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Vitamin D, Immune function and acute respiratory infection among athletes; A Systematic Review

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Abstract
A systematic review of observational studies and randomized controlled trials was conducted to examine the association of vitamin D, acute respiratory infection, and immune markers among athletes; and also to determine the effects of vitamin D supplementation on these same variables. Eleven eligible trials were identified through PubMed, Medline, Embase, Cochrane Central Register of Controlled Trials, and Google scholar search. Five observational studies and six randomized controlled trials with 631 subjects. Published studies were few, more studies showing no effect of vitamin D supplementation on the duration, severity, and frequency of respiratory infection occurrence. A few studies showed that vitamin D supplementation increased salivary IgA and cathelicidin secretion rates. Insufficient evidence exists regarding the association and effects of supplementation on serum vitamin D concentration with respiratory infection and immune biomarkers among athletes.

Keywords: vitamin, athletes, acute respiratory tract infection, immune markers

Introduction

Vitamin D is known for its role in bone-formation, through the regulation of calcium and phosphorus metabolism. It is also involved in the regulation of immune response. Vitamin D receptors (VDRs) are present in immune cells, including T lymphocytes, B lymphocytes, and antigen presenting cells, indicating its role as a genetic modulator of immunity. These cells express the vitamin D-activating enzyme, 1-α-hydroxylase (CYP27B1) signifying that vitamin D is functionally important to the immune system [1].

Respiratory infection accounts for 35% to 65% of non-injury related illness among athletes [2], occurring frequently among those training indoors [3]. It has been suggested that overtraining, psychological stress, disrupted sleep patterns, and poor nutrition among athletes can compromise host defence and increase susceptibility to respiratory infections [4]. Heavy exercise is believed to be a prominent risk factor for acute respiratory infection (ARI) in athletes [5] and vitamin D might help decrease this risk. A systematic review that included 23 studies with 2,313 athletes showed 56 percent had vitamin D inadequacy and prevalence varied significantly by geographical location [6]. At present, it is not clear whether serum vitamin D concentration is associated with incidence of ARI in athletes, and whether vitamin D supplementation can reduce or prevent ARI in this population [7]. Owens *et al.* [8] observed that many athletes now take vitamin D supplements as part of their everyday dietary regimen. However, the authors pointed out the need to clarify "what physiological functions relevant to athletes can be optimized by maintenance of adequate vitamin D status." The present review seeks to examine the best available evidence regarding the association of vitamin D, ARI, and immune function among athletes using findings from published observational studies and randomized controlled trials (RCTs). Specific objectives are to

1) Examine the association of 25(OH)D serum levels with the following variables:

- Acute respiratory infection (ARI) in terms of
  - Number of symptom days (duration of ARI)
  - Severity of ARI symptoms
  - Number of symptoms per ARI episode

- Markers of immune function
  - Salivary IgA (concentration, secretion rate)
  - Pro-inflammatory cytokines (TNF-α)

- Anti-microbial peptides (cathelicidin, lactoferrin)

2) Determine the effects of vitamin D supplementation on these same variables.

Materials and methods

Search strategy

Databases searched were PubMed, Medline, Embase, the Cochrane Central Register of Controlled Trials, and Google scholar to identify studies that evaluated vitamin D in athletes and the effects of supplementation on their immune status. Studies published up to January 2021 were included. Search terms used were vitamin D ('vitamin D', 'vitamin', 'cholecalciferol', 'hydroxycholecalciferol', 'calcifediol', 'ergocalciferol', 'calcidiol', 'vitamin D/blood/25-hydroxyvitamin D'), immunity ('respiratory infection', 'respiratory tract infection', 'morbidity', 'immune markers', 'immune dysfunctions'), and athletes ('endurance sports', 'sportsman', 'sportswoman', 'active individuals', 'competitors', 'exercise').

The inclusion criteria were: (1) studies done on athletes; (2) observational studies that examined the association of serum vitamin D level with respiratory infection and biomarkers of immune function; (3) randomized controlled trials (RCTs) that examined the effects of vitamin D supplementation on respiratory infection and biomarkers of immune function.

