, the US Institute of Medicine and UK National Osteoporosis Society defined calcifediol levels as deficiency <30 nmol/L, insufficiency 30-50 nmol/L, and sufficiency >50 nmol/L. Additionally, the World Health Organization, European Society for Clinical and Economic Aspects of Osteoporosis, and the German Nutrition Society considered 25(OH)D level <25 nmol/L as a deficiency. Contrastingly, most health institutions or societies have defined a toxic level of 25(OH)D when >125 nmol/L, yet the evidence is limited and the toxicity incidence rare(20). Therefore, the definitions have been characterized depending on two criteria: the maximal suppression of PTH and adequate intestinal calcium absorption(10)

The Effect of Vitamin D Deficiency on Health

Hypovitaminosis D may contribute to several physical, psychological, and mental disorders(21–26). For instance, rickets in children and osteomalacia in adults are strongly associated with severe hypovitaminosis D(21). Further, low VitD levels may suppress the recovery or progress the symptom of some neurological disorders like multiple sclerosis(22), Parkinson(23), and Alzheimer(24). In addition, VitD level status have shown to has an inverse relationship with depression(25). Clinically, osteomalacic myopathy have described as proximal myopathy that accompanied with bone ache in response to severe hypovitaminosis D(2,21). Furthermore, muscle function has shown to be influenced in people with hypovitaminosis D(26). From the above-mentioned studies, hypovitaminosis D may affect function, limit activity, or restrict quality of life.

Prevalence of Vitamin D Deficiency

VitD deficiency is highly prevalent worldwide among various ages, gender, races, and life cultures(20,21,23,27,38,46–51). In the Kingdom of Saudi Arabia, VitD deficiency has a widespread occurrence within different regions and ages(27). For instance, it is an epidemic in central(16,28–31), western(28,32,33), eastern(28,34), and northern(35) regions. In addition, VitD deficiency was found among elderly(31,33), adults(28–30,34,35), and pediatric(16,28,30,32,36) populations. In particular, the prevalence of VitD deficiency among Saudi children(28,32,36) and adolescents(16,30,36) has exhibited alarming statistics. However, these statistics must be interfering with other multidisciplinary capabilities needed to guard the health of this population.

Vitamin D Supplementation

The prescription of VitD supplementation depends on four variables: form like ergocalciferol (D_2) and cholecalciferol (D_3), dose, frequency, and duration)(37). VitD is recommended for general health at 400 International Unit per day (IU/d) for infants and children, 800 IU/d for adolescents, ≥800 IU/d for adults, and 1000 – 2000 IU/d for the elderly and post-menopausal women. For bone health, the recommended dose varies from 800 IU/d to 1000 IU/d, but it may redouble once prescribed for the prevention of rickets, osteomalacia, and risk of falls and fractures(38).

Regardless of the effects of VitD supplementation on the muscle strength, the prescribed dose and

frequency of VitD supplementation toward muscle health have varied. Seven reviews(39–45) discussed the effects of VitD supplementation on muscle strength and/or power by summarizing the studies in the field of interest. Consequently, VitD from 400 IU/d within six months up to 600,000 IU as a single dose. In detail, the following doses: 400 IU/d, 1000 IU/d, 2000 IU/d, and 60,000 IU/week were commonly used in the previous trials, but the difference was the period of intervention.

Pediatric is a critical age stage that involves infancy, childhood, and adolescence, in which the body grows continuously depending on well-organized genetic and hormonal system. In addition, any disturbance to this system may lead to permanent or transient development disorders(46). Accordingly, VitD and growth hormone are under synergetic relationship in which VitD supplementation stimulate Insulin-like Growth Factor-1 (IGF-1) that stimulates a special enzyme to increase the active VitD synthesis in the kidney(46). Lastly, VitD supplementation have shown to have minimal effect on children height(47). In this sense, the question is to what extent the pediatric skeletal muscle strength is changed in response to VitD dose, frequency, and duration of supplementation in clinical trials were highly heterogenous because most of the trials used different methods. However, the method of supplementation ranged

supplementation. Accordingly, it is anticipated that pediatric skeletal muscle strength may improve with vitamin D supplementation.

Previous Systematic Reviews in The Field of Interest

Despite the numerous reviews on the effect of VitD supplementation on muscle strength(39–45), pediatric research is limited as most studies have covered adults and elderly. Further, some of these reviews were not precise while testing the skeletal muscle strength in which the muscle power measurements were included and reported as the muscle strength examination. In addition, some of these reviews have reported their conclusions without consideration of the muscle group size or anatomical position. ***(Table 1)*** summarize the previous systematic reviews that discussed the effect of VitD supplementation on skeletal muscle strength.

Table 1) Previous systematic reviews in the effect of vitamin D supplementation on the skeletal muscle strength.

Authors, Date of Publication	**Number of Studies, Participants**	**Review Description**	**Outcome Measurements**	**Conclusion**
Zhang et al. In 2019(45)	8 RCTs N= 284	Effect of VitD supplementation on the upper and lower limb muscle strength and power within athletes (*Without age limitation*)	Handgrip, bench press, bench pull, and/or chin-up *as upper limbs tests* back squat, leg press, and/or quadriceps/ hamstring peak torque *as lower limbs tests*	Although a significant effect on lower limbs muscles was found, there was no effect on the upper limb muscles

Rosendahl-Riise et al. In 2017(44)	15 RCTs N= 2408	Effect of VitD supplementation on hand grip and other muscles strength within a community of dwelling older individuals. *(age >65 Y)*	Handgrip and other muscles strength	No significant improvements in muscles strength found
Chiang et al. In 2017(42)	6 RCTs N=undetermined	Effect of VitD supplementation on muscle strength within athletes. *(Age 18–45 Y)*	Handgrip, bench press, back squat, leg press, leg-back lift, bodyweight bench press, and/or isometric quadriceps contraction	Despite the significant finding within two studies, most of the included studies found no significant effect
Tomlinson et al. In 2014(43)	6 RCTs + one CT N= 310	Effect of VitD supplementation on the muscle strength within healthy adults *(Age 18–40 Y)*	Handgrip, bench press, pinch press, chest press, squat, leg press, calf peak torque, and/or isometric quadriceps contraction	A significant improvement in the upper and lower extremities muscles strength was found
Beaudart et al. In 2014(41)	29 RCTs N= 5615	Effect of VitD supplementation on muscle strength *(Without age limitation)*	Grip, quadriceps, and leg extension strength	Minor significant improvements in the examined lower limb muscles strength were found but not in grip strength
Muir et al. In 2011(40)	13 RCTs N= 2286	Effect of VitD supplementation on the muscle strength within older adults	Maximal isometric torque of selected muscles of lower limbs, grip strength, timed chair stands, and/or knee flexion/extension peak torque	A significant effect of VitD supplementation on muscle strength was found
Stockton et al. In 2011(39)	17 RCTs N= 5072	Effect of VitD supplementation on the muscle strength within adults	Grip strength, proximal upper limb muscles, and/or proximal lower limb muscles	No significant improvement in the upper and lower limbs muscles strength was found

Study Significance

Despite the high prevalence of VitD deficiency among pediatric population(27), the effect of VitD supplementation on pediatric skeletal muscle strength was not highlighted in the previous reviews(39–45). Therefore, the effects of VitD supplementation on pediatric skeletal muscle strength should be investigated. Thus, knowing this information will guide the healthcare providers and institutions to include or exclude VitD assay when investigating the pediatric skeletal muscle strength. However, the positive conclusions of this review may have a clinical benefit by minimizing the treatment period, enhancing the treatment efficacy, and improving the quality of life in pediatric with myopenia.

Objectives

This study aims to systematically review the current literature that have investigated the effect of VitD supplementation on muscle strength in pediatric population.

Methodology

Study registration

The study protocol was registered in the international prospective register of systematic reviews PROSPERO with a registration number CRD42022314030 on May 10, 2022. This study is a systematic review of previously published studies. It did not involve the collection of primary data from human participants or animals. Therefore, ethical approval from an institutional review board was not required.

Search strategy

This review has followed the guidelines by the preferred reporting for systematic reviews and meta-analysis (PRISMA) statement of 2020(48) which was designed in 2009 and developed in 2020 by multidisciplinary groups. Thus, the relevant experimental studies (Randomized Controlled Trials) published in English language and focused on the effect of vitamin D supplementation on pediatric skeletal muscle strength were included. Furthermore, these studies were found after searching the following databases (PubMed, Cochrane (CENTRAL), Medline, Science Direct, CINAHL, Saudi Digital Library (SDL)) from the start of the indexing until June 2022. Two reviewers independently screened titles and abstracts to identify potentially eligible studies, followed by full-text assessment of the selected articles to determine final inclusion based on predefined eligibility criteria. Any disagreements during the selection process will be resolved through discussion and consensus with third reviewer. The following keywords and MeSH terms were used: ("Vitamin D" OR "Vitamin D2" OR "Vitamin D3" OR "25-hydroxyvitamin D" OR "25(OH)D" OR "1,25-dihydroxyvitamin D" OR "1,25(OH)2D" OR cholecalciferol OR ergocalciferol OR calcitriol) AND (supplement OR supplementation) AND (muscle*) AND (strength OR function OR performance OR power) AND (pediatric OR child* OR adolescen* OR young OR boy OR girl).

Study Selection

Inclusion Criteria

This review included any study meeting the following inclusion criteria based on PICO approach in which: ($P_{participant}$) is pediatric, those who are able to implement the muscle strength measurement procedures; ($I_{intervention}$) is the intervention group, those who used oral Vitamin D supplementation only without any limitation in dose and duration; ($C_{comparison}$) is the control group, those who underwent placebo supplementation;

($O_{outcome}$) is the outcome measurement, in which skeletal muscle strength must be measured before and after the intervention.

Exclusion Criteria

Any study with participants with an abnormal medical condition or using additional supplement or medicine were excluded.

Methodological quality assessment

The studies were assessed and rated using The Physiotherapy Evidence Database (PEDro) scale(49). The PEDro scale is a checklist of 11-items rated as excellent methodological quality (9-10), good (6-8), fair (4-5), and poor (<4).

Data extraction

The following data were extracted from each included study: author, date of publication, sample size, age, gender, country, season, latitude, 25(OH)D level at baseline and at the end of the supplementation course, VitD supplement dose and form, intervention duration, study groups, muscle group, muscle strength measure, and results.

Results

Literature search

A total of 1980 records were found in PubMed, Cochrane (CENTRAL), Medline, Science Direct, CINAHL, and SDL. In addition, we searched Google Scholar and the bibliography of similar reviews to ensure that relevant studies were not neglected. After screening, 1963 records were excluded for many reasons while we have excluded an extra twelve studies in the screening for eligibility process after full text reading. Consequently, five randomized controlled trials meeting the review criteria were included(47,50–53). The search strategy following the flow diagram of PRISMA 2020 is illustrated in (*Figure 2)*.

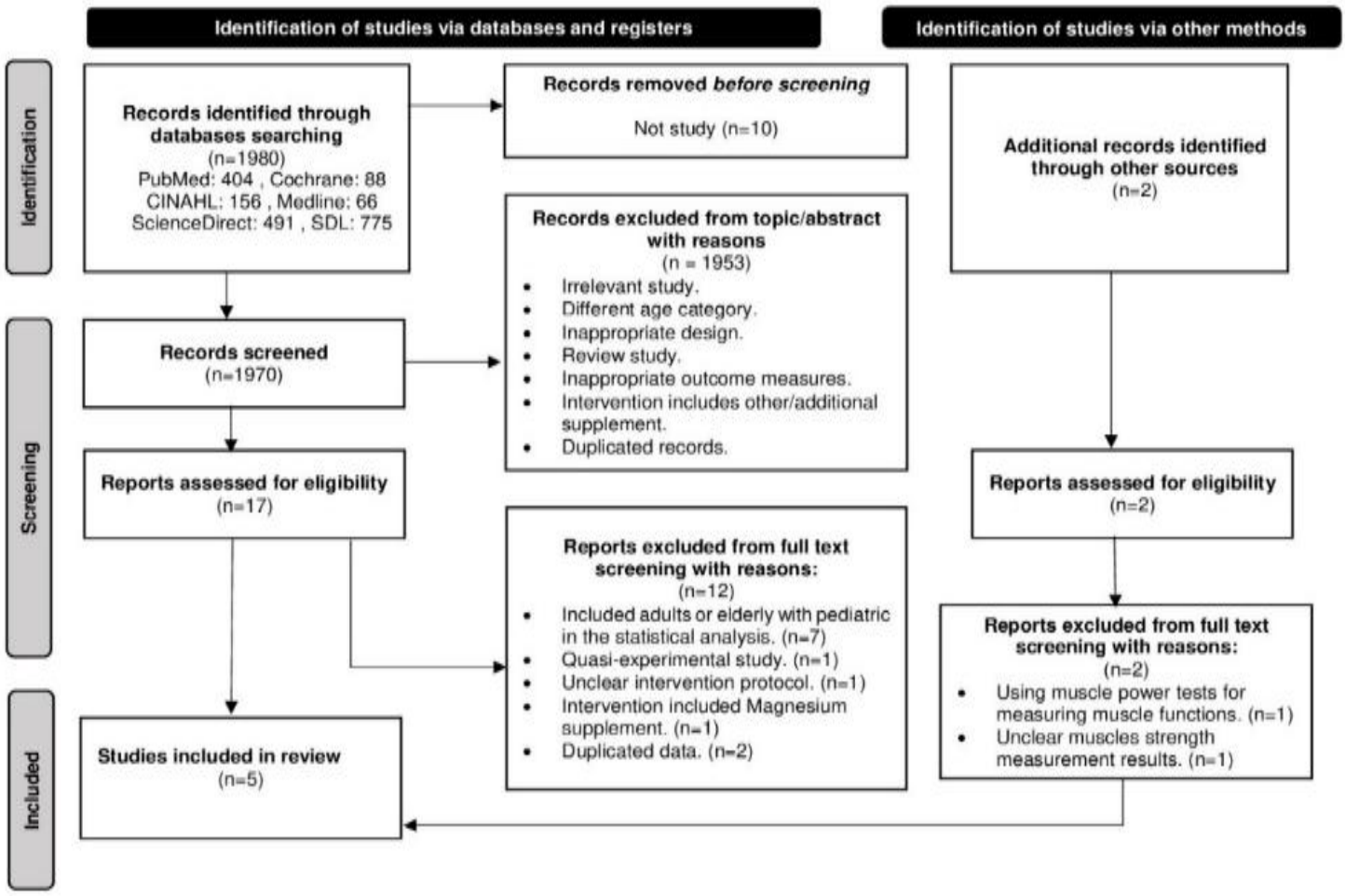

Figure 2. PRISMA 2020 flow diagram for the literature selection process

Methodological quality assessment

The methodological quality of the included studies was assessed using the PEDro scale. Scores ranged from 8 to 10, with a median score of 9 out of 10. According to PEDro score interpretation criteria, four studies were classified as excellent quality (scores 9–10), indicating a very low risk of bias, while one study was rated as good quality (score 8), reflecting acceptable methodological rigor with only minor limitations. (Table 2).

Table 2. PEDro assessment for the methodological quality of evidence.

Study	**PEDro Scale Item**											**Total**
(Author, Date)	**1***	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	
Mortensen, 2019(47)	√	√		√	√		√	√	√	√	√	8
Wright, 2018(53)	√	√	√	√	√	√	√	√	√	√	√	10
Dubnov-Raz, 2015(51)	√	√	√	√	√	√	√	√	√	√	√	10
Mitchell, 2013(50)	√	√		√	√	√	√	√	√	√	√	9
Fuleihan, 2006(52)	√	√		√	√	√	√	√	√	√	√	9
Total	5	5	2	5	5	4	5	5	5	5	5	-

*Column “1” is not included in the calculation of the total score

Studies characteristics

A total of 747 subjects were recruited in the included studies. The ages of the participants ranged between 5 and 16 years while the overall mean was 12.6 years. Altogether, 34.3% and 65.7% were males and females, respectively. The average body mass index (BMI) in each study ranged between 15.7 and 21.1 kilogram per meter square (kg/m^2), while the overall mean of the BMI was 19.4 kg/m^2. Regarding the study location: two studies were conducted in the Middle East(51,52) while the other studies were conducted in the United States(53), Denmark(47), and New Zealand(50). Athletes were considered in two studies(50,51) and three studies involved non-athletes(47,52,53). Only three studies reported the season that the intervention trial was performed(47,51,53), that is, two studies were conducted in winter(47,53) while one study was conducted in autumn and winter(51).

The average of 25(OH)D levels at baseline in all the participants ranged between 35 nmol/L and 77.5 nmol/L, with a mean of <50 nmol/L in one study(52), 50–75 nmol/L in three studies(47,51,53) and ≥75 nmol/L in one study(50). At the end of the intervention, the average of 25(OH)D levels was raised significantly in the experimental groups and decreased within the participants in the control group in all studies.

Each study used different supplementation methods, including four variables: VitD form, dose, frequency, and length of intervention. Cholecalciferol (D_3) supplement was used in all studies, in which the doses ranged between 0 international Unit (IU) as a placebo and 50,000 IU. However, the frequency of supplementation ranged from daily in three studies(47,51,53), weekly in one study(52) or monthly(50). The length of the intervention was twelve weeks in two studies(51,53), twenty weeks in one study(47) and one year in the remaining two studies(50,52). Regarding the experimental subgroups (treatment arms), two studies(47,52) used two arms against the control group, one study(53) used four arms against the control group, while the other two studies(50,51) randomly assigned the participants into either experimental or control groups.

The handgrip strength was measured in all the studies using the Handgrip Dynamometer, and the results were interpreted as kilograms in four studies(47,50,51,53) or pound square inch (PSI) in the other study(52). The instruments used for measuring the handgrip strength were the Squeeze Handgrip Dynamometer in two studies(47,52), Smedley's Handgrip Dynamometer in two studies(50,51), and Jamar$^+$ Digital Handgrip Dynamometer in the remaining studies(53). The knee muscle strength was measured in one study(50), bilaterally using the Biodex Isokinetic Dynamometer as the torque of concentric extension, concentric flexion, eccentric extension, and eccentric flexion in which the strength unit was the Newton meter (Nm).

The change in pediatric skeletal muscle strength after VitD supplementation was reported differently. However, the following data *(pre-intervention, post-intervention, pre to post change, and probability value)* were reported in one study(50), while the remaining studies ignored the probability value(47,51–53), pre-post change(47,52), or (pre and post) results(53).

The average handgrip strength in the control groups changed from 9.4kg(47), 109kg(53), 27.9kg(51) and 11.5psi(52) to 10kg, 117kg, 27.7kg, and 13psi, respectively. On the other hand, the average handgrip strength prior and after VitD intervention were (11kg-11.5kg)(47), (10.9kg-11.2kg)(47), (120kg-139kg)(51), (27.1kg-27.6kg)(50), (11psi-

20.1psi)(52) and (10.9psi-17.4psi)(52). *Wright et al 2018*(53) reported the results differently as the average of the change in handgrip strength within all groups (overall Δ pre-post = 0.74kg) in which the overall mean at baseline was 18kg. Additionally, they tested the correlation of the 25(OH)D level with handgrip strength before and after the intervention; however, the overall correlation at baseline and after the intervention was r=-0.21 and r=0.04, respectively.

Regarding the isotonic knee muscle strength, *Mitchell*(50) found a significant effect of VitD supplementation on the right knee concentric extension (p=0.02), right knee eccentric extension (p=0.007), and left knee eccentric extension (p=0.002). In contrast, no meaningful effect of VitD supplementation on handgrip strength was found in all the studies except for that of *Fuleihan et. al.*(52) who found a significant effect on the experimental groups; however, no probability values were reported. (Table 3a & 3b) demonstrate the summary of the included studies.

Table 3a. Summary of the included RCTs

Study	**Sample Size (N)**	**Subject Description**	**Age**	**Location Latitude Season**	**Anthropometric Measures**	
(Author, Date)	With Gender Distribution		(x̄±SD)		Height(cm) (x̄±SD)	Weight (kg) (x̄±SD)
Mortensen 2019(47)	N=130	Healthy Children	(4 - 8) y	Denmark	♂ 122.1 ±10.8	♂ 23.7 ±4.9
	♂ 61		6.6 ±1.5	55°N	♀ 121.9 ±10.8	♀ 23.3 ±5.6
	♀ 69			Winter		
Wright 2018(53)	N=324	Healthy Children and Adolescent	(9 - 13) y	United State	Overall	Overall
	♂ 162		11.3 ±1.2	(34°N and 40°N)	151±9	47.4±12.2
	♀ 162			Winter		
Dubnov-Raz 2015(51)	N=53	Adolescent Swimmers	(12 - 18) y	(Palestinian-occupied Territories)	**C** (165 ±9)	**C** (57 ±14)
	♂ 33		**C** (14.1 ±1.8)	(31°55'N - 32°40'N)	**I** (167 ±9)	**I** (56 ±10)
	♀ 20		**I** (13.9 ±1.6)	Autumn and Winter		
Mitchell 2013(50)	N=61	Female Adolescent Athletes	(13 - 18) y	New Zealand	BMI **C** (20.2 ±2.5 kg/m^2)	
			C (14 [13,15])	Latitude*	BMI **I** (19.5 ±2.2 kg/m^2)	
			I (14 [13,16])	Without season limitation		
			SD*		Height and Weight*	
Fuleihan 2006(52)	N=179	Healthy Female School Children and Adolescent	(10-17) y	Lebanon	**C** (154 ±10)	**C** (48 ±11)
			C (13.6 ±2.1)	Latitude*	$\mathbf{I}_{1400}$ (152 ±9)	$\mathbf{I}_{1400}$ (47 ±11)
			$\mathbf{I}_{1400}$ (13 ±2.1)	Without season limitation	$\mathbf{I}_{14000}$ (152 ±10)	$\mathbf{I}_{14000}$ (47 ±13)

			I_{14000} (13.1 ±2.2)			

x̄ (mean), SD (standard deviation), ♂ (male), ♀ (female), **C** (control/placebo group), **I** (experimental/intervention group), * (not reported)

Table 3b. Summary of the included RCTs

Study (Author, Date)	**VitD Supplement** (Form, Dose, ***Length of Intervention***)	**Serum 25(OH)D (nmol/L) (x̄±SD)**		**Muscle Strength Measurement**	**The Results of The Change in Muscle Strength after VitD Supplementation** (Pre, Post and/or Δ pre-post) and P_{value} (x̄±SD)
		Baseline	**Post-Intervention**		
Mortensen 2019(47)	D_3	N=117	N=117	Handgrip strength	N=117
	(0, 400 or 800)	**C** (55.6 ±1.7)	**C** (31.4 ±1.2)	Using	**C** pre(9.4 ±0.5), post(10 ±0.6)
	IU/day	I_{400IU} (56.9 ±2.1)	I_{400IU} (61.8 ±1.7)	*Squeeze Dynamometer*	I_{400IU} pre(11 ±0.6), post(11.5 ±0.6)
	Within 20weeks	I_{800IU} (58.6 ±2.1)	I_{800IU} (76 ±1.8)		I_{800IU} pre(10.9 ±0.5), post(11.2 ±0.5)
					Strength unit was kg
					The score was the average peak strength of ≥3 trails in both hands
					P results*
Wright 2018(53)	D_3	N=318	N=294	Handgrip strength	N=266
	(0, 400, 1000, 2000 or 4000) IU/day	**C** (71.5 ±18.6)	**C** (61.4 ±2.9)	Using	Overall pre (18 ±9.5)
	Within 12weeks	I_{400IU} (71.4 ±19.5)	I_{400IU} (77 ±2.6)	*Jamar⁺ Digital Dynamometer*	**Δ** pre-post (0.74±2.06)
		I_{1000IU} (71.1 ±19.7)	I_{1000IU} (91.4 ±2.6)		Strength unit was kg
		I_{2000IU} (65.8 ±7.3)	I_{2000IU} (103.4 ±2.7)		The score was the average of 3 trails in non-dominant hand
		I_{4000IU} (70 ±17.5)	I_{4000IU} (146.1 ±3)		(**P** and post) results*
	D_3	**C** (62 ±11.5)	**C** (50.7 ±10.5)	Handgrip strength	N=47
Dubnov-Raz 2015(51)	(0 or 2000) IU/day	**I** (61 ±12.3)	**I** (74 ±16.3)	Using	**C** pre(109 ±42), post(117 ±45)
	Within 12weeks			*Smedley's Dynamometer*	**Δ** pre-post (9.7 ±16.8)
					I pre(120 ±48), post(139 ±50)
					Δ pre-post (14.6 ±17.5)
					Strength unit was kg
					The score was the sum of both hands results (highest score of 3 trails)
					P results*
Mitchell 2013(50)	D_3	**C** (74 [64.5,88.5])	**C** (69.5 [58,108])	Handgrip strength using	N=54
	(0 or 50,000) IU/month	**I** (77.5 [63.5,92])	**I** (99 [75.5,112.5])	*Smedley's Dynamometer*	**Handgrip strength** (kg)
	Within 12months				**C** pre(27.9 ±6.1), post(27.7 ±5.2)
		SD*	SD*	Isokinetic peak torque of knee extensors and flexors using	**Δ** pre-post (-0.3 ±3.7), **P** (0.7)
				Isokinetic Dynamometer	**I** pre(27.1 ±5.3), post(27.6 ±5.7)
					Δ pre-post (0.4 ±2.5), **P** (0.4)

					⍰ The score was the best attempt of 2 trails in both hands	
					Knee muscles isokinetic peak torque (Nm)	
					1- Rt con. ext.	**C Δ** pre-post (3.95 ±15.7), **P**(0.2)
						I Δ pre-post (10.8 ±21.3), **P**(0.02)
					2-Rt con. flex.	**C Δ** pre-post (1.35 ±10.9), **P**(0.52)
						I Δ pre-post (0.5 ±12.1), **P**(0.81)
					3-Rt ecc. ext.	**C Δ** pre-post (16.2 ±40.1), **P**(0.04)
						I Δ pre-post (18.3 ±31.7), **P**(0.007)
					4-Rt ecc. flex.	**C Δ** pre-post (0.7 ±8.6), **P**(0.69)
						I Δ pre-post (0.4 ±12.2), **P**(0.86)
					5-Lt con. ext.	**C Δ** pre-post (8.7 ±20.9), **P**(0.04)
						I Δ pre-post (11.6 ±29.7), **P**(0.06)
					6-Lt con. flex.	**C Δ** pre-post (0.3 ±6.9), **P**(0.83)
						I Δ pre-post (1.3 ±9), **P**(0.46)
					7-Lt ecc. ext.	**C Δ** pre-post (25.4 ±31.3), **P**(<0.001)
						I Δ pre-post (20.8 ±31.1), **P**(0.002)
					8-Lt ecc. flex.	**C Δ** pre-post (0.2 ±9.6), **P**(0.9)
						I Δ pre-post (2.45 ±6.6), **P**(0.07)
Fuleihan 2006(52)	D_3 (0, 1400 or 14000) IU/week Within 12months	N=168 **C** (35 ±17.5) I_{1400IU} (35 ±22.5) $I_{14000IU}$ (35 ±20)	N=166 **C** (40 ±20) I_{1400IU} (42.5 ±15) $I_{14000IU}$ (95 ±77.5)	Handgrip strength using Squeeze Dynamometer	N=166 **C** pre (11.5 ±2.2), post as **% of Δ** (13.5% ±18.5%) I_{1400IU} pre (11 ±2.2), post as **% of Δ** (20.1% ±19.7%) $I_{14000IU}$ pre (10.9 ±2.2), post as **% of Δ** (17.4% ±16%) ⍰ Strength unit was PSI ⍰ **P** results* ⍰ The score was the average of 3 trails (hand*)	

x̄ (mean), SD (standard deviation), C (control/placebo group), I (experimental/intervention group), * (not reported), P (probability value), Δ pre-post (the change magnitude in muscle strength measurement prior and after the intervention), con. (concentric muscle contraction), ecc. (eccentric muscle contraction), flex. (flexion), ext. (extension), Rt (right), Lt (left), PSI (pound-force per square inch), % of Δ (the percent of change).

Discussion

The purpose of this systematic review was to investigate the effects of VitD supplementation on skeletal muscle strength in pediatric volunteers. This review included five RCTs that recruited pediatric healthy participants and excluded the studies that recruited unhealthy participants or used another supplement with VitD. The strategy applied for searching the databases for the trials of interest was illustrated following the PRISMA 2020 statement, in which five RCTs met the review criteria and were evaluated as good to excellent methodological quality based on the PEDro scale. The included trials were conducted in heterogeneous settings using different materials. However, the trials have assigned the same form of supplementation, that is, D_3, and measured the handgrip strength. Only *Fuleihan et. al.*(52) found significant effects on the handgrip strength after the intervention by D_3 supplement. On the other hand, *Mitchell*(50) measured the effects of VitD supplementation on the isokinetic strength of

knee muscles and found significant results on three of the eight measurements.

Comparison with previous reviews

There are seven systematic reviews and/or meta-analyses of either randomized or not controlled trials that have discussed the effects of VitD supplementation on skeletal muscle strength. However, these reviews used different criteria and reported various conclusions. The number of studies that have been involved in these reviews ranged from six(42,43) to twenty-nine(41), in which the sample size ranged from 284(45) to 5615(41) participants while the current review included five studies that recruited 747 children and/or adolescents. In addition to our review, *Zhang et. al.*(45) and *Beaudart et. al.*(41) included pediatric studies with studies of other populations; however, other reviews failed to involve pediatric trials.

Although the average baseline 25(OH)D level was inconsistently reported in previous reviews, the <75 nmol/L level was manifested in these reviews. However, our review found that the participants included had either deficient or insufficient 25(OH)D levels. This finding is consistent with the results of *Zhang et. al.*(45), *Rosendahl-riise et. al.*(44), *Beaudart et. al.*(41), *Tomlinson et. al.*(43), *Muir et. al.*(40), *Chiang et. al.*(42), and *Stockton et. al.*(39), which confirmed that VitD deficiency or insufficiency is a prevalent condition worldwide.

Calcifediol (25(OH)D) levels are commonly represented by two units, nmol/L or ng/ml, in which 1 ng/ml equals 2.5 nmol/L. For instance, the unit of nmol/L was used in three of the five studies(47,50,53) in our review while the remaining studies(51,52) used ng/ml. However, 25(OH)D levels were defined inconsistently depending on the maximal PTH suppression and adequacy of calcium absorption from the intestine(10). Further, the classification heterogeneity between a multitude of health institutions and societies was based on PTH suppression thresholds ranging from 30 nmol/L to 50 nmol/L. However, the trials in our review defined the VitD deficiency as either <50 nmol/L(50–53), which is the preferred threshold level used in many trials or <30 nmol/L(47) that have been defined previously as severe deficiency(10).

The level of 25(OH)D is fluctuating in response to many factors including season and latitude(16). However, the change in 25(OH)D level is not directly related to these factors, but it may depend on the seasonal climate and solar zenith angle "the angle between the solar radiation and the vertical direction". For instance, the climate in winter may limit the solar radiation in some countries while the hot weather in the summer of other countries may restrain the outdoor time that helps for enough sun exposure(47,50).

The meaningful effects of VitD supplementation on 25(OH)D levels were observed in most of the experimental studies despite the variety in supplementation dose, frequency, and period of intervention. However, in our review, the levels of 25(OH)D within the experimental groups were improved by responding to various VitD supplementation methods. Altogether, 25(OH)D levels increased with low and high doses as well as with short and long duration. Furthermore, the positive change in 25(OH)D levels was approximately 9% with 400 IU/d for 12 to 20 weeks in two studies(47,53). However, this finding was inconsistent with the other review(41) that included adults and geriatric populations, in which the change was significantly higher. Hence, we may conclude that the low dose of VitD supplementation within a longer period could be

more beneficial to the elderly than that for younger individuals. In contrast, the high dose effects of VitD supplementation on 25(OH)D were higher than that of the low dose in both our review and previous reviews(39–45), but the effects percentage was heterogenous in the trials(51,53) that used a similar method. Moreover, this heterogeneity was shown in previous reviews among different ages and populations. This conclusion guides us toward many physiological or manufactural variables that may limit or enhance the change in 25(OH)D.

Several non-experimental studies have demonstrated that the skeletal muscle functions were better with high 25(OH)D concentrations among adults(54,55), the elderly(11) and adolescents(12). Accordingly, this finding exhibits the beneficial roles of VitD in the enhancement of skeletal muscle regeneration and suppressing its degeneration(8,9). However, the cause-and-effect relationship needs to be cited from the experimental studies in the field of interest. Therefore, numerous systematic reviews(39–45) have discussed the effects of VitD supplementation on the muscle strength in several ages except children via various methods, however, the conclusions were inconsistent.

The current systematic review found that VitD supplementation did not improve pediatric handgrip strength in three studies(47,50,53) while it was improved in two studies(51,52). Accordingly, *Dubnov-Raz et. al.*(51) reported that the significant change in pediatric handgrip strength after the intervention may not be related to VitD supplementation, although the handgrip strength was also improved within the participants in the control group. Consequently, the positive change in the handgrip strength was 9% and 12% in the experimental and control groups, respectively. However, this improvement may be associated with muscular adaptation for athletic training or the participant being familiar with the handgrip measure instruments. In contrast the contrary, there is only one trial in our review that manifested the causation between VitD supplementation and handgrip strength. *Fuleihan et. al.*(52) found >60% improvement in handgrip strength within the experimental groups of premenarchal girls versus 17% within the control group.

In our review, four studies(47,50,51,53) did not find any positive changes in pediatric handgrip strength responding to VitD supplementation despite the methodological variety. Thus, our finding is compatible with that of *Rosendahl et. al.*(44), *Stockton et. al.*(39) and *Zhang et. al.*(45) who included studies on the elderly, adults, and athletes, respectively. Additionally, the review of *Beaudart et. al.*(41) found the same findings over sixteen studies. In contrast, the significant positive effect that found in one study was compatible with the report of Manoy et. al.(18) who recruited the elderly with hypovitaminosis D. Consequently, VitD supplementation may have a beneficial effect on handgrip strength once ≥1400 IU/week is administered for a long period. Further, handgrip muscle wasting in premenarchal girls and sarcopenic elders with hypovitaminosis D could be attributed to hormonal or aging changes, hence, VitD supplementation was effective for handgrip strength improvement.

The effects of VitD supplementation on proximal muscle strength of the lower extremity have been widely discussed. For instance, *Zhang et. Al.*(45), *Muir et. Al.*(40), *Tomlinson et. Al.*(43), and *Beaudart et. al.*(41) found a significant positive effect of VitD supplementation on knee muscle strength, although the characteristics of the participants were not similar. This finding was observed in one study(50) included in our review

that recruited athletic adolescents; though, this conclusion must be carefully considered. In detail, *Mitchell*(50) reported that despite the positive results, 50,000 IU/month of VitD supplementation for one year does not contribute to improved knee muscle strength. Therefore, the positive findings may be attributed to the muscle adaptation to the training program in athletes in which the knee muscle strength in some measurements also improved within the participants in the control group. Furthermore, the average of the eccentric contraction results of the left Quadriceps at the end of the study was higher in the control group (P<0.001) than that of the experimental group (P=0.002). Additionally, the same effect was found while measuring the concentric contraction of the same muscle, but a significant effect was found in the control group only (P=0.04). Moreover, the reviews of *Rosendahl et. al.*(44) and *Stockton et. al.*(39) reported similar results in adults and the elderly.

Finally, the beneficial effect of VitD supplementation on muscle strength was noticed in the participants with VitD deficiency and not in healthy individuals. Consequently, this finding may guide us to another factor that could be affecting muscle strength indirectly because of hypovitaminosis D. However, our conclusion is compatible with the report by *Visser et. al.*(11) in which they addressed the inverse association between PTH and muscle strength in the elderly. Otherwise, the VitD supplementation method may not be related to the muscle strength rather than the essential effect on serum 25(OH)D concentration. Hence, any dose, frequency and period that have been proven to rise 25(OH)D concentrations beyond the threshold level (50 nmol/L) may improve muscle strength in pediatric individuals.

Strength and Limitation

The current systematic review was conducted following the updated statement by The Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA 2020)(48). Additionally, we assessed the methodological quality of the included randomized clinical trials using the PEDro scale(49) in which the excellent grade was predominant in the included studies. Furthermore, we considered the criteria for including RCTs in our review as a strength factor, thus we defined clear and specified criteria. Hence, this is the first systematic review that was confined to healthy pediatric volunteers and excluded the studies that recruited subjects with a disease to minimize confounding and clinical heterogenity. Further, we excluded any study that had variables that may affect the causality between VitD supplementation and muscle strength such as co-supplementation with calcium or another vitamin. Regarding the group for comparison, we only accepted the studies that compared the experimental and control groups in which the participants in the control group must be free from any disease or disorder and used placebo supplementation. Moreover, our review has a strict criterion for the muscle strength measures, thus have excluded studies that reporting the muscle power tests as a strength measurement.

This systematic review was limited by the number of RCTs that have met the inclusion criteria in the available databases. Consequently, the available data in the included trials was limited. For instance, only one study recruited children with ages under eight years, while the skeletal muscle strength measurement was not diverse in the included RCTs. Additionally, the inter-study heterogeneity while measuring the muscle strength affected our critical analysis that aimed to provide meaningful conclusions. Further,

measurement bias may have been introduced by handgrip strength familiarity and learning effects in pediatric participants. Inconsistent reporting of familiarization procedures and testing protocols across studies limited data extraction and prevented adjustment for this potential bias, which may have influenced observed strength outcomes.

Although a meta-analysis was initially considered, quantitative synthesis was not feasible due to heterogeneity in muscle strength outcome measures, variability in vitamin D supplementation protocols, and inconsistencies in data reporting across studies. As a result, a narrative synthesis supported by structured tables was deemed the most appropriate approach to ensure accurate interpretation of the evidence.

Conclusion

The current systematic review concluded that, while most of the included trials showed no significant effect of VitD supplementation on pediatric skeletal muscle strength, VitD supplementation may help improving the muscle strength among premenarchal girls with VitD deficiency.

Finally, VitD might be beneficial toward pediatric skeletal muscle strength that VitD may enhance physical performance, functional ability, and playfulness at home and school. Moreover, our recommendation is directed toward the health institutions for providing health awareness about the importance of maintaining sufficient levels of VitD status for protecting muscle health in pediatric population.

Author Contributions

All authors significantly contributed to the work reported, including conception, study design, execution, data acquisition, analysis, and interpretation. They actively participated in drafting, revising, or critically reviewing the manuscript, provided final approval of the version to be published, agreed on the journal submission, and accepted accountability for all aspects of the work.

Data Availability Statement

The authors will transparently provide the primary data underpinning the findings or conclusions of this article, without any unjustified reluctance. If need from editorial team.

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Conflicts of Interest

The authors declare no potential conflicts of interest related to the research, writing, or publication of this work.

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