Research Square

Preprints are preliminary reports that have not undergone peer review.
They should not be considered conclusive, used to inform clinical practice,
or referenced by the media as validated information.

Vitamin D status and its association with disease activity in Libyan children with juvenile idiopathic arthritis

Zeinab Ashour Ewaz

doprf@yahoo.com

Tripoli children teaching hospital

Awatif Abushhaiwia

Tripoli children teaching hospital

Elhassan Bashir Dawi

Tripoli children teaching hospital

Mabruka Zletni

Tripoli children teaching hospital

Ramzi Mohamed

Free Libyan laboratory

Ebtisam Khawaja

Tripoli children teaching hospital

Research Article

Keywords: Vitamin D, 25-hydroxyvitamin D, Juvenile idiopathic arthritis, Disease activity, JADAS27, Libya

Posted Date: November 25th, 2026

DOI: https://doi.org/10.21203/rs.3.rs-11555539/v1

License: This work is licensed under a Creative Commons Attribution 4.0 International License.
Read Full License

Additional Declarations: Competing interest reported. The data analyzed in this were collected directly by the authors and are available in an anonymized SPSS dataset. Access to the dataset can be provided by the corresponding author upon reasonable request, subject to applicable ethical and institutional requirements.

Vitamin D status and its association with disease activity in Libyan children with juvenile idiopathic arthritis

Zeinab Ashour Ewaz doprf@yahoo.com (Tripoli children teaching hospital), Awatif Abushhaiwia a.Abushhwaiwia@uot.edu.ly (Tripoli children teaching hospital),Mabruka Ahmed Zletni mabrukazletni2018@gmail.com(Tripoli children teaching hospital), Elhassan Bashir Dawi hassandawi@gmail.com,(Tripoli children teaching hospital),Ramzi Mohamed Mansur Ramzi.mohammed@yahoo.com(free Libyan laboratory), Ebtisam Saleh Khawaja Ebtisamkawaja@gmail.com (Tripoli children teaching hospital).

Abstract

Background: Vitamin D modulates immune function and has been proposed as an environmental determinant of juvenile idiopathic arthritis (JIA), but evidence in children remains limited and inconsistent.

Objective: To compare vitamin D status in Libyan children with JIA and healthy controls and to examine its association with disease activity.

Methods: In this case control study (Tripoli Children's Hospital, May 2018–August 2019), 55 children with JIA and 56 healthy controls matched for age and ancestry were enrolled. Serum 25-hydroxyvitamin D [25(OH)D] was measured by electrochemiluminescence immunoassay (deficiency <30, insufficiency 30–50, sufficiency >50 nmol/L). Disease activity was scored with the 27-joint Juvenile Arthritis Disease Activity Score (JADAS27).

Results: Mean age was 10.1 ± 4.3 years in cases and 9.2 ± 3.8 years in controls; 74.5% of cases and 55.4% of controls were female. Mean 25(OH)D was higher in cases (33.5 ± 25.4 vs 23.6 ± 15.3 nmol/L; P = 0.014), and deficiency was less frequent (60.0% vs 83.9%; P = 0.006), whereas combined insufficiency or deficiency was similar (80.0% vs 87.5%; P = 0.31). Vitamin D status was not significantly associated with JADAS27 category (P = 0.38), JIA subtype (P = 0.30) or disease duration (P = 0.23).

Conclusions: Low vitamin D status was highly prevalent in both children with JIA and controls and was not associated with disease activity. Small sample size, single-center design and absent data on vitamin D intake limit interpretation; larger prospective multicenter studies are needed.

Trial Rigistration: clinical trial number: not applicable**.**

Keywords: Vitamin D; 25-hydroxyvitamin D; Juvenile idiopathic arthritis; Disease activity; JADAS27; Libya

Introduction

Vitamin D is essential for the development, growth and maintenance of a healthy skeleton from birth throughout life, and its major function is the maintenance of calcium homeostasis [1]. Vitamin D also contributes to the regulation of the immune system, and although it is difficult to establish a solid relationship between its deficiency and autoimmune rheumatologic diseases, a strong relationship has been described between vitamin D deficiency and systemic lupus erythematosus and rheumatoid arthritis in adults [2]. Awareness of its immunological role followed the discovery of vitamin D receptors (VDRs) in almost all immune cells, including activated CD4+ and CD8+ T cells, B cells, neutrophils and antigen-presenting cells such as macrophages and dendritic cells [3]. Through VDR activation, the biologically active metabolite $1,25(OH)_2D$ influences immune modulation, cellular growth, proliferation and apoptosis; it decreases the production of tumor necrosis factor-α and pro-inflammatory interleukins (IL-1, IL-6, IL-23) by macrophages and promotes tolerogenic dendritic cells [3].

Vitamin D deficiency and insufficiency have therefore been considered an important environmental determinant of juvenile idiopathic arthritis (JIA) [4]. JIA is the most common chronic rheumatic disease of childhood and an important cause of short- and long-term disability [5]. It is defined as chronic arthritis of unknown cause lasting at least 6 weeks in children younger than 16 years, and it comprises a group of clinically distinguishable subtypes that share chronic synovitis as a unifying feature. Its etiopathogenesis is complex and incompletely understood. Reported prevalence ranges from 0.07 to 4.01 per 1000 children and incidence from 0.008 to 0.226 per 1000 children per year; this variation is attributed to differences in diagnostic criteria, case definitions and case ascertainment, and possibly to genetic, ethnic, environmental and lifestyle influences [6].

Vitamin D status is influenced by VDR genotype, ethnically related skin tone and clothing, environmental variation and nutritional intake [3]. In adults with rheumatoid arthritis, lower serum 25(OH)D has been associated with higher disease activity [7]. Vitamin D deficiency is commonly defined as a serum 25(OH)D concentration below 30 nmol/L, insufficiency as 30–50 nmol/L and sufficiency as above 50 nmol/L; these thresholds derive from an Institute of Medicine review focused on skeletal outcomes in healthy populations, which concluded that information was inadequate to set intake recommendations for other biological roles of vitamin D [8]. The Endocrine Society suggests an optimal 25(OH)D concentration of 75 nmol/L and

recommends that children receiving medications such as anticonvulsants, glucocorticoids and antifungals be given at least two to three times more vitamin D than their age group requires; these recommendations are not specific for children with chronic arthritis [9].

A systematic review and meta-analysis published in 2013 found no clear link between vitamin D status and chronic arthritis in children at that time; a meta-analysis of three studies within it reported a prevalence of vitamin D insufficiency of 82% in JIA, and only three of the included studies applied the International League of Associations for Rheumatology (ILAR) criteria [10]. Since then, case control and cross-sectional studies have continued to relate 25(OH)D to JIA and its activity with inconsistent results [11–19]. We therefore aimed (1) to evaluate vitamin D status in children with JIA at Tripoli Children's Hospital compared with healthy children matched for age and ancestry, and (2) to examine the association between serum 25(OH)D and disease activity in JIA.

Methods

Study design and setting

This case control study was conducted in the rheumatology department of Tripoli Children's Hospital, Tripoli, Libya, from 16 May 2018 to 7 August 2019.

Participants

A total of 111 children were included: 55 children with JIA (cases) and 56 healthy controls matched for age and genetic ancestry (siblings and cousins). Cases were children diagnosed with JIA of any ILAR subtype, with either active or inactive disease. Controls were completely healthy children who were not taking any supplements. Both sexes were eligible, and the legal guardians had to agree to the child's participation. Children with JIA and comorbid diseases, children (or guardians) who refused to participate, and non-Libyan children were excluded.

Procedures and measurements

Two structured interviews were conducted. During the first, at the outpatient visit, the researcher introduced the study to parents and patients, explained its purpose, obtained agreement to participate and arranged the choice of controls. During the second, parents, patients and controls were assessed: disease activity in patients by history, examination and investigations, and general health in controls by history and general examination. Blood samples were collected at the second interview. Information from the interviews and from

detailed review of patient files was recorded on two purpose-designed data sheets, one for cases and one for controls.

Weight (kg) and height (cm) were measured and plotted on the 2000 growth charts of the US National Center for Health Statistics in collaboration with the National Center for Chronic Disease Prevention and Health Promotion. Musculoskeletal examination used the pediatric Gait, Arms, Legs and Spine (pGALS) screen.

Disease activity

Disease activity was assessed with the Juvenile Arthritis Disease Activity Score (JADAS), which has four components: (1) physician global assessment of disease activity (0–10, where 0 = no activity); (2) parent/patient global assessment of well-being (0–10, where 0 = very well); (3) number of joints with active disease; and (4) erythrocyte sedimentation rate (ESR). We used the 27-joint reduced count (JADAS27) for its greater feasibility; it includes the cervical spine, elbows, wrists, metacarpophalangeal joints, proximal interphalangeal joints, hips, knees and ankles, and is a valid surrogate for the full joint count. ESR was normalized to a 0–10 scale as (ESR − 20)/10, with values below 20 mm/h set to 0 and values above 120 mm/h set to 10. The JADAS27 total is the sum of the four components (range 0–57).

Patients were classified as inactive (score <1 in all JIA categories) or as having minimal disease activity (score >1 and ≤2 for oligoarticular JIA; >1 and ≤3.8 for polyarticular JIA). Scores above 3.2 for oligoarticular and above 5.1 for polyarticular JIA were considered to indicate active (high) disease. Systemic-onset JIA, rheumatoid factor (RF)-negative polyarthritis, RF-positive polyarthritis and extended oligoarthritis were analyzed with the polyarticular group; the remaining ILAR categories were assigned to the polyarticular group if more than four joints and to the oligoarticular group if four or fewer joints were affected during the disease course.

Laboratory methods

Blood samples were drawn in the morning during outpatient visits by the same nurse and analyzed by the same technician in the same laboratory. In patients, complete blood count, ESR, C-reactive protein (CRP), serum calcium, phosphorus, alkaline phosphatase and 25(OH)D were requested; in controls, serum 25(OH)D, calcium, phosphorus and alkaline phosphatase were measured. Serum 25(OH)D was measured by electrochemiluminescence binding assay (ECLIA) on a Cobas e 411 analyzer (Roche). Vitamin D deficiency was defined as 25(OH)D <30 nmol/L, insufficiency as 30–50 nmol/L and sufficiency as >50 nmol/L [8].

Statistical analysis

Data were coded, tabulated and analyzed with SPSS version 22. Continuous variables are presented as mean ± standard deviation (SD) and range and were compared between groups with Welch's t-test. Categorical variables are presented as number (percentage) and were compared with the Pearson chi-square test or Fisher's exact test; for tables larger than 2 × 2 with small expected counts, the Fisher–Freeman–Halton exact test (Monte Carlo estimate) was used. All tests were two-sided, and $P < 0.05$ was considered statistically significant.

Ethical considerations

Approval for the study was obtained from the Libyan Board of Health Specialities, Scientific Council of Pediatrics [approval reference and date to be added]. Verbal consent was obtained from the parents or legal guardians and from older children.

Results

Participants

A total of 111 children were included: 55 with JIA and 56 healthy controls. Mean age was 10.1 ± 4.3 years in cases and 9.2 ± 3.8 years in controls (P = 0.25; Table 1). Females accounted for 74.5% of cases, consistent with the female predominance of JIA, and 55.4% of controls (P = 0.047). Residence did not differ between groups: 41.8% of cases and 41.1% of controls lived in Tripoli.

Table 1 Demographic characteristics of children with JIA (cases) and controls

Variable	JIA cases (n = 55)	Controls (n = 56)	P value
Age at evaluation, years, mean ± SD	10.1 ± 4.3	9.2 ± 3.8	0.25[a]
Sex, n (%)			
Male	14 (25.5)	25 (44.6)	0.047[b]
Female	41 (74.5)	31 (55.4)	
Residence, n (%)			
Tripoli	23 (41.8)	23 (41.1)	0.94[c]
Outside Tripoli	32 (58.2)	33 (58.9)	

[a] Welch's t-test; [b] Fisher's exact test; [c] Pearson chi-square test. JIA, juvenile idiopathic arthritis; SD, standard deviation.

Clinical characteristics of children with JIA

Two patients (3.6%) had a family history of juvenile arthritis, and 42 (76.4%) had no family history of any of the listed rheumatologic conditions (Table 2). Age at disease onset ranged from 1 to 14 years (mean 5.3 ± 3.3 years), and age at evaluation ranged from 2 years 3 months

to 19 years (Table 3). Mean weight was 35.4 ± 17.5 kg and mean height 135.0 ± 20.2 cm. Uveitis was present in 4 patients (7.3%).

According to the ILAR classification, systemic-onset JIA and seronegative polyarthritis were the most frequent subtypes (18 patients each, 32.7%), followed by persistent oligoarthritis (7, 12.7%), extended oligoarthritis (5, 9.1%), psoriatic arthritis (4, 7.3%) and seropositive polyarthritis (3, 5.5%) (Figure 1). By JADAS27, 24 patients (43.6%) had inactive disease, 27 (49.1%) had minimal disease activity and 4 (7.3%) had high disease activity.

Table 2 Family history of rheumatologic disease in children with JIA (n = 55)

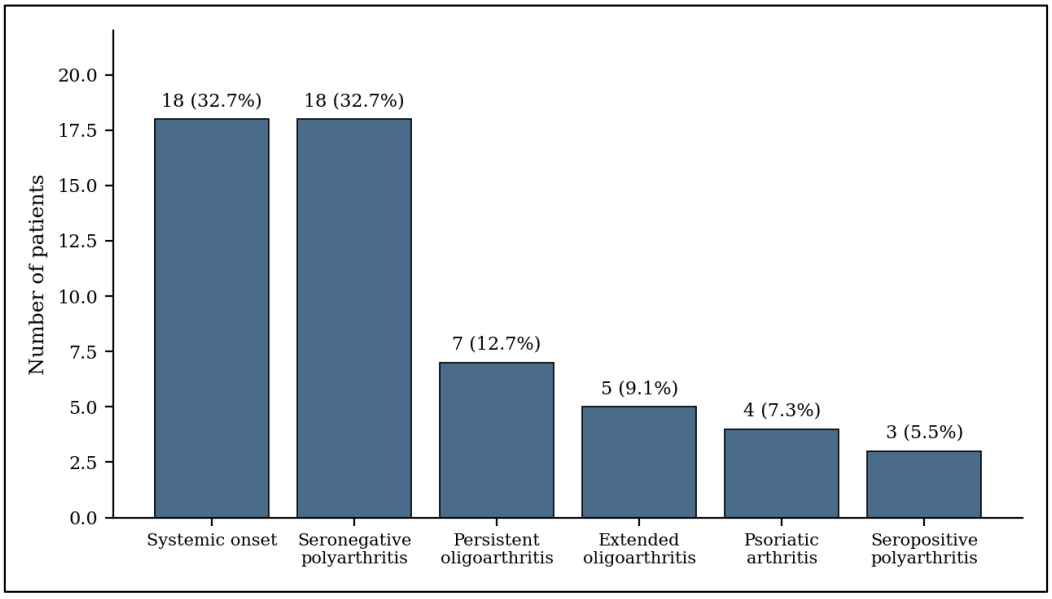
Family history	n	%
JIA	2	3.6
Psoriasis	6	10.9
Rheumatoid arthritis and psoriasis	2	3.6
Systemic lupus erythematosus	1	1.8
Rheumatoid arthritis	2	3.6
None	42	76.4
Total	55	100.0

Table 3 Clinical characteristics of children with JIA (n = 55)

Characteristic	Value
Age at evaluation, years, mean ± SD (range)	10.1 ± 4.3 (2.3–19)
Age at onset, years, mean ± SD (range)	5.3 ± 3.3 (1–14)
Sex, n (%)	
Male	14 (25.5)
Female	41 (74.5)
Weight, kg, mean ± SD	35.4 ± 17.5
Height, cm, mean ± SD	135.0 ± 20.2
ILAR subtype, n (%)	
Systemic onset	18 (32.7)
Seronegative polyarthritis	18 (32.7)
Persistent oligoarthritis	7 (12.7)
Extended oligoarthritis	5 (9.1)
Psoriatic arthritis	4 (7.3)
Seropositive polyarthritis	3 (5.5)
Uveitis, n (%)	4 (7.3)
Disease activity (JADAS27), n (%)	

Characteristic	Value
Inactive	24 (43.6)
Minimal disease activity	27 (49.1)
High disease activity	4 (7.3)

Figure 1 Distribution of JIA subtypes according to the ILAR classification (n = 55)



Laboratory findings and treatment

Antinuclear antibodies were positive in 2 patients (3.6%) and RF in 4 (7.3%); HLA-B27 was tested in 2 patients only and was negative in both. ESR was elevated in 21 patients (38.2%) and CRP was positive in 14 (25.5%) (Table 4). Methotrexate (oral or injectable) was used in 53 patients (96.4%), nonsteroidal anti-inflammatory drugs in 49 (89.1%) and corticosteroids, for variable periods, in 48 (87.3%) (Table 5). Other agents (etanercept, infliximab, leflunomide and azathioprine) were each used in a small number of patients [numbers to be confirmed from patient records].

Table 4 Laboratory findings in children with JIA (n = 55)

Test	Positive / high, n (%)	Negative / normal, n (%)	Unknown, n (%)
Antinuclear antibodies	2 (3.6)	50 (90.9)	3 (5.5)
Rheumatoid factor	4 (7.3)	49 (89.1)	2 (3.6)
ESR	21 (38.2)	34 (61.8)	–
C-reactive protein	14 (25.5)	41 (74.5)	–

ESR, erythrocyte sedimentation rate. HLA-B27 was tested in 2 patients (both negative).

Table 5 Medical treatment of children with JIA (n = 55)

Treatment	n	%
Methotrexate (oral or injectable)	53	96.4
Nonsteroidal anti-inflammatory drugs	49	89.1
Corticosteroids	48	87.3

Biochemical markers and vitamin D status

Serum calcium and phosphorus did not differ significantly between cases and controls (Table 6). Mean serum 25(OH)D was significantly higher in cases than in controls (33.5 ± 25.4 vs 23.6 ± 15.3 nmol/L; P = 0.014).

Table 6 Biochemical markers and serum 25(OH)D in children with JIA and controls

Variable	JIA cases (n = 55) mean ± SD (range)	Controls (n = 56) mean ± SD (range)	P value
Calcium, mg/dL	9.54 ± 0.76 (7.8–11.9)	9.64 ± 0.66 (7.77–11.12)	0.46[a]
Phosphorus, mg/dL	4.73 ± 0.87 (3.3–7.0)	4.94 ± 0.80 (3.2–7.0)	0.19[a]
Alkaline phosphatase, U/L	221.5 ± [SD to be confirmed] (46–1396)	228.0 ± 64.8 (66.5–366)	[P to be recalculated]
25(OH)D, nmol/L	33.5 ± 25.4 (5–100)	23.6 ± 15.3 (4.5–98.5)	0.014[a]

[a] Welch's t-test. 25(OH)D, 25-hydroxyvitamin D.

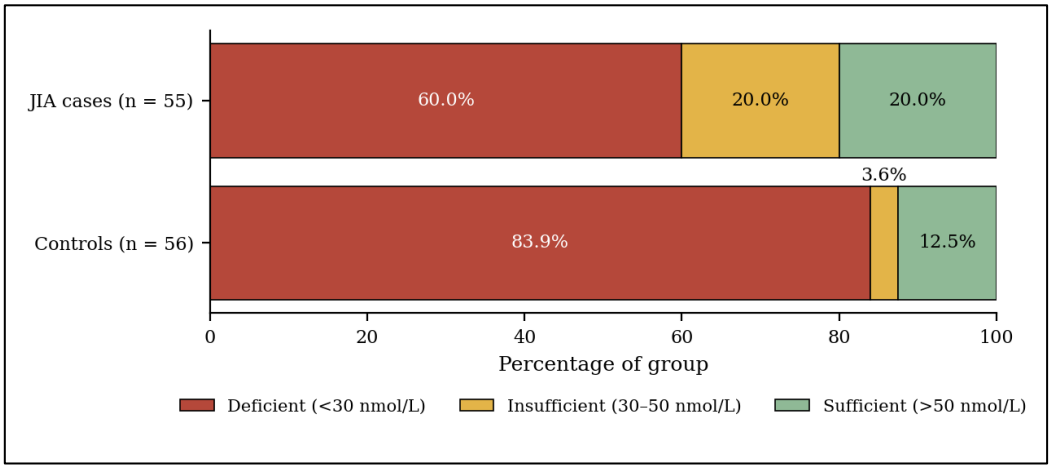
The distribution of vitamin D status differed between groups (P = 0.008; Table 7, Figure 2). Deficiency was present in 33 cases (60.0%) and 47 controls (83.9%) (P = 0.006); insufficiency in 11 cases (20.0%) and 2 controls (3.6%); and sufficiency in 11 cases (20.0%) and 7 controls (12.5%). Insufficiency or deficiency together was found in 44 cases (80.0%) and 49 controls (87.5%) (P = 0.31).

Table 7 Vitamin D status in children with JIA and controls

Vitamin D status	JIA cases (n = 55), n (%)	Controls (n = 56), n (%)	P value
Sufficient (>50 nmol/L)	11 (20.0)	7 (12.5)	0.008[a]
Insufficient (30–50 nmol/L)	11 (20.0)	2 (3.6)	
Deficient (<30 nmol/L)	33 (60.0)	47 (83.9)	0.006[b]
Insufficient or deficient	44 (80.0)	49 (87.5)	0.31[b]

[a] Pearson chi-square test (overall distribution); [b] Fisher's exact test.

Figure 2 Vitamin D status in children with JIA and controls



Vitamin D status and disease characteristics

Vitamin D status was not significantly associated with disease activity according to JADAS27 (P = 0.38; Table 8). Among the four children with high disease activity, one was vitamin D sufficient, two were insufficient and one was deficient. Vitamin D status did not differ significantly between JIA subtypes (P = 0.30; Table 9) or according to disease duration (P = 0.23; Table 10). Deficiency was found in 14 of 28 patients (50.0%) with a disease duration of less than 5 years, 17 of 24 (70.8%) with 5 to 10 years and 2 of 3 (66.7%) with more than 10 years.

Table 8 Vitamin D status according to disease activity (JADAS27), n (%) of 55 patients

Disease activity	Sufficient	Insufficient	Deficient
High disease activity (n = 4)	1 (1.8)	2 (3.6)	1 (1.8)
Minimal disease activity (n = 27)	6 (10.9)	6 (10.9)	15 (27.3)
Inactive (n = 24)	4 (7.3)	3 (5.5)	17 (30.9)
Total (n = 55)	11 (20.0)	11 (20.0)	33 (60.0)

P = 0.38 (Fisher–Freeman–Halton exact test).

Table 9 Vitamin D status according to JIA subtype, n (%)

Vitamin D status	Systemic onset (n = 18)	Persistent oligo (n = 7)	Extended oligo (n = 5)	Seronegative poly (n = 18)	Seropositive poly (n = 3)	Psoriatic (n = 4)
Sufficient	2 (11.1)	1 (14.3)	0 (0)	7 (38.9)	1 (33.3)	0 (0)
Insufficient	6 (33.3)	0 (0)	1 (20.0)	3 (16.7)	0 (0)	1 (25.0)
Deficient	10 (55.6)	6 (85.7)	4 (80.0)	8 (44.4)	2 (66.7)	3 (75.0)

P = 0.30 (Fisher–Freeman–Halton exact test). Oligo, oligoarthritis; poly, polyarthritis.

Table 10 Vitamin D status according to disease duration, n (%)

Vitamin D status	<5 years (n = 28)	5–10 years (n = 24)	>10 years (n = 3)
Sufficient	5 (17.9)	5 (20.8)	1 (33.3)

Vitamin D status	<5 years (n = 28)	5–10 years (n = 24)	>10 years (n = 3)
Insufficient	9 (32.1)	2 (8.3)	0 (0)
Deficient	14 (50.0)	17 (70.8)	2 (66.7)

P = 0.23 (Fisher–Freeman–Halton exact test).

Discussion

In this case control study of 55 Libyan children with JIA and 56 healthy controls, low vitamin D status was highly prevalent in both groups: 80.0% of patients and 87.5% of controls had insufficient or deficient 25(OH)D. Patients had a higher mean 25(OH)D concentration and a lower prevalence of deficiency than controls, and vitamin D status was not significantly associated with disease activity, JIA subtype or disease duration.

The finding that mean 25(OH)D was higher in patients than in controls differs from the expectation that children with chronic inflammatory arthritis would have lower concentrations. Several explanations are possible, including vitamin D supplementation or greater clinical attention in children already under specialist care, but vitamin D intake from food and supplements was not assessed in either group, so these remain hypotheses. The very high prevalence of deficiency among controls (83.9%) suggests that hypovitaminosis D is common among healthy Libyan children, although our controls were relatives of patients and may not represent the general pediatric population. The 80% prevalence of insufficiency or deficiency in our patients is of a similar magnitude to the 82% insufficiency reported in a meta-analysis of three JIA studies [10]; comparisons across studies are nevertheless limited by the lack of consensus on the ideal 25(OH)D concentration in children and by differences in the assays used, which may misclassify vitamin D status.

We found no significant association between vitamin D status and disease activity measured by JADAS27. The proportion of children with high disease activity was 9.1% (1 of 11) among those with sufficient, 18.2% (2 of 11) among those with insufficient and 3.0% (1 of 33) among those with deficient 25(OH)D, but only four patients had high disease activity, so the study had little power to detect such an association. Results in the literature are inconsistent. Lower 25(OH)D concentrations in children with active disease have been reported [11,12,15], whereas a study in Moroccan children found a relationship in univariate but not in multivariate analysis [13], and Pelajo et al. found no significant correlation between 25(OH)D and JADAS27 [18]. A Finnish study reported higher 25(OH)D concentrations in patients with active than with inactive disease [16].

Vitamin D status did not differ significantly between JIA subtypes in our study, although the subgroups were small. Deficiency was found in 6 of 7 patients (85.7%) with persistent oligoarthritis and 4 of 5 (80.0%) with extended oligoarthritis, compared with 10 of 18 (55.6%) with systemic-onset JIA. An abstract by Nisar et al. reported lower 25(OH)D in systemic JIA [17]. We also found no significant relationship with disease duration: deficiency was present in 50.0% of patients with a disease duration under 5 years and in 70.8% of those with 5 to 10 years ($P = 0.23$). This agrees with the absence of an association between 25(OH)D and disease duration reported by Munekata et al. [14]. Long-term cohort studies are needed to clarify this relationship.

Our study has several limitations. The sample was small, and some subtype, activity and duration groups contained very few patients, so non-significant results should not be read as evidence of no association. The study was conducted at a single center. Vitamin D intake from diet and supplements was not assessed in either group; season of sampling, sun exposure, clothing and body mass index were not analyzed; and a single measurement of 25(OH)D was available per child. Patients were already receiving treatment, including corticosteroids (87.3%) and methotrexate (96.4%), which may influence 25(OH)D concentrations and inflammatory status, and a study of newly diagnosed, untreated patients would be needed to address this. The sex distribution differed between cases and controls ($P = 0.047$) and no adjusted analyses were performed. Controls were siblings and cousins of the patients, who share genetic and environmental factors and are not fully independent observations. Finally, multiple comparisons were performed without adjustment. The strengths of the study are the inclusion of a control group, 25(OH)D measurement in a single laboratory with a standardized assay, the use of ILAR classification and JADAS27, and recruitment at a specialized pediatric rheumatology clinic in one of the largest children's hospitals in Libya.

These findings suggest that low vitamin D status is common among Libyan children, including those with JIA, and should be interpreted in that context when vitamin D is measured in children with JIA. The study cannot determine whether vitamin D supplementation influences the course of JIA.

Conclusions

Vitamin D deficiency and insufficiency were highly prevalent in both Libyan children with JIA (80.0%) and healthy controls (87.5%). Patients had higher mean 25(OH)D and less frequent deficiency than controls, and no significant association was found between vitamin D status

and disease activity, JIA subtype or disease duration. Prospective, multicenter studies with larger samples, including data on vitamin D intake and treatment and ideally newly diagnosed patients, are recommended to assess health outcomes related to vitamin D status in children with JIA.

Declarations

Ethical approval : this study was conducted in accordance with the ethical principles of Helsinski and relevant national and institutional guidelines and regulations. Ethical approval was obtained from the Libyan Board of Medical Specialties, Scientific Council of Pediatrics 2018.

Consent to participate: Verbal consent was obtained from parents or legal guardians and from older children.

Consent for publication: Not applicable .The manuscript does not contain identifiable individual participants' data.

Funding: This study was self-funded by the authors; and received no financial support from any external funding agency.

Competing interests: The authors declare no competing interests.

Acknowledgements: The authors thank Dr. Elhassan Bashir Dawi for revising this research.

Abbreviations

25(OH)D, 25-hydroxyvitamin D; ALP, alkaline phosphatase; ANA, antinuclear antibodies; CRP, C-reactive protein; ECLIA, electrochemiluminescence binding assay; ESR, erythrocyte sedimentation rate; ILAR, International League of Associations for Rheumatology; IOM, Institute of Medicine; JADAS27, Juvenile Arthritis Disease Activity Score using a 27-joint count; JIA, juvenile idiopathic arthritis; pGALS, pediatric Gait, Arms, Legs and Spine; RF, rheumatoid factor; SD, standard deviation; VDR, vitamin D receptor.

References

1. Holick MF. Vitamin D deficiency. *N Engl J Med*. 2007;357:266–81.

2. Pelajo CF, Lopez-Benitez JM, Miller LC. Vitamin D and autoimmune rheumatologic disorders. *Autoimmun Rev*. 2010;9(7):507–10.

3. Baeke F, Takiishi T, Korf H, et al. Vitamin D: modulator of the immune system. *Curr Opin Pharmacol*. 2010;10:482–96.

4. Ellis JA, Munro JE, Ponsonby AL. Possible environmental determinants of juvenile idiopathic arthritis. *Rheumatology (Oxford)*. 2010;49(3):411–25.

5. Ravelli A, Martini A. Juvenile idiopathic arthritis. *Lancet*. 2007;369(9563):767–78.

6. Manners PJ, Bower C. Worldwide prevalence of juvenile arthritis: why does it vary so much? *J Rheumatol*. 2002;29:1520–30.

7. Sabbagh Z, Markland J, Vatanparast H. Vitamin D status is associated with disease activity among rheumatology outpatients. *Nutrients*. 2013;5:2268–75.

8. Institute of Medicine, Food and Nutrition Board. *Dietary reference intakes for calcium and vitamin D*. Washington, DC: National Academies Press; 2010.

9. Holick MF, Binkley NC, Bischoff-Ferrari HA, et al. Evaluation, treatment, and prevention of vitamin D deficiency: an Endocrine Society clinical practice guideline. *J Clin Endocrinol Metab*. 2011;96:1911–30.

10. Nisar MK, Masood F, Cookson P, Sansome A, Östör AJK. What do we know about juvenile idiopathic arthritis and vitamin D? A systematic literature review and meta-analysis of current evidence. *Clin Rheumatol*. 2013;32:729–34.

11. Dağdeviren-Çakır A, Arvas A, Barut K, Gür E, Kasapçopur Ö. Serum vitamin D levels during activation and remission periods of patients with juvenile idiopathic arthritis and familial Mediterranean fever. *Turk J Pediatr*. 2016;58:125–31.

12. Çomak E, Doğan ÇS, Uslu-Gökçeoğlu A, Akbaş H, Özdem S. Association between vitamin D deficiency and disease activity in juvenile idiopathic arthritis. *Turk J Pediatr*. 2014;56:626–31.

13. Bouaddi I, Rostom S, El Badri D, Hassani A, Chkirate B, Abouqal R, et al. Vitamin D concentrations and disease activity in Moroccan children with juvenile idiopathic arthritis. *BMC Musculoskelet Disord*. 2014;15:115.

14. Munekata et al. Serum 25-hydroxyvitamin D and biochemical markers of bone metabolism in patients with juvenile idiopathic arthritis. *Braz J Med Biol Res*. 2013;46:98–102.

15. Tang X, Mingyue L. Association between vitamin D concentrations with disease activity and bone mineral density of juvenile idiopathic arthritis patients. *Int J Rheum Dis*. 2016;19:158 (abstract, 18th APLAR Congress, China, 26–29 September 2016).

16. Miettinen ME, Kinnunen L, Harjutsalo V, Reinert-Hartwall L, Lamberg-Allardt C, Tuomilehto J, et al. Serum 25-hydroxyvitamin D in juvenile idiopathic arthritis patients in Finland (letter). *Clin Exp Rheumatol*. 2013;31:988.

17. Nisar M, Cookson P, Masood F, Sansome A, Ostor A. Is there a link between vitamin D and juvenile idiopathic arthritis? *Ann Rheum Dis* (EULAR Annual European Congress of Rheumatology abstract, 12–15 June 2013). 2013:72.

18. Pelajo CF, Lopez-Benitez JM, Kent DM, Price LL, Miller LC, Dawson-Hughes B. 25-Hydroxyvitamin D levels and juvenile idiopathic arthritis: is there an association with disease activity? *Rheumatol Int*. 2012;32:3923–9.

19. Rosiles VH, Salazar CD, Velázquez RM, Ruiz RR, et al. Determination of 25(OH)D serum levels in children with systemic lupus erythematosus and juvenile idiopathic arthritis. *Bol Med Hosp Infant Mex*. 2015;72:99–105.