The following data were extracted from the eligible studies: (1) general characteristics (title, first author, journal and year of publication); (2) participants and their characteristics (field of sports, age and gender); (3) type of study (observational, RCTs); (4) vitamin D (intervention doses, routes of administration, and trial duration); (5) relevant independent and dependent variables (serum vitamin D level, serum or salivary immune markers, and symptoms of respiratory infections); (6) method of analysis for each relevant independent and dependent variable; (7) summary results.

Methodological quality was assessed using the Cochrane Collaboration's risk of bias method and the NESR Risk of Bias for Nutrition Observational Studies. Two assessors (WS, SA) evaluated the observational studies and randomized controlled trials (RCTs).

Results

Our search identified 68 vitamin D studies on ARI and markers of immune function that were assessed for eligibility (figure 1). Of these, 11 studies fulfilled the eligibility criteria. Five observational and six randomized controlled trials were included. All randomized controlled studies administered oral vitamin D3 to participants in the intervention arm given as a daily dose. One of the studies [14] did not have vitamin D as the sole supplement; it included fish oil and protein.

Table 1 presents the characteristics of eligible studies

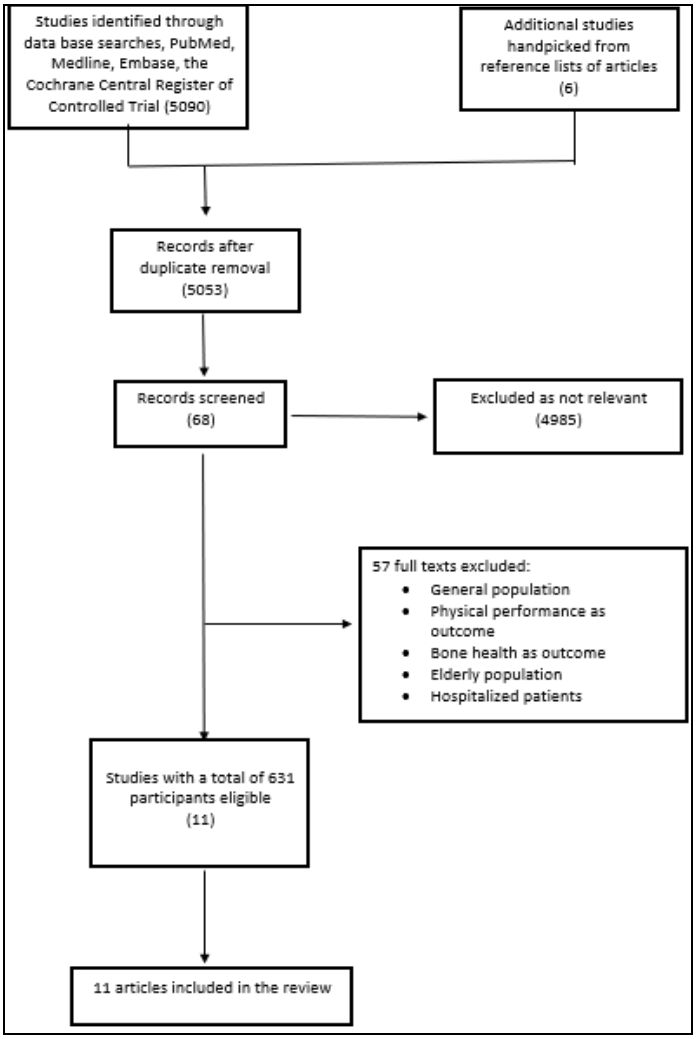

Fig 1: Flow chart for the selection of studies

Table 1: Characteristics of included studies

Author (year)	No. of subjects	Gender	Age	Analytical method to measure 25(OH)D	Type of vitamin D supplement and dose	Baseline serum 25(OH)D of subjects
A. Observational studies						
He *et al*. (2013) [15]	225	M 157 F 68	21+-3yr	HPLC-MS	N/A	Optimum/adequate = 62% Inadequate/deficient = 48%
Scullion *et al*. (2018) [16]	53	All female	----	----	N/A	High vitamin D concentrations seen in subjects
Fikratkerimov *et al*. (2019) [17]	40	All male	19-24	ELISA	N/A	83% vitamin D insufficient (15 out of 18 subjects)
Willis *et al*. (2012) [18]	19	M=9 F=10	19-45	CLIA	N/A	Insufficient/deficient = 53%; Sufficient = 47%
Barcal *et al*. (2016) [19]	19	All male	>18	RIA	N/A	Insufficient/deficient = 73.7%; Sufficient = 26.3%
B. RCTs						
Jung *et al*.(2018) [9]	25	All male	19-22	CLIA	5000 IU D3/daily for 4 weeks	Vitamin D insufficient (31.3±1.39 nmol/L)
Dubnov-Raz *et al*. (2014) [12]	55	----	12-21	RIA	2000 IU D3 daily for 12 weeks	Vitamin D insufficient (<30 ng/ml)
He *et al*. (2016) [10]	39	----	20.4+-1.9	HPLC-MS	5000 IU D3/day for 14 weeks	Sufficient plasma total 25(OH)D concentrations in treatment and placebo groups before intervention
Mayan *et al*. (2015) [13]	82	----	12-16	RIA	2000 IU daily for 12 weeks	67% had vitamin D insufficiency
DaBoit *et al*. (2015) [14]	42	26 M 16 F	26.8+-4.4	----	10 ug D3/ twice a day for 16 weeks (supplement also contained 550 mg DHA, 550 mg EPA, 8 g whey protein isolate)	----
Lewis *et al*. (2013) [11]	32	19 M 13 F	>18	----	4000 IU daily for 6 months	No athlete was vitamin D deficient

N/A = not applicable
---- Unable to obtain information

Risk of bias was assessed using Cochrane Collaboration's risk of bias method and modified NESR Risk of Bias for Nutrition Observational Studies. The 5 observational studies showed low to moderate risk of bias. All of the RCTs exhibited moderate risk of bias. Overall, the quality of included studies was rated as low to moderate.

Table 2 presents the results of studies that examined the association between serum 25(OH)D levels and acute respiratory infections (ARI), and the effects of vitamin D supplementation on ARI. Published studies were few. Favourable findings from observational studies were not consistently borne out by RCTs. Overall, there were more RCTs showing no effect of vitamin D supplementation on the duration of ARI, severity of ARI symptoms, and frequency of ARI occurrence, compared to those showing an effect.

One observational study [15] showed significantly longer duration of symptom days among vitamin D deficient athletes compared to those with optimum/adequate/inadequate vitamin D status. Out of 2 RCTs, one study [14] showed significantly shorter duration of symptom days in the vitamin D supplemented group compared to a placebo group, but information regarding baseline serum vitamin D levels could not be obtained.

One observational study [15] showed significantly greater symptom severity scores among vitamin D deficient athletes. In contrast, two RCTs [12, 14] (1 of which was conducted among vitamin D insufficient subjects) consistently showed no difference in reported symptom severity scores between supplemented and unsupplemented groups. One RCT[9] among vitamin D insufficient athletes showed that vitamin D supplemented subjects had significantly lesser total symptoms per ARI episode compared to the placebo group.

Table 2: Vitamin D and acute respiratory infection

ARI characteristic	Author (year)	Vitamin D variable observed/ Supplement given	Adequacy of baseline serum 25(OH)D	Results
1. Number of symptom days (duration)				
Observational	He *et al*.	Vitamin D status	Optimum = 11 (5%)	Number of symptom days was significantly

studies	(2013)[15]		Adequate (50-99.9 nmol/L) = 128 (57%)	greater in vitamin D deficient athletes than those with optimum/adequate/inadequate vitamin D status
			Inadequate (30-49.9 nmol/L) = 68 (30%)	Optimum 1 (0-6)*
			Deficient (<30 nmol/L) = 18 (8%)	Adequate 4 (0-8)* Inadequate 4 (1-8)* Deficient 9 (3-17) *P* = 0.04
RCTs	Da Boit *et al*. (2015) [14]	10 ug D3/ twice a day for 16 weeks (supplement also contained 550 mg DHA, 550 mg EPA, 8 g whey protein isolate)	-----	Number of symptom days was significantly shorter in vitamin D-supplemented group compared to control group Number of symptom days (Mean ± SD) Vitamin D supplemented group = 1.72 ± 1.67* Control group = 2.79 ± 1.76 *P*<0.05
	Dubnov-Raz *et al*. (2014) [12]	2000 IU D3 daily for 12 weeks	Vitamin D insufficient (<30 ng/ml)	No significant effect of supplementation on duration of URI
				Number of symptom days (Mean ± SD)
				Vitamin D supplemented group = 4.3 ± 1.6
				Placebo group = 5.1 ± 2.2
				Estimate (95% CI) = - 0.9 (-2.5, +0.8)
				Effect in percentage scale = -17% (-50%, +7%)
2. Severity of ARI symptoms				
Observational studies	He *et al*. (2013) [15]	Vitamin D status	Optimum = 11 (5%) adequate (50-99.9 nmol/L) = 128 (57%)	Vitamin D deficient subjects reported significantly higher symptom severity scores than those with optimum/adequate/inadequate vitamin D status
			Inadequate (30-49.9 nmol/L) = 68 (30%)	Symptom severity score median (IQR)
			Deficient (<30 nmol/L)= 18 (8%)	Optimum 43 (38-52)* Adequate 47 (40-69)* Inadequate 62 (46-74)* Deficient 102 (67-199) P value 0.013
RCTs	Da Boit *et al*. (2015) [14]	10 ug D3/ twice a day for 16 weeks (supplement also contained 550 mg DHA, 550 mg EPA, 8 g whey protein isolate)	-----	No difference in severity of symptoms between vitamin D supplemented and control groups
	Dubnov-Raz *et al*. (2014) [12]	2000 IU D3 daily for 12 weeks	Vitamin D insufficient Serum 25(OH)D<30 ng/ml	No difference in severity of URI symptoms between vitamin D supplemented and control groups URI severity score Mean (±SD) Vitamin D supplemented group = 4.7 (1.6) Placebo group = 4.4 (1.4) Estimate (95% CI) = +0.3 (-1.0, +1.6) Effect in% scale = +7% (-24%, +37%)
3. Number of symptoms per episode				
RCTs	Jung *et al*. (2018) [9]	5000 IU daily for 4 weeks	Vitamin D insufficient (31.3±1.39 nmol/L)	Vitamin D supplemented group had significantly lower total symptoms compared to placebo group.
				Total URTI symptoms Mean ± SD
				Vitamin D supplemented group = 14.7 ± 1.64
				Placebo group = 22.7 ± 2.27
				P value = 0.015

N/A = not applicable
---- Unable to obtain information
DHA = docosahexaenoic acid
EPA- eicosapentaenoic acid

Table 3 shows the results of studies that examined the association between vitamin D status and markers of immune function and the effects of supplementation on these markers. Immune function markers examined were the following: salivary IgA, cathelicidin, TNF-α. A few studies consistently showed that vitamin D supplementation increased salivary IgA secretion rate [14, 15] and cathelicidin concentration and secretion rates [10, 15]. Vitamin D (as serum concentration or use as a supplement) did not appear to influence other markers of immune function.

1. Salivary IgA (sIgA)

sIgA secretion rate. An observational study [15] showed significantly higher sIgA secretion rates among athletes with optimum vitamin D status compared to those with adequate/inadequate/deficient status. Similarly, one RCT [10] showed significantly increased sIgA secretion among vitamin D supplemented athletes compared to placebo.

2. Cathelicidin

Cathelicidin concentration. An observational study [15] showed that athletes with high vitamin D status had significantly higher cathelicidin concentrations compared to those with low vitamin D status. One RCT [10] showed that vitamin D supplementation significantly increased cathelicidin concentrations compared to a placebo group.

Cathelicidin secretion rate. One [10] showed that vitamin D supplementation significantly increased cathelicidin secretion rate compared to placebo.

3. TNF-α

Two observational studies [17, 18] showed that Vit. D deficient and insufficient athletes had significantly higher levels of TNF-α compared to vit. D sufficient controls. Among elite runners, every 72% increase in 25(OH)D concentrations reduced TNF-α concentrations by half [18].

Table 3: Vitamin D and markers of immune function

	Author (year)	Vitamin D variable examined/ supplement	Adequacy of baseline serum 25(OH)D	Results		
1. Salivary IgA (sIgA) secretion rate						
Observational studies	He *et al*. (2013) [15]	Vitamin D status	Optimum = 11 (5%) Adequate (50-99.9 nmol/L) = 128 (57%)	Athletes with optimum vitamin D status had significantly higher median sIgA secretion rate than those with adequate/inadequate/deficient status		
			Inadequate (30-49.9 nmol/L) = 68 (30%)	s-IgA secretion rate (ug/min) median (IQR)		
			Deficient (<30 nmol/L) = 18 (8%)	Optimum 38.7 (30.3-48.6) Adequate 22.9 (14.2-36.6)* Inadequate 19.5 (12.7-32.3)* Deficient 23.6 (14.8-32.9)* P = 0.018		
RCTs	Da Boit *et al*. (2015) [14]	10 ug D3/ twice a day for 16 weeks (supplement also contained 550 mg DHA, 550 mg EPA, 8 g whey protein isolate)	-----	sIgA secretion rate did not differ between treatment and control groups		
	He *et al*. (2016) [10]	5000 IU D3/day for 14 weeks	Sufficient plasma total 25(OH)D concentrations in treatment and placebo groups before intervention	sIgA secretion rate increased significantly in the vitamin D supplement group but not in placebo group		
			Median (IQR) nmol/L - Treatment group = 54.5 (43.2-71.0)	Treatment Week	Resting sIgA secretion rate (ug/min) Median	
			- Placebo group = 57.0 (38.7-71.0)		Vitamin D3 supplemented	Placebo
				Week 0	58.8	---
				7	87.2	---
				14	70.5	---
				P value	0.026	NS
				Effect size	0.32	---
2. Cathelicidin concentration						
Observational	He *et al*.	Vitamin D status	High vit. D status	Athletes with high vitamin D status had significantly		

studies	(2013) [15]		(plasma 25(OH)D>90 nmol/L)	higher cathelicidin concentrations compared to the low vit. D status group		
			Mid-level vit. D status (plasma 25(OH)D 33-90 nmol/L)	Cathelicidin concentration Mean ± SD (ng/mL)		
			Low level vitamin D status (plasma 25(OH)D<33 nmol/L)	High vitamin D status 32.2 ± 11.9* Mid-level vitamin D status 27.7 ± 10.6 Low level vitamin D status 24.5 ± 7.5* P = 0.023		
RCTs	He *et al*. (2016) [10]	5000 IU D3 daily for 14 weeks	Sufficient plasma total 25(OH)D concentrations in treatment and placebo groups before intervention	Plasma cathelicidin concentration increased significantly in vitamin D supplementation group after 14 weeks but not in placebo group		
			Median (IQR) nmol/L	% change in plasma cathelicidin concentration after 14 weeks		
			Treatment group = 54.5 (43.2-71.0)	Vitamin D supplemented group = 15.0%;		
			Placebo group = 57.0 (38.7-71.0)	Placebo group = 5.4%		
				Effect size = 0.75; *p*=0.025		
3. Cathelicidin secretion rate						
RCTs	He *et al*. (2016) [10]	5000 IU D3 daily for 14 weeks	Sufficient plasma total 25(OH)D concentrations in treatment and placebo groups before intervention	Cathelicidin secretion rate significantly increased in vitamin D supplemented group but not in placebo group		
			Median (IQR) nmol/L		Cathelicidin secretion rate (ng/min)	
			Treatment group = 54.5 (43.2-71.0)	Week	Vitamin D group	Placebo
			Placebo group = 57.0 (38.7-71.0)	0	0.076	-----
				7	0.103	-----
				14	0.090	-----
					P=0.03	NS
4. TNF-α						
Observational studies	Fikratkerimov *et al*. (2019) [17]	Vitamin D status	Mostly vitamin D insufficient (15 out of 18 subjects)	Vitamin D deficient and insufficient athletes had significantly higher levels of TNF-α compared to vitamin D sufficient controls		
				TNF-α (pg/mL) Mean ± SD		
			Deficient = 5	Deficient 31 ± 11.9*		
			Insufficient = 10	Insufficient 22 ± 7.1*		
			Sufficient = 3	Sufficient 9 ± 15		
			Sufficient controls = 12	Insufficient controls 4.1 ± 2.7		
				* significantly different from controls $p<0.05$		
	Willis *et al*. (2012) [18]	Vitamin D status	Insufficient = 42% Deficient = 11% Sufficient = 47%	Regression analysis results: For every 72% increase in 25(OH)D concentrations, TNF-α concentrations were cut in half		
	Barcal *et al*. (2016) [19]	Vitamin D status	Mostly insufficient Sufficient = 5 (26.3%); Insufficient = 12 (63.2%); deficient = 2 (10.5%)	No correlation between TNF-α and vit. D status		
RCTs	Lewis *et al*. (2013) [11]	4000 IU daily for 6 months	No athlete was vitamin D deficient	No difference in TNF-α between supplement and placebo groups; TNF-α did not correlate with 25(OH)D		
			Mean 25(OH)D = 57±16 ng/mL; 88% had >40 ng/ml		Change in TNF-α	
					Change	*P* value
				Baseline to midpoint	0.18	0.47

				Midpoint to endpoint	-0.11	0.64
				Baseline to endpoint	-0.38	0.88

N/A = not applicable
---- Unable to obtain information
DHA = docosahexaenoic acid
EPA- eicosapentaenoic acid
TNF= tumor necrosis factor

Discussion

The present study examined the best available evidence regarding the association of serum vitamin D concentration with ARI and markers of immune function among athletes, and the effects of supplementation on these variables. Studies were few (5 observational studies, 6 RCTs). One observational study [15] showed an inverse association between serum 25(OH)D and ARI, but this was not consistently borne out by RCTs. Overall, there were more RCTs showing no effect of vitamin D supplementation on the duration of ARI, severity of ARI symptoms, and frequency of ARI occurrence, compared to those showing an effect. With respect to markers of immune function, a few studies consistently showed that higher vitamin D serum level or supplementation increased salivary IgA secretion rate [10, 15] as well as cathelicidin concentration and secretion rates [10, 15]. Vitamin D (as serum concentration or as a supplement) did not appear to influence other markers of immune function that were examined.

The paucity of studies, most of which were rated as moderate quality, and inconsistent findings indicate that insufficient evidence exists regarding the role of vitamin D in reducing or preventing the occurrence of ARI among athletes and in improving markers of immune function. While vitamin D consistently increased salivary IgA and cathelicidin secretion rates which can potentially protect against ARI, more studies using larger samples and athletes of varying ethnicities are needed to confirm these results.

A few meta-analyses of RCTs performed in the general population reported statistically significant protective effects of vitamin D on development of upper respiratory tract infections[20, 21] while others reported no significant effects.[22-24] Martineau *et al*[25] conducted a systematic review and meta-analysis of 10,933 individual participant data from 25 randomized, double blind, placebo controlled trials of supplementation with vitamin D3 or vitamin D2.

Among patients with inflammatory lung disease, vitamin D supplementation reduced the secretion of inflammatory cytokines involved in the lung inflammatory process and increased the transcription of cathelicidin[26] While the current review fails to show beneficial effects of vitamin D in reducing or preventing ARIs, findings from a few studies consistently showed that vitamin D increased the levels of some markers of immune function (i.e., salivary IgA and cathelicidin).

Salivary IgA. The present review suggests that salivary IgA secretion rates increase with increasing vitamin D levels. One of the most promising markers associated with ARI incidence is the level of salivary immunoglobin A, with reduced S-IgA having been demonstrated to be associated with higher ARI incidence in athletic groups. Previous studies showed that among high-performance athletes, a consistent biomarker for identifying and monitoring risk of upper respiratory symptoms is the concentration or excretion rates of salivary IgA [2] IgA is recognized as the first line of defense against harmful environmental factors, due to its dominance in the immune system of mucous membranes [27]. According to Gleeson and Pyne[2], one consensus of studies among elite athletes in different sports is that low levels of salivary IgA concentration and/or secretion rates, and declining levels over a training period are associated with increased risk of upper respiratory symptoms.

Cathelicidin. The present review shows increased cathelicidin concentration and secretion rates with increased vitamin D levels or supplementation. Cathelicidin is an antimicrobial peptide (AMP) present in neutrophils and epithelial cells [28]. AMPs constitute important components of innate immunity, having direct antimicrobial activity and the ability to modulate innate immune responses of the host [28].

Limitations of the present review. The current review shows that very few studies examined the role of vitamin D, ARI, and immune function among athletes. Studies used small sample sizes, varying supplement doses and type of supplement (one study used vitamin D supplement combined with omega-3 fatty acids and protein), different exercise intensities (elite and recreational athletes as subjects), and some studies were conducted among non-deficient subjects. These variations made comparability of results difficult.

Analytical methods used in the reviewed studies to quantify serum 25(OH)D comprised high-pressure liquid chromatography–tandem mass spectrometry [10, 15] and immuno-assays [9, 12, 13, 17-19] Isotope dilution liquid chromatography-tandem mass spectrometry (LC-MS/MS) is considered the referent method because it detects both $25(OH)D_2$ and $25(OH)D_3$. [23]

Technical problems exist regarding the use of 25(OH)D to diagnose hypovitaminosis D which may cause misinterpretation of results [29] These include the tight binding of 25(OH)D to its carrier vitamin D binding protein (DBP), and the different vitamin D metabolites circulating in the blood [30]. Prior to determination, 25(OH)D needs to be dissociated from its carriers. The dissociation step must be highly efficient to obtain accurate quantification.[29] Automated immunoassays do not always achieve total dissociation of 25(OH)D and fail to correctly quantify 25(OH)D, but the issue is not adequately addressed in current clinical guidelines [29] Total circulating 25(OH)D is the sum of two metabolites: $25(OH)D_2$ and $25(OH)D_3$. [30] The ideal method of measurement should equally detect both metabolites.

Standardization of the different assays is key to achieving comparable results across different methods and manufacturers, and is critical for the establishment of common clinical cut-offs for use in routine practice [29].

Analytical issues that still need to be resolved include: 1) refinement of gold-standard methods for quantification of vitamin D metabolites and assay standardization to make serum values directly comparable between studies and clinical centers [29, 30]; 2) consideration whether the traditional vitamin D deficiency cut-off, based on the non-

standardized Diasorin radioimmunoassay, needs to be adjusted for those assays that are VDSP-standardized [29].

Another issue is that overall consensus is lacking with respect to the definitions of vitamin D deficiency, insufficiency, sufficiency [30] Cut-off levels of 25(OH)D have been recommended by the U.S. Institute of Medicine (IOM)[31] and the U.S. Endocrine Society (ES) [32].

Romagnoli *et al*. [30] pointed out that the IOM and ES differences on the definition of 'sufficiency' generated different recommendations about vitamin D intakes.

As a result of these differences, the worldwide prevalence of low vitamin D status varies according to the level of 25(OH)D utilized to define sufficiency [30, 33]

In the present review, six studies used ES classification [11, 13, 15, 17-19] only 2 used IOM [9, 10] the other 3 made no mention in their articles.

The individual's baseline vitamin D level is important since those with normal or near-normal levels receiving vitamin D supplementation are unlikely to exhibit physiological benefits [33] It has been emphasized that only those with depleted vitamin D stores should receive supplementation to ensure treatment efficiency and minimize risk of adverse events [33 In the present review, 7 studies examined the effects of supplementation on deficient subjects [9, 12, 13, 15, 17-19] while 3 included non-deficient subjects [10, 11, 16]. One had no information [14]

Conclusions

On the basis of this current Review, insufficient evidence exists regarding the association of serum vitamin D concentration with ARI and markers of immune function among athletes, and the effects of supplementation on these variables. A few studies consistently showed that vitamin D increased salivary IgA secretion rate and cathelicidin concentration and secretion which can potentially protect against ARI. However more studies using larger samples and athletes of varying ethnicities are needed to confirm these results.

Limitations of included studies were: (1) small sample sizes and very few studies examined the role of vitamin D, ARI, and immune function among athletes (2) no standard classification and definition of vitamin D deficiency (3) no standardize methods used to quantify 25(OH)D (4) gene polymorphisms, sun exposure, skin pigmentation, body composition not included as variables (5) baseline vitamin D level not uniform, some studies were conducted among non-deficient subjects.

Therefore issues that need to be addressed by future investigations are: (1) to increase sample size (2) to use only a single classification and definition for vitamin D sufficiency (IOM or ES) (3) to use HPLMC-MS to quantify 25(OH)D (4) to include gene polymorphisms, sun exposure, skin pigmentation among the variables examined.

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