Uniwersytet Medyczny w Białymstoku
Wydział Lekarski z Oddziałem Stomatologii i Oddziałem Nauczania w Języku Angielskim

Lek. Maciej Konrad Stawicki

Status witaminy D u dzieci z wybranymi chorobami reumatycznymi

Vitamin D status in selected juvenile rheumatic diseases

Rozprawa doktorska

Promotor: Prof. dr hab. n. med. Jerzy Konstantynowicz

Promotor pomocniczy: Dr n. med. Paweł Abramowicz

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Spis treści

Wykaz stosowanych skrótów

ALP *(Alkaline phosphatase)* – fosfataza alkaliczna

BMI *(Body mass index)* – wskaźnik masy ciała

CaMKII *(Ca2+/calmodulin-dependent protein kinase II)* – kinaza białkowa II zależna od Ca^{2+}/kalmoduliny

CD40 *(Cluster of differentiation 40)* – białko CD40

CRP *(C-reactive protein)* – białko C-reaktywne

CYP27B1*(Cytochrome P450 family 27 subfamily B member 1/ 25-Hydroxyvitamin D 1-alpha-hydroxylase)* – 1-alfa-hydroksylaza 25-hydroksywitaminy D, białko 1 z podrodziny B, rodziny 27 cytochromu P450

CYP2R1 *(Cytochrome P450 family 2 subfamily R member 1/ vitamin D 25-hydroxylase)* – 25-hydroksylaza witaminy D; białko 1 z podrodziny R, rodziny 2 cytochromu P450

DMARDs *(Disease-modifying anti-rheumatic drugs)* – leki modyfikujące przebieg choroby

DNA *(Deoxyribonucleic acid)* – kwas dezoksyrybonukleinowy

FGF-23 *(Fibroblast growth factor-23)* – czynnik wzrostu fibroblastów 23

GKS – Glikokortykosteroidy

IFN-α *(Interferon alpha)* – interferon alfa

IFN-γ *(Interferon gamma)* – interferon gamma

IKKβ *(Inhibitor of nuclear factor kappa B kinase subunit beta)* – inhibitor podjednostki beta jądrowego czynnika kappa B

IQR *(Interquartile range)* – rozstęp międzykwartylowy/ćwiartkowy

JADAS27 *(Juvenile Arthritis Disease Activity Score-27)* – skala aktywności młodzieńczego idiopatycznego zapalenia stawów na podstawie oceny 27 stawów

jSLE *(juvenile Systemic Lupus Erythematosus)* – młodzieńczy toczeń rumieniowaty układowy

jSSc *(juvenile Systemic Scleroderma)* – młodzieńcza twardzina układowa

jDM *(juvenile Dermatomyositis)* – młodzieńcze zapalenie skórno-mięśniowe

MAP kinazy *(mitogen-activated protein kinases)* – kinazy białkowe aktywowane mitogenami

MIZS – młodzieńcze idiopatyczne zapalenie stawów

MTX – metotreksat

OB – odczyn Biernackiego

PDIA3 *(Protein disulfide-isomerase A3)* – białkowa izomeraza dwusiarczkowa A3

PFAPA *(Periodic fever, aphthous stomatitis, pharyngitis and cervical adenitis)* – zespół gorączek cyklicznych z towarzyszącymi aftami, ostrym zapaleniem gardła oraz zapaleniem węzłów chłonnych szyjnych

PI3K *(Phosphoinositide 3-kinase)* – kinaza 3'-fosfatydyloinozytolu

PKC *(Protein kinase C)* – kinaza białkowa C

PLA2 *(Phospholipase A2)* – fosfolipaza A2

PTH *(Parathormone)* – parathormon

RANKL *(Receptor activator for nuclear factor κ B ligand)* – ligand aktywatora receptora jądrowego czynnika κ B

RXR *(Retinoid X receptor)* – receptor kwasu 9-cis-retinowego

SP1 *(Specificity protein 1)* – czynnik transkrypcyjny Sp1/ białko specyficzności 1

SP1 *(Specificity protein 3)* – czynnik transkrypcyjny Sp3/ białko specyficzności 3

STAT1 *(Signal transducer and activator of transcription 1)* – przetwornik sygnału i aktywator transkrypcji 1

TLR2/4/8 *(Toll-like receptor 2/4/8)* – receptory Toll-podobne 2/4/8

TNF-α *(Tumor necrosis factor alpha)* – czynnik martwicy nowotworów alfa

UVB *(Ultraviolet B radiation)* – promieniowanie ultrafioletowe B

VDBP *(Vitamin D binding protein)* – białko wiążące witaminę D

VDR *(Vitamin D Receptor)* – receptor dla witaminy D

VDREs *(Vitamin D-response elements)* – elementy odpowiedzi dla witaminy D

WHO *(World Health Organization)* – Światowa Organizacja Zdrowia

Wykaz tabel i rycin

1. Wykaz publikacji stanowiących rozprawę doktorską

Niniejsza rozprawa doktorska pt. *Status witaminy D u dzieci z wybranymi chorobami reumatycznymi* powstała w ramach Studiów Doktoranckich Uniwersytetu Medycznego w Białymstoku. w oparciu o cykl dwóch publikacji naukowych. Obydwie zostały opublikowane w czasopismach z listy Journal Citation Reports.

a. **Stawicki Maciej Konrad**, Abramowicz Paweł, Sokolowska Gabriela, Wołejszo Sebastian, Grant William Burgess, Konstantynowicz Jerzy. *Can vitamin D be an adjuvant therapy for juvenile rheumatic diseases?* Rheumatology International 2023, 43(11):1993-2009. doi: 10.1007/s00296-023-05411-5.

IF = 4.0, punktacja MNiSW / MEiN = 70
Praca poglądowa

b. **Stawicki Maciej Konrad**, Abramowicz Paweł, Góralczyk Adrian, Młyńczyk Justyna, Kondratiuk Anna, Konstantynowicz Jerzy. *Prevalence of vitamin D deficiency in patients treated for juvenile idiopathic arthritis and potential role of methotrexate: a preliminary study.* Nutrients 2022, 14,8, 9 pp. doi: 10.3390/nu14081645

IF = 5.9, punktacja MNiSW / MEiN = 140
Praca oryginalna

Łączna wartość Impact Factor według JCR dla wymienionego cyklu wynosi 9,9 oraz 210 punktów według wykazu czasopism naukowych MNiSW / MEiN.

2. Zestawienie publikacji uwzględniające wartość Impact Factor (IF) oraz punktację MNiSW / MEiN

Rodzaj publikacji	Liczba	Impact Factor	Punktacja MNiSW / MEiN
Prace włączone do rozprawy doktorskiej	2	9,9	210
Prace, które nie zostały włączone do rozprawy doktorskiej	1	4	70
Streszczenia zjazdowe	8	-	-
Razem	11	13,9	280

3. Wstęp dotyczący tematyki rozprawy doktorskiej

Pomimo przeszło 100 lat od jej odkrycia i naukowego zdefiniowania [1], witamina D nadal pozostaje przedmiotem zainteresowania badaczy na całym świecie, z rosnącą wręcz – zwłaszcza w ostatnich trzech dekadach – skalą badań i liczbą publikacji [2,3]. Rola witaminy D wykracza dalece poza jej działanie przeciwkrzywicze, które przez wiele lat postrzegane było jako jedyny aksjomat. W ujęciu biochemicznym witamina D jest hormonem steroidowym, pozyskiwanym egzogennie z pożywienia lub suplementów jako jedna z witamin rozpuszczalnych w tłuszczach oraz na drodze endogennej syntezy, która stanowi jej główne źródło w ludzkim organizmie. Synteza witaminy D zachodzi w skórze kręgowców z 7-dehydrocholesterolu, przy udziale energii promieniowania słonecznego UVB o długości fali 290-315 nm [4]. Powstający w wyniku tej reakcji cholekalcyferol jest przy pomocy specyficznego transportera (Vitamin D-binding protein – VDBP) przenoszony do wątroby. Tam, przy pomocy 25-hydroksylazy (CYP2R1) z grupy cytochromu P450, ulega przekształceniu do kalcydiolu [25-(OH)D]. W następnym etapie związany z VDBP kalcydiol jest transportowany do nerek, gdzie kolejny enzym z grupy cytochromu P450 – 1α-hydroksylaza (CYP27B1), przekształca kalcydiol w kalcytriol [1,25$(OH)_2$D] – biologicznie aktywną formę witaminy D [5].

Witamina D wywiera swoje działanie poprzez swoisty receptor (Vitamin D receptor – VDR), należący do rodziny jądrowych receptorów steroidowych, który pełni funkcję jądrowego czynnika transkrypcyjnego. Według dostępnych danych oddziaływanie aktywowanego VDR na ekspresję genów odbywa się przy wsparciu RXR (Retinoid X receptor), który pozwala na stworzenie heterodimerycznego kompleksu wiążącego się z DNA. Wspomniana heterodimeryzacja zwiększa powinowactwo wiązania VDR do swoistych sekwencji DNA znanych jako elementy odpowiedzi na witaminę D (VDREs) i ułatwia regulację ekspresji genów [6]. Aktywacja VDR przez połączenie z 1,25$(OH)_2$D powoduje zmianę struktury biochemicznej receptora pozwalając na odłączenie białek hamujących jego funkcję oraz ewentualne połączenie z koaktywatorami [7,8]. Występowanie VDR zostało potwierdzone w prawie wszystkich tkankach budujących ludzki organizm (tkance kostnej, mięśniowej, tłuszczowej, nerwowej, naczyniach krwionośnych, trzustce, nerkach, układzie rozrodczym, komórkach układu odporności) [9–11]. Poza działaniem regulującym ekspresję genów postuluje się również szereg szybszych, niegenomowych efektów działania witaminy D. Wynikają one z aktywacji

wewnątrzkomórkowych cząsteczek sygnałowych (PKC, PI3K, MAP kinazy, CaMKII oraz PLA2) oddziałujących na czynniki transkrypcyjne (m.in. SP1, SP3, RXR). Ponadto, kalcytriol reguluje wiązanie VDR z białkami docelowymi (STAT1, IKKβ), umożliwiając krzyżową regulację ekspresji genów przez ligandy (m.in. IFN-α i TNF-α). Istnienie takiego mechanizmu – bardzo efektywnego z punktu widzenia fizjologii – pozwala na bezpośrednią regulację procesów immunologicznych oraz działanie przeciwwirusowe. Dodatkowo aktywacja receptora dla CD40, IFN-γ oraz TLR2/4/8 nasila ekspresję VDR oraz CYP27B1 zwiększając dostępność kalcytriolu i jego odziaływanie na wydzielanie mediatorów immunologicznych [12–14]. Mechanizm wyzwalania szybkich, pozagenomowych efektów działania witaminy D nie został w pełni wyjaśniony. Wiadomo jednak, że istotną rolę odgrywa w nim PDIA3, któremu przypisuje się rolę błonowego receptora dla witaminy D [13,15].

Istnieje wiele różnych wariantów polimorficznych genu kodującego VDR, warunkujących różnice w budowie i funkcjonowaniu receptora w kontekście jego powinowactwa do witaminy D, interakcji z koaktywatorami oraz aktywności transkrypcyjnej. Stąd też liczne, chociaż nie wszystkie, doniesienia w literaturze oraz silne dowody naukowe potwierdzają znaczenie polimorfizmów genu kodującego VDR w fenotypie wielu schorzeń. Niektóre warianty VDR mogą być związane ze zwiększoną podatnością na określone choroby, np. choroby autoimmunizacyjne [16–18].

Historycznie i w rozumieniu tradycyjnym, za klasyczne działanie witaminy D uznawany jest jej regulacyjny wpływ na stężenie wapnia we krwi. Aktywowany przez $1,25(OH)_2D$ VDR promuje wzrost wchłaniania wapnia w jelitach, wzrost reabsorpcji wapnia w kanalikach dystalnych nefronu oraz intensyfikację uwalniania wapnia ze szkieletu poprzez stymulację dojrzewania oraz aktywacji osteoklastów przy pomocy wydzielanego przez osteoblasty RANKL [3,19]. Promowanie powyższych procesów skutkuje wzrostem stężenia wapnia, skorelowanym ściśle ze wzrostem stężenia parathormonu (PTH) oraz czynnika wzrostu fibroblastów (FGF-23). Opisywane działania podlegają ścisłej kontroli i regulacji w oparciu o precyzyjne mechanizmy sprzężeń zwrotnych [20]. Odmiennie, w przypadku prawidłowego stężenia wapnia w krwi, działanie witaminy D polega na wyzwalaniu mechanizmów antyresorpcyjnych chroniących szkielet poprzez pobudzanie dojrzałych osteoblastów i nasilenie procesu osteogenezy [12]. Mechanizmy

warunkujące tak różnorodne, zależne od bieżącego stężenia witaminy D, efekty działania pozostają w dalszym ciągu przedmiotem badań.

Opisywana wcześniej powszechna ekspresja VDR warunkuje szerokie spektrum działania witaminy D, wykraczające znacznie poza regulację homeostazy wapnia [3,14,19,21]. Plejotropowe tj. wielofunkcyjne działanie witaminy D jest utożsamiane z rozwojem biologii ewolucyjnej, genetyki fizjologicznej i medycznej oraz technik molekularnych. Szeroko udokumentowany plejotropizm witaminy D polega między innymi na jej wpływie na sekrecję insuliny, oddziaływaniu na układ sercowo-naczyniowy, modyfikowaniu procesów immunologicznych, modulowaniu reakcji zapalnych, efektów proapoptotycznych i/lub antyproliferacyjnych [12,19,22].

Immunomodulujące działanie witaminy D jest związane z hamowaniem odporności swoistej przy jednoczesnym pobudzaniu odporności wrodzonej. W rezultacie supresja prozapalnych komórek Th1 i Th17 zmniejsza mediowaną przez nie odpowiedź zapalną. Następuje również stymulacja transformacji komórek dendrytycznych w podtypy o zwiększonej tolerancji immunologicznej. Dodatkowo, dzięki działaniu wit. D, zwiększona zostaje produkcja komórek T-regulatorowych odpowiedzialnych za hamowanie procesów zapalnych [22,23]. Jednocześnie wytwarzany lokalnie przez obecną w monocytach i makrofagach 1α-hydroksylazę (CYP27B1) kalcytriol – aktywna forma witaminy D – pobudza limfocyty B do syntezy immunoglobulin, hamując równolegle produkcję autoprzeciwciał oraz stabilizując śródbłonek naczyń [12,24]. Dodatkowo udowodniony wpływ witaminy D na produkcję katelicydyny, peptydu o silnych właściwościach przeciw drobnoustrojom chorobotwórczym, wskazuje na wyjątkowo ważny udział witaminy D w ochronie przed infekcjami bakteryjnymi i wirusowymi [25,26].

Według dostępnego piśmiennictwa niedobór witaminy D, definiowany z reguły i według najczęściej używanych kryteriów jako obniżenie stężenia 25(OH)D w krwi poniżej 20 ng/ml (50 nmol/l), stanowi istotny problem w światowej populacji [27–29]. Kontrowersje dotyczące określenia wartości granicznej 25(OH)D i progów ilościowych odpowiadających adekwatnemu zaopatrzeniu w witaminę D lub niedoborom (*sufficiency, deficiency, insufficiency*) są nadal bardzo szeroko dyskutowane, istotnie przy tym wpływając na rekomendacje i wytyczne. To zagadnienie wykracza oczywiście poza zakres przedmiotowy rozprawy. Niezależnie jednak od przyjętych i stosowanych w praktyce

wartości referencyjnych oraz definicji, deficyt witaminy D pozostaje zjawiskiem globalnym i ważnym z punktu widzenia zdrowia publicznego. Do potencjalnych przyczyn znaczącego rozpowszechniania niedoboru witaminy D należy niedostateczna endogenna synteza warunkowana przez warunki geograficzne i niedostateczne nasłonecznienie [30]. Problemem o rosnącym znaczeniu jest ograniczanie ekspozycji skóry na promieniowanie słoneczne poprzez stosowanie filtrów, odzieży ochronnej, jako działanie profilaktyczne w kontekście nowotworów skóry oraz przeciwdziałające procesom starzenia [31]. Kolejne aktualizacje światowych oraz lokalnych rekomendacji dotyczących profilaktyki oraz leczenia niedoborów witaminy D potwierdzają korzyści oraz bezpieczeństwo jej stosowania [32,33]. Poziom witaminy D uważany według aktualnych rekomendacji za adekwatny (30-50 ng/ml) pozwala na osiągnięcie pełni korzystnego wpływu na układ kostny i gospodarkę wapniową [19,34]. Otwartym pozostaje pytanie, jaki poziom witaminy D jest wystarczający do osiągnięcia wszystkich pozaszkieletowych efektów jej działania [15,35,36]

Plejotropowe działanie witaminy D obejmujące również efekty przeciwzapalne oraz immunomodulujące, powszechność jej niedoboru w populacji ogólnej oraz doniesienia o rosnącej częstości występowania chorób autoimmunizacyjnych [37], w tym chorób reumatycznych [38], stały się punktem wyjścia do poszukiwania zależności pomiędzy poziomem zaopatrzenia w witaminę D i chorobami z tej grupy, również w populacji pediatrycznej. Na przestrzeni ostatnich lat przeprowadzono liczne badania w poszukiwaniu roli witaminy D w patogenezie chorób reumatycznych włączając między innymi reumatoidalne zapalenie stawów, twardzinę układową, toczeń rumieniowaty układowy i spondyloartropatie [39–43]. Dostępne dane dotyczą w przeważającej części populacji dorosłej. Badania oceniające wpływ witaminy D na procesy odpowiadające za rozwój oraz przebieg chorób reumatycznych dotyczące populacji dziecięcej są zdecydowanie mniej liczne Jednakże w badanych grupach dzieci dotkniętych MIZS [44–47], młodzieńczym SLE [48–50], młodzieńczą SSC [51], młodzieńczym DM [50] odnotowywano niższe stężenie witaminy D w porównaniu do zdrowych rówieśników. Brakuje solidnych danych wyjaśniających mechanizmy warunkujące opisywane różnice. Długotrwały, zwłaszcza ciężki, niedobór witaminy D znacznie upośledza natomiast regulację mechanizmów immunologicznych, prowadząc w efekcie do zaostrzenia procesów zapalnych [52,53].

Powodem podjęcia rozważań na temat statusu witaminy D u dzieci z chorobami reumatycznymi jest rosnąca ranga tego zjawiska, tzn. coraz częstsze występowanie tych schorzeń w populacji wieku rozwojowego. Znajduje to swoje odzwierciedlenie przede wszystkim w obserwacjach klinicznych, w danych epidemiologicznych i w praktyce, z drugiej zaś strony wiąże się z dynamicznym rozwojem dziedziny medycyny, jaką jest reumatologia dziecięca. Mimo wielu dostępnych opcji terapeutycznych o potwierdzonej skuteczności, trwają poszukiwania nowych leków przeciwreumatycznych oraz innych wspomagających form farmakoterapii w reumatologii dorosłej i dziecięcej. Należy przy tym podkreślić, że procesy rejestracji nowych substancji lub leków – w tym głównie antyreumatycznych modyfikujących przebieg choroby (*Disease-modifying anti-rheumatic drugs*, DMARDs) – są znacznie trudniejsze w populacji pediatrycznej niż w populacji dorosłej. Wynika to częściowo z natury chorób reumatycznych u dzieci i rzadkiego ich występowania, częściowo zaś z obwarowań natury etycznej. W leczeniu wspomagającym chorób reumatycznych u dzieci podejmuje się próby wykorzystania poznanych już wcześniej substancji lub suplementów, ale w nowym kontekście klinicznym i terapeutycznym. Dzięki swojemu plejotropowemu działaniu, obejmującemu wpływ immunomodulujący na procesy zapalne, witamina D stanowi interesujący i obiecujący cel dalszych badań. W związku z udowodnionym korzystnym, plejotropowym działaniem witaminy D, zapewnienie jej prawidłowego stężenia jest rekomendowane jako jeden z elementów leczenia wspomagającego w wielu chorobach przewlekłych, we wszystkich grupach wiekowych.

W badaniach składających się na niniejszą rozprawę doktorską podjąłem się określenia statusu witaminy D u dzieci leczonych z powodu MIZS oraz zależności między aktywnością choroby, postaciami klinicznymi, stosowanym leczeniem a stężeniem 25(OH)D. Wyniki nielicznych opublikowanych dotychczas badań sugerują niekorzystny (pośredni lub – rzadziej – bezpośredni) wpływ niektórych DMARDs na stężenie witaminy D, podkreślając jednocześnie celowość i efektywność suplementacji witaminy D wśród dzieci chorujących na MIZS.

4. Cel pracy

Głównym założeniem badawczym niniejszej pracy była ocena statusu witaminy D u dzieci i młodzieży leczonych z powodu młodzieńczego idiopatycznego zapalenia stawów (MIZS; *juvenile idiopathic arthritis*, JIA).

Cele pracy obejmowały:

1. Ocenę zaopatrzenia w witaminę D dzieci i młodzieży chorych na MIZS

2. Określenie powiązań między stężeniem 25-hydroksywitaminy D [25(OH)D] w krwi, klinicznymi wykładnikami aktywności choroby i leczeniem stosowanym w MIZS

3. Poszukiwanie potencjalnych czynników ryzyka niedoboru witaminy D w grupie pacjentów z MIZS

5. Omówienie publikacji składających się na rozprawę doktorską

Pierwszą publikację w zestawieniu stanowi artykuł poglądowy *Can vitamin D be an adjuvant therapy for juvenile rheumatic diseases?* (Stawicki MK et al. Rheumatol Int 2023), w którym przeanalizowano dostępne piśmiennictwo i dobrej jakości dane w poszukiwaniu informacji na temat roli witaminy D w leczeniu wybranych chorób reumatycznych u dzieci. W tej pracy mającej charakter *narrative review* w sposób szczególny skoncentrowano się na suplementacji i leczeniu witaminą D w kontekście terapii stosowanych współcześnie w reumatologii dziecięcej, podejmując próbę określenia obecnego stanu wiedzy w tym obszarze. We wstępie artykułu zwięźle scharakteryzowano budowę chemiczną, właściwości biochemiczne oraz plejotropowe działanie witaminy D, ze szczególnym uwzględnieniem jej wpływu na procesy które mogą być zaangażowane w patogenezę oraz warunkować przebieg chorób autoimmunizacyjnych, w tym schorzeń reumatycznych w populacji dziecięcej.

Celem tego artykułu było poszukiwanie, krytyczna obiektywna analiza oraz podsumowanie dostępnych danych na temat potencjalnej roli witaminy D w leczeniu wybranych chorób reumatycznych u dzieci.

Materiał i metody

Przeszukano bazy Medline/PubMed, EMBASE, Scopus, zebrano i podsumowano dostępne dane z piśmiennictwa dotyczące wpływu suplementacji i optymalnego stężenia witaminy D na przebieg wybranych chorób reumatycznych u dzieci. Do dalszej analizy wzięto pod uwagę wyłącznie artykuły napisane w języku angielskim dotyczące pacjentów poniżej 18-tego roku życia. Preferowane były prace najnowsze, z największą liczbą cytowań. Dokonano również analizy piśmiennictwa dla wybranych publikacji, aby dodatkowo zweryfikować, czy nie zostały pominięte istotne dla tematu badania. Nie ustanowiono kryterium czasowego dla wyszukiwanych publikacji. Ostatecznie wszystkie zidentyfikowane artykuły przeszły wstępną ocenę pod względem spełnienia kryteriów włączenia na podstawie tytułu i streszczenia, a następnie oceny treści pełnotekstowej dokonanej niezależnie przez dwóch badaczy. Wszelkie niejasności były rozstrzygane drogą dyskusji, polemiki naukowej i poprzez konsensus. Ostatecznie przeanalizowano publikacje dotyczące znacznej części chorób z dziedziny reumatologii dziecięcej z ostatniej dekady, czyli takich chorób jak młodzieńcze idiopatyczne zapalenie stawów (MIZS / JIA) oraz

znacznie rzadziej występujące schorzenia: młodzieńczy toczeń rumieniowaty układowy (jSLE), młodzieńcza twardzina układowa (jSS), młodzieńcze idiopatyczne miopatie zapalne, choroba Behçeta, młodzieńcze zespoły gorączek cyklicznych, zespół PFAPA, rodzinna gorączka śródziemnomorska (FMF).

Wyniki i podsumowanie artykułu Stawicki et al. Rheumatol Int 2023

Witamina D wywiera szerokie spektrum korzystnych efektów na komórki ludzkiego organizmu. Szereg badań in vitro oraz in vivo potwierdza plejotropowe działanie witaminy D, włączając regulacyjny wpływ na układ immunologiczny, działanie immunomodulujące w chorobach autozapalnych, w tym chorobach reumatycznych wieku dziecięcego. Choroby zaliczanie do tej grupy nie należą do najczęstszych problemów dotykających pacjentów w wieku rozwojowym, ale wywierają istotne z punktu widzenia populacyjnego oraz długotrwałe implikacje prowadzące do obniżenia jakości życia pacjentów, rzutując jednocześnie na ich dalsze funkcjonowanie w dorosłości. Niedobór witaminy D dotyka znaczący odsetek światowej populacji, stanowiąc coraz istotniejszy problem, również wśród dzieci obciążonych chorobami reumatycznymi. Dostępne piśmiennictwo dotyczące badanej tematyki jest ograniczone. Niedostateczna ilość wiarygodnych danych może wynikać z zastosowania metodologii – charakterystycznej i sprawdzonej w badaniach nad lekami, pomijającej jednak unikalne właściwości biochemiczne witaminy D. Klasycznie i konwencjonalnie rozumiane szkieletowe efekty wywierane przez witaminę D są związane ze stężeniem 25(OH)D w surowicy i mogą być zróżnicowane w zależności od jej poziomu wyjściowego oraz zastosowanej dawki (trudność w ocenie efektu biologicznego wiąże się z metodologią). Adekwatne stężenie witaminy D, pozwalające na pełne ujawnienie jej działania pozaszkieletowego, szczególnie związanego z regulowaniem procesów autoimmunologicznych pozostaje nieustalone. W większości analizowanych prac używano takiej samej dawki witaminy D dla wszystkich uczestników, bez potwierdzenia czy była ona skuteczna dla zapewnienia wystarczającego poziomu 25(OH)D.

Zebrane dane, mimo obiecującego charakteru, są niewystarczające do odpowiedzi na pytanie o uzupełniającą rolę witaminy D w leczeniu chorób reumatycznych u dzieci. Aby było to możliwe, koniecznie jest przeprowadzanie większej ilości badań, szczególnie dobrze zaprojektowanych prospektywnych badań klinicznych z randomizacją. Biorąc pod uwagę dużą częstość występowania niedoboru witaminy D w światowej populacji, należy

zachęcać dzieci i osoby dorosłe do suplementacji witaminy D według aktualnych dostępnych rekomendacji.

Drugą pracę w cyklu stanowi wieloautorski artykuł zatytułowany *Prevalence of vitamin D deficiency in patients treated for juvenile idiopathic arthritis and potential role of methotrexate: a preliminary study* (Stawicki MK et al. Nutrients 2022)

Celem powyższej pracy była analiza poziomu zaopatrzenia w witaminę D oraz częstości występowania jej niedoboru wśród dzieci z młodzieńczym idiopatycznym zapaleniem stawów (MIZS). Dodatkowo poszukiwano korelacji pomiędzy stężeniem witaminy D a stanem klinicznym, wynikami innych badań laboratoryjnych, zastosowanym leczeniem obejmującym metotreksat (MTX) oraz glikokortykosteroidy (GKS).

Materiał i metody

Badaniem o charakterze przekrojowym objęto 189 pacjentów leczonych w Klinice oraz w przyklinicznej Poradni Reumatologicznej UDSK w Białymstoku z powodu MIZS, w stabilnej fazie choroby. Rozpoznanie zostało ustalone na podstawie powszechnie przyjętych obowiązujących kryteriów diagnostycznych (wg EULAR, ACR, ILAR). Ocena kliniczna pacjentów została dokonana na podstawie badania przedmiotowego oraz testów funkcjonalnych, następnie dokonywano pomiarów antropometrycznych (masy ciała, wzrostu, BMI) przy użyciu standardowych metod pomiarowych zgodnych z wytycznymi WHO. Aktywność choroby została zmierzona przy użyciu skali JADAS27 (*Juvenile Arthritis Disease Activity Score*). W kolejnym etapie pobrano krew do oznaczenia wybranych parametrów laboratoryjnych. Poziom witaminy D oceniano na podstawie pomiaru stężenia 25(OH)D we krwi metodą immunoenzymatyczną przy użyciu testu Immulite®2000 Immunoassay System Siemens AG, Munich, Germany. Dodatkowo dokonano oznaczenia stężenia białka C-reaktywnego (CRP), odczynu opadania krwinek czerwonych (OB), stężenia wapnia, fosforanów, aktywności fosfatazy alkalicznej (ALP). Niedobór witaminy D określono na podstawie rekomendacji Institute of Medicine oraz aktualnych wytycznych dla Europy Środkowej jako stężenie 25(OH)D mniejsze niż 20 ng/ml. Zgromadzone dane zostały następnie poddane analizie statystycznej przy użyciu oprogramowania STATISTICA (ver. 13.3, Tibco Software Inc., Palo Alto, CA, USA) oraz statsmodels.org (ver. 0.13.2). Normalność rozkładu została sprawdzona przy pomocy testu Shapiro-Wilka. Zmienne o rozkładzie normalnym zostały wyrażone przy pomocy średnich

i odchyleń standardowych. Przy braku normalności rozkładu wyniki zostały zaprezentowane przy pomocy mediany i IQR. Następnie zastosowano test t-Studenta lub test U Manna-Whitneya w zależności od rodzaju rozkładu zmiennej. Pary zmiennych zostały porównane przy pomocy testu korelacji rang Pearsona. Ostatecznie zbadano zależności pomiędzy stężeniem 25(OH)D oraz masą ciała, BMI, dawką MTX, dawką GKS, CRP, OB, stężeniem wapnia, potasu oraz aktywności ALP przy pomocy wielomianowej regresji logistycznej.

Wyniki

W badaniu brało udział 113 dziewczynek i 76 chłopców rasy kaukaskiej, nieobciążonych innymi chorobami przewlekłymi, które mogłyby wpływać na stężenie witaminy D lub metabolizm kostny. Mediana wieku pacjentów wyniosła 13,12 lat (3-17,7 lat, IQR 6,23). Żaden z pacjentów w chwili kwalifikacji do badania nie przyjmował preparatów zawierających witaminę D. Wśród wszystkich pacjentów 49% (n=93) miało ustalone rozpoznanie MIZS o początku nielicznostawowym (*oligoarthritis*), u 44% (n=83) pacjentów zdiagnozowano MIZS o początku wielostawowym, a u 7% (n=13) postać o początku uogólnionym. Wszyscy pacjenci w chwili kwalifikacji do badania byli w remisji lub mieli minimalną aktywność choroby zgodnie ze skalą JADAS27.

Jedynym lekiem modyfikującym przebieg choroby stosowanym u badanych pacjentów był MTX podawany doustnie lub podskórnie w dawce 10–20 mg na m^2 powierzchni ciała na tydzień. Pomostowej terapii glikokortykosteroidami (GKS) wymagało 73 pacjentów (38,6%). Strukturę badanej populacji ilustruje Tabela 1.

Tabela 1. Charakterystyka badanej grupy pacjentów (* podane wartości mediany i rozstępu międzykwartylowego tam, gdzie były wyliczone).

	Liczba pacjentów (n = 189)
Wiek (lata) *	13,12 (6,23)
Chłopcy/Dziewczynki	76/113
Masa ciała (kg) *	48,5 (24,0)
Wzrost (cm) *	155,0 (28,0)
BMI (kg/m2) *	19,58 (5,26)
MIZS o początku wielostawowym (n; %)	83 (43,9%)
MIZS o początku nielicznostawowym (n; %)	93 (49,2%)
MIZS o początku uogólnionym (n; %)	13 (6,9%)
Pacjenci leczeni GKS (n; %)	73 (38,6%)
Pacjenci leczeni MTX (n; %)	84 (44,4%)

Mediana stężenia witaminy D wynosiła w badanej grupie 15,0 ng/ml (IQR 12,0). Niedobór witaminy D stwierdzono u 127 uczestników badania (67,2 %). Stężenie witaminy D nie było zależne od płci, wieku, postaci klinicznej, aktywności choroby, bądź wskaźników stanu zapalnego. Stężenie 25(OH)D wykazywało odwrotną zależność z BMI (r= -0,19). Potwierdzono słabą, ale istotną statystycznie dodatnią korelację stężenia witaminy D ze stężeniem wapnia (r= 0,19). Znaleziono zależność pomiędzy stężeniem witaminy D i zastosowanym leczeniem wśród pacjentów z MIZS. Rodzaj leczenia oddziaływał na stężenie wapnia i fosforu wśród dziewczynek i chłopców. Pacjenci z niedoborem witaminy D wymagali istotnie wyższej dawki MTX w porównaniu do pacjentów u których stężenie 25(OH)D było wyższe niż 20 ng/ml ($p<0,05$). Tabela 2 przedstawia charakterystykę badanej grupy w zależności od stężenia 25(OH)D.

Tabela 2. Charakterystyka pacjentów z MIZS biorących udział w badaniu w odniesieniu do stężenia 25(OH)D powyżej lub poniżej 20 ng/ml (* przedstawione średnia i odchylenie standardowe lub ** mediana i rozstęp międzykwartylowy).

	Niskie stężenie 25(OH)D <20 ng/mL	**Prawidłowe stężenie 25(OH)D ≥20 ng/mL**	**Wartość p**
Liczba pacjentów (%)	127 (67,2%)	62 (32,8%)	
Wiek (lata) **	13,34; (5,18)	11,84 (8,32)	0,19
Masa ciała (kg) **	50,0 (22,0)	45,35 (33,0)	0,14
Wzrost (cm) **	156,5 (25,0)	148,00 (37,5)	0,15
BMI (kg/m2) **	19,81 (4,88)	19,06 (6,1)	0,17
Dawka dobowa GKS (mg) **	5,0 (5,0)	5,00 (5,0)	0,29
Dawka tygodniowa MTX (mg) ** na m2 powierzchni ciała	15,0 (7,5)	12,5 (7,5)	0,02
CRP (mg/l) **	1,0 (3,7)	1,6 (12,0)	0,23
25(OH)D (ng/ml) **	12,0 (8,0)	25,5 (6,0)	<0,001
Ca (mmol/l) *	2,48 ± 0,09	2,52 ± 0,12	0,01
P (mg/dl) *	4,50 ± 0,63	4,54 ± 0,72	0,76
ALP (U/l) **	165,0 (138,0)	172,0 (124,0)	0,70
OB (mm/h) **	11,50 (22,0)	19,0 (30,0)	0,05
Punktacja w skali JADAS27 **	1,5 (0,7)	1,5 (0,5)	0,64

Zależność wymaganej dawki MTX od stężenia 25(OH)D została potwierdzona współczynnikiem korelacji Pearsona, wskazującym na odwrotną korelację pomiędzy tymi zmiennymi ($r= -0,33$, $p<0,05$). Co więcej wykazano również istotną statystycznie odwrotną korelację pomiędzy dawką MTX a stężeniem wapnia ($r = -0,31$, $p < 0,05$) i fosforanów ($r = -0,42$, $p < 0,05$). Nie znaleziono natomiast istotnego związku pomiędzy dawką MTX oraz stężeniem ALP. Odmiennie, nie wykazano istotnej korelacji pomiędzy dobową dawką GKS oraz stężeniem 25(OH)D. Wykazano jednak istotną statystycznie odwrotną korelację pomiędzy dawką GKS oraz stężeniem ALP ($r = -0,79$, $p <0,05$),

wapnia (r = -0,23, p <0,05) i fosforanów (r = -0.27, p < 0,05) u badanych pacjentów. Zbadane zależności zostały przedstawione w Tabeli 3.

Tabela 3. Korelacje dwóch zmiennych dla dawki MTX, dawki GKS, stężenia wapnia, fosforanów u dzieci leczonych z powodu MIZS.

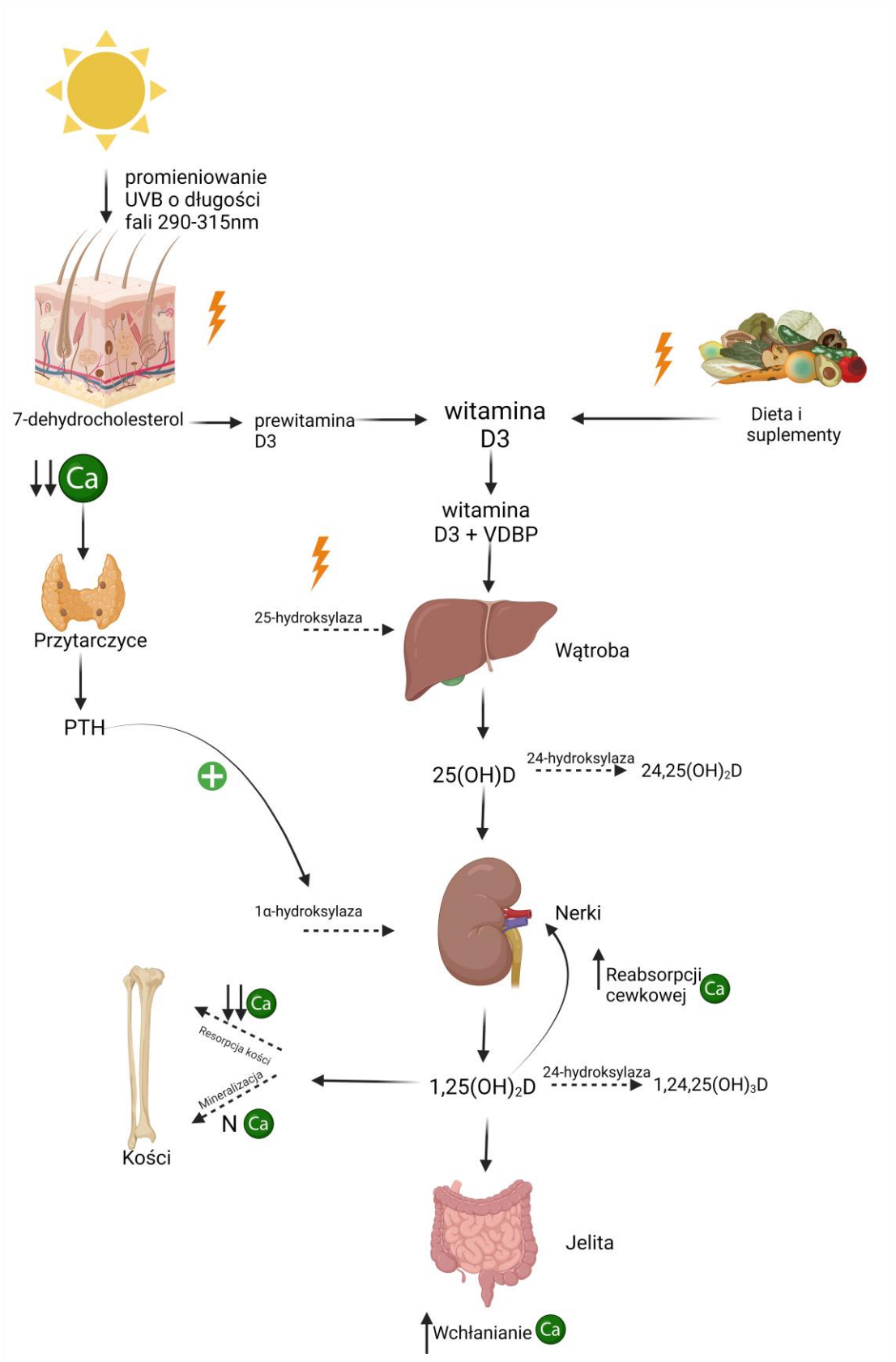
	Dawka tygodniowa MTX na m^2 powierzchni ciała	**Dawka dobowa GKS**
25(OH)D	r = -0,33; p = 0,003	r = -0,08; p = 0,26
Stężenie wapnia	r = -0,31; p = 0,01	r = -0,23; p = 0,01
Stężenie fosforanów	r = -0,42; p = 0,03	r = -0,27; p = 0,004
ALP	r = -0,14; p = 0,17	r = -0,79; p = 0,004

W kolejnym etapie analizy wykonano wielomianową regresję logistyczną modelu zawierającego określone zmienne – zgodnie z Tabelą 4. Spośród czynników uwzględnionych w modelu tylko tygodniowa dawka MTX wykazywała istotną, odwrotną zależność ze stężeniem 25(OH)D (współczynnik 1,79, p< 0,05). Nie udało się natomiast potwierdzić istotnego statystycznie związku stężenia 25(OH)D z innymi zmiennymi uwzględnionymi w modelu.

Tabela 4. Wyniki wielomianowej regresji logistycznej przeprowadzonej do analizy wieloczynnikowej parametrów związanych ze stężeniem 25(OH)D.

	Współczynnik	**Błąd standardowy (SE)**	**95% przedział ufności (95% CI)**		**Wartość P**
Masa ciała	0,09	0,40	-0,69	0,87	0,82
BMI	-0,08	0,32	-0,70	0,54	0,80
GKS dawka dobowa	0,18	0,21	-0,24	0,60	0,41
MTX dawka tygodniowa na m^2 pow. ciała	1,79	0,74	0,33	3,24	0,02
CRP (mg/l)	-0,29	0,23	-0,74	0,17	0,21
OB (mm/h)	-0,72	0,23	-0,51	0,37	0,75
Ca (mmol/l)	-0,13	0,19	-0,51	0,24	0,48
P (mg/dl)	0,32	0,21	-0,10	0,73	0,13
ALP (U/l)	0,01	0,20	-0,37	0,40	0,94

Rycina 1. Mechanizm powstawania witaminy D oraz jej działania na gospodarkę wapniową z uwzględnieniem możliwych interakcji metotreksatu (MTX) oznaczonych symbolem ⚡.



Wnioski z badania opublikowanego w Nutrients (Stawicki et al. 2022)

Deficyt witaminy D wyrażony suboptymalnym stężeniem 25(OH)D dotyczył znaczącej części pacjentów z MIZS, niezależnie od płci, wieku, stopnia aktywności choroby, manifestacji klinicznej, parametrów stanu zapalnego. Długotrwała terapia MTX wydaje się być związana z obniżonym stężeniem witaminy D (Ryc. 1). Ponadto z analizy danych tej pracy wynika, że stosowanie GKS u pacjentów z MIZS wpływa w istotny sposób na stężenie wapnia i fosforanów w krwi, a jednocześnie nie wpływa na stężenie 25(OH)D. Uzyskane wyniki sugerują potrzebę odpowiedniej suplementacji witaminy D wśród pacjentów chorych na MIZS, w szczególności tych leczonych przewlekle MTX. Z uwagi na ograniczenia wynikające z charakteru przeprowadzonego badania (*cross-sectional observational study*), ustalenie mechanizmów mogących ewentualnie odpowiadać za uzyskane tu wyniki wymagałoby dalszych odpowiednio zaplanowanych badań prospektywnych. Konieczne wydaje się badanie każdego pacjenta z MIZS leczonego MTX pod względem zaopatrzenia w witaminę D oraz rozważenie systematycznej suplementacji witaminy D. Optymalne wydaje się postępowanie oparte o mierzalny i kontrolowany efekt dawkowania (tzw. *dose-response effect* / *dose-response study*).

6. Publikacje stanowiące rozprawę doktorską

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REVIEW

Can vitamin D be an adjuvant therapy for juvenile rheumatic diseases?

Maciej K. Stawicki[1] · Paweł Abramowicz[1] · Gabriela Sokolowska[2] · Sebastian Wołejszo[1] · William B. Grant[3] · Jerzy Konstantynowicz[1]

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Abstract
Vitamin D, known for its essential role in calcium and bone homeostasis, has multiple effects beyond the skeleton, including regulation of immunity and modulation of autoimmune processes. Several reports have shown suboptimal serum 25 hydroxyvitamin D [25(OH)D] levels in people with different inflammatory and autoimmune rheumatic conditions, and an association between 25(OH)D levels, disease activity and outcomes. Although most available data pertain to adults, insights often are extended to children. Juvenile rheumatic diseases (JRDs) are a significant health problem during growth because of their complex pathogenesis, chronic nature, multisystemic involvement, and long-term consequences. So far, there is no definitive or clear evidence to confirm the preventive or therapeutic effect of vitamin D supplementation in JRDs, because results from randomized controlled trials (RCTs) have produced inconsistent outcomes. This review aims to explore and discuss the potential role of vitamin D in treating selected JRDs. Medline/PubMed, EMBASE, and Scopus were comprehensively searched in June 2023 for any study on vitamin D supplementary role in treating the most common JRDs. We used the following keywords: "vitamin D" combined with the terms "juvenile idiopathic arthritis", "juvenile systemic scleroderma", "juvenile systemic lupus erythematosus", "juvenile inflammatory myopathies", "Behcet disease", "periodic fever syndromes" and "juvenile rheumatic diseases". Observational studies have found that serum 25(OH)D concentrations are lower in juvenile idiopathic arthritis, juvenile systemic lupus erythematosus, juvenile systemic scleroderma, Behcet disease and proinflammatory cytokine concentrations are higher. This suggests that vitamin D supplementation might be beneficial, however, current data are insufficient to confirm definitively the complementary role of vitamin D in the treatment of JRDs. Considering the high prevalence of vitamin D deficiency worldwide, children and adolescents should be encouraged to supplement vitamin D according to current recommendations. More interventional studies, especially well-designed RCTs, assessing the dose–response effect and adjuvant effect in specific diseases, are needed to determine the potential significance of vitamin D in JRDs treatment.

Keywords Vitamin D · Juvenile idiopathic arthritis · Juvenile systemic lupus erythematosus · Juvenile systemic scleroderma · Idiopathic inflammatory myopathies · Periodic fever syndromes

✉ Jerzy Konstantynowicz
jurekonstant@o2.pl

Maciej K. Stawicki
stawicki.m.k@gmail.com

Paweł Abramowicz
pawel.abramowicz@umb.edu.pl

Gabriela Sokolowska
gsokolowska18@gmail.com

Sebastian Wołejszo
sebastian.wolejszo7@gmail.com

William B. Grant
wbgrant@infionline.net

[1] Department of Pediatrics, Rheumatology, Immunology, and Metabolic Bone Diseases, Medical University of Bialystok, University Children's Clinical Hospital in Bialystok, Waszyngtona Street 17, 15274 Bialystok, Poland

[2] University Children's Clinical Hospital in Bialystok, Bialystok, Poland

[3] Sunlight, Nutrition, and Health Research Center, San Francisco, CA, USA

Introduction

Vitamin D's role in the human body extends beyond maintaining the skeleton's mineral balance. A secosteroid hormone, vitamin D exerts its functions via the vitamin D receptor (VDR), a transcription factor found in the skin, muscle, skeleton, kidney, adipose tissue, pancreas, blood vessels, brain, breast tissue, placenta, and immune cells. Vitamin D not only is synthesized mainly in the skin through sun exposure but also is obtained through supplements and, to a lesser extent, dietary sources such as fish and fortified foods [1].

Vitamin D has been extensively studied in various health issues, including chronic and infectious diseases. Although the evidence regarding its significance and preventive role is not entirely consistent, well-designed studies generally support the notion that vitamin D offers several health benefits across the stages of life [2–4].

Juvenile rheumatic diseases (JRDs) encompass a range of conditions affecting joints, tendons, muscles, ligaments, and bones, as well as vital organs such as the lungs, heart, and kidneys. The exact causes of most JRDs and connective tissue diseases are not fully understood, and their etiology is believed to be multifactorial [5]. Therefore, treatment of those conditions often targets multiple mechanisms or symptoms. Management protocols for JRDs are disease-specific, and many therapies rely on classical or biological disease-modifying antirheumatic drugs (DMARDs). Given the chronic nature of those conditions, which affect children's present and future health, managing JRDs typically involves long-term treatment strategies that require regular monitoring of therapeutic outcomes, advantages, and potential adverse reactions [6].

Previous researchers have investigated how adequate serum 25-hydroxyvitamin D [25(OH)D] concentration affects juvenile and adult rheumatic diseases. However, findings have been inconsistent and data regarding the pediatric population remain limited [7–10]. Likewise, beneficial effects of vitamin D intake and supplementation have been observed in patients with various chronic diseases, including those with rheumatic diseases [11–14]. Vitamin D's positive influence on disease progression and outcomes is probably due to its role in maintaining bone turnover, calcium homeostasis, muscle function, and mineral metabolism, as well as regulating immune and inflammatory responses [4, 15]. The existing literature emphasizes the importance of maintaining high or optimal concentrations of serum 25(OH)D in shaping the clinical manifestations of rheumatic diseases, although the available data focus mainly on the adult population. Vitamin D's potential therapeutic role in JRD remains poorly understood.

This review aims to assess vitamin D's specific role as a treatment component or therapeutic agent in JRDs. We sought to gather and summarize the available evidence on vitamin D supplementation in selected juvenile rheumatic conditions.

Methods

Medline/PubMed, EMBASE, and Scopus were comprehensively searched in June 2023 for any study on vitamin D supplementary role in treating the most common JRDs. We used the following keywords: "vitamin D" combined with the terms "juvenile idiopathic arthritis", "juvenile systemic scleroderma", "juvenile systemic lupus erythematosus", "juvenile inflammatory myopathies", "juvenile rheumatic diseases", "Behcet disease", "periodic fever aphthous stomatitis pharyngitis and adenopathy syndrome", "familial Mediterranean fever", "hyper-IgD syndrome", "cryopyrin-associated periodic syndrome", "tumor necrosis factor receptor-associated periodic syndrome", "periodic fever syndromes". The search strategies for each database can be found in Appendix. No publication date restriction was applied. Only papers in English regarding populations younger than 18 years were taken into consideration. Most recent and most cited publications were in favor. In addition, we screened the reference lists of the selected publications to ensure that no potentially relevant studies were missed. Forward references searching of included studies was conducted using Web of Science to identify other research that has referenced any article of interest. Finally, all identified articles were screened for eligibility, first based on their title and abstract, followed by a review of their full text carried out by two independent reviewers (MS and GS), and any conflicts were resolved by consensus.

Vitamin D: chemistry, metabolism, optimal serum concentration, and supplementation guidelines

Cholecalciferol, vitamin D, is produced in the epidermis from 7-dehydrocholesterol upon exposure to solar energy. Solar UVB radiation (wavelength, 290–315 nm) breaks the chemical bond between carbon atoms 9 and 10, forming previtamin D_3, which is later converted into chemically stable vitamin D_3, known as cholecalciferol. After attaching to the transporting molecule, vitamin D-binding protein (VDBP), cholecalciferol travels to the liver.

Excessive sun exposure does not result in overproduction or intoxication of vitamin D; sunlight decomposes any surplus. Organic synthesis is the richest source of vitamin D, but it also can be obtained through dietary intake (e.g., fish, meat, offal, mushrooms, eggs, fortified food) and supplementation [1, 16].

When reaching the liver, cholecalciferol is converted by oxidases related to cytochrome P450 (CYP2R1 is believed to be the first 25-hydroxylase) into calcidiol [25(OH)D]. From the human liver, the VDBP–25(OH)D complex is then transported to the kidneys, where 1α-hydroxylase Cyp27B1, another CYP450-related enzyme, maintains conversion to calcitriol [1,25$(OH)_2$D], the biologically active form of vitamin D. Calcitriol increases the intestinal absorption of calcium and phosphate, increases expression of fibroblast growth factor 23, and decreases parathyroid hormone (PTH) production. All the above factors control calcitriol production in feedback mechanisms [15, 16]. Increased expression of 25-hydroxyvitamin D-24-hydroxylase, which catabolizes calcitriol to an inactive form, self-regulates the concentration of calcitriol.

Vitamin D's positive influence on skeletal health is well-known and thoroughly described. Vitamin D plays a major protective role against rickets and osteomalacia [4]. It helps regulate calcium homeostasis and has a positive influence on bone mineral density (BMD) [7]. Given that VDR and CYP27B1 are present in many cell types [17], vitamin D has a vast range of potential nonskeletal effects. It is related to the proliferation and differentiation of epidermal cells and improves wound healing [18]. Evidence also exists to substantiate vitamin D's beneficial effects in reducing cardiovascular risk factors and the frequency of cardiovascular events [14]. Unfortunately, those findings do not fully correspond to the results of interventional studies owing to their incorrect design [19, 20].

Skin synthesis is a major source of vitamin D [21]. However, its production can be limited by factors such as weather conditions and geographical location. For example, in Central Europe, sufficient sun availability for vitamin D synthesis occurs only between late April and early September [22]. Other limitations include skin type, age, use of sunscreens that can reduce UVB radiation absorption by 90–95%, cancer awareness, and wearing clothing that covers arms and legs [21].

The concentration of 25(OH)D is considered the most appropriate indicator of vitamin D status, representing both synthesized and supplemented vitamin D with a half-life of 2–3 weeks. Current recommendations define concentrations below 20 ng/ml as deficient and concentrations of 21–29 ng/ml as insufficient [23, 24]. An optimal concentration is considered to be between 30 and 50 ng/ml, with levels above 30 ng/ml being significant and sufficient for positive effects on the skeletal system [16, 24]. Discussions are ongoing regarding whether that concentration of 25(OH)D also confers full extraskeletal effects [4, 25]. Despite vitamin D's widespread and positive influence on human health, population studies reveal that vitamin D deficiency remains a global concern [16, 26–28].

Supplementation and treatment of vitamin D deficiency are regularly reevaluated. According to current recommendations, daily supplementary and therapeutic doses range from 400 to 2000 IU/day [23–29], which can achieve a concentration of 25(OH)D above 29 ng/ml. Several studies have confirmed the safety and lack of observed side effects for higher doses [30, 31]. Recommendations emphasize that dosage should be adjusted based on individual patient factors, including comorbidities and obesity. Doses should be modified accordingly, considering both the increased requirement for vitamin D and the potential toxic effects of excessive doses. Pending reliable data from well-designed clinical trials, general recommendations for the healthy population are typically followed.

Multipotential and pleiotropic effects of vitamin D

Vitamin D's biological actions are moderated by the VDR, a transcription factor expressed not only in muscle and bone cells but also in a spectrum of human tissues including immune cells [32]. Vitamin D-activated VDR is believed to have multiple binding sites throughout the genome with the possibility to affect the regulation of multiple gene transcription [15, 32, 33]. The genetic process by which 1,25$(OH)_2$D exerts its effects includes the direct attachment of activated VDR to particular DNA sequences known as vitamin D response elements located near target genes. That binding can either activate or suppress transcription [33]. In addition, vitamin D exerts rapid effects that occur independently of gene transcription. Those nongenomic actions involve binding to membrane receptors, regulating calcium homeostasis, influencing ion channels, influencing cellular differentiation and proliferation, exhibiting anti-inflammatory effects, and potentially affecting neurological processes [34].

Vitamin D and bones

Among vitamin D's various functions in the body, the most essential is to maintain proper skeletal balance. Vitamin D is responsible mainly for maintaining adequate calcium levels. When serum calcium decreases, PTH secretion is stimulated, leading to the synthesis of calcitriol. Calcitriol enhances intestinal calcium absorption, which depends on dietary intake, solubility, and intestinal capacity [35]. Both PTH and calcitriol promote calcium reabsorption in the kidneys' distal

tubules while inhibiting phosphate reabsorption, directly or indirectly [36].

Vitamin D and PTH also induce calcium mobilization. Along with interleukin 6 (IL-6), they stimulate osteoblasts to express the receptor activator of NF-κB ligand (RANKL). RANKL interacts with the RANK receptor on osteoclast progenitor cells, facilitating osteoclast maturation and later activation. Osteoblasts produce osteoprotegerin, a decoy receptor for RANKL, which helps regulate the osteoclastic response [37]. Activated osteoclasts are responsible for bone resorption, leading to increased serum calcium levels [38]. The elevated calcium level, resulting from increased intestinal absorption and bone resorption, activates receptors that reduce PTH production and then decrease $1,25(OH)_2D$. In addition to increasing bone resorption, vitamin D also restricts bone mineralization, enhancing calcitriol's hypercalcemic effect [34].

Furthermore, prolonged vitamin D deficiency, leading to deficient phosphate levels, is proven to disrupt the balance of cartilaginous growth plates in animal models [39, 40]. Dysregulation of hypertrophic chondrocyte apoptosis promotes cartilage expansion and widening by reducing chondrocyte apoptosis, resulting in delayed growth plate mineralization in children. Moreover, decreased vascular endothelial growth factor and RANKL restrict vascularization as well as the production and differentiation of chondrocytes and osteoclasts [41].

Conversely, vitamin D exerts opposite effects when calcium levels are sufficient. Stimulating the VDR promotes mature osteoblasts, leading to anabolic and antiresorptive effects and increased bone mass. The antiresorptive effect is mediated by a decreased RANKL/osteoprotegerin ratio, whereas the anabolic effect may be associated with increased expression of LRP5 [34].

The physiological significance of the diverse and sometimes opposing effects of VDR signaling in osteogenic cells is still not fully understood and requires further investigation.

Vitamin D and immunity

Vitamin D exerts a significant influence on the immune system and plays a crucial role in modulating both innate and adaptive immunity in various ways. The active form of vitamin D, $1,25(OH)_2D$, hinders the adaptive immune response while enhancing innate immunity. Additionally, local production of $1,25(OH)_2D$ by monocytes and macrophages, leads to the production of immunoglobulins by B lymphocytes and reduces the synthesis of autoimmune antibodies [34]. Vitamin D also plays a beneficial role in stabilizing endothelial membranes [42].

Many studies have shown vitamin D's preventive effects against bacterial and viral infections, achieved by inducing the production of the antimicrobial peptide cathelicidin (LL-37) and reactive oxygen species [3, 43]. That mechanism is particularly crucial, because infections pose a significant risk for autoimmune diseases [44].

In immune cells, intracrine production of $1,25(OH)_2D$ influences adaptive immunity by inhibiting T-cell-driven inflammation and transforming dendritic cells into a more tolerogenic state, characterized by the production of IL-10. Consequently, dendritic cells' ability to present antigens and activate T cells decreases [45]. In addition, $1,25(OH)_2D$ suppresses the production of IL-12, IL-23, and IL-6, thereby inhibiting the development of Th1 cells that produce gamma interferon (IFN-γ) and IL-2, as well as Th17 cells that produce IL-17 [46].

Furthermore, an increase occurs in the production of T regulatory cells that exert suppressive effects on inflammatory processes [47–49]. Those diverse effects of vitamin D make it an intriguing subject for researchers investigating autoimmune diseases.

Other extraskeletal effects of vitamin D

Because VDR is expressed in a variety of human cells, different effects of vitamin D are observed. Many are under investigation without firm conclusions. Although available data remain scarce, administering standard doses of vitamin D to vitamin D-deficient older patients seems to improve muscle function and play a beneficial role in decreasing the incidence of falls [50, 51]. In addition, vitamin D's contribution to bone health, which supports muscles, can help prevent fractures. More well-designed trials are required to establish the optimal serum 25(OH)D concentration and dosage for vitamin D to exert a positive muscular effect.

Both in vitro and in vivo studies postulate the relationship between vitamin D and cancer, especially colon cancer. Low vitamin D status is linked with several cancers, whereas vitamin D influences cell maturation, differentiation, and apoptosis [34, 52]. As well as being involved in angiogenesis, vitamin D can regulate the metastatic potential of many tumors [53, 54]. Unfortunately, even large clinical studies failed to prove that vitamin D supplementation is related to a lower incidence of cancer or better outcomes. Some of those failures were due to inappropriate study design [52, 54, 55]. Also, Mendelian randomization studies reported no relationship between serum 25(OH)D and cancer incidence except for ovarian cancer [56].

A strong connection also is evident between a complete absence of vitamin D action and negative cardiovascular effects arising from preclinical studies, including biochemical, genetic, and animal data. Vitamin D can decrease the risk of cardiovascular disease by mitigating factors such as vascular inflammation, endothelial

dysfunction, smooth muscle cell proliferation, hypertension, and secondary hyperparathyroidism [57]. Although some intervention studies conducted confirmed a positive association between higher 25(OH)D concentration and better control of systolic and diastolic blood pressure [58], others produced conflicting results [59]. The causal nature of the associations between vitamin D and cardiovascular disease remains uncertain, and further research is needed to explore potential differences across patient populations [19].

Effects of vitamin D on juvenile rheumatic diseases

Beginning in childhood or adolescence, JRDs encompass a spectrum of diseases that affect the connective tissue and musculoskeletal system. All such diseases share similar symptomatology, although each has specific symptoms [5]. Although the pathomechanisms of those diseases have not been fully understood, genetic, environmental, and immune-related mechanisms are believed to contribute to the pathogenesis. JRDs are originally associated mainly with arthritis, but the possibility of systemic involvement varies depending on the type of disease [6, 60].

As mentioned, vitamin D deficiency is a growing problem in the world's population, including children and adolescents though biogeographical, ecological and ethnic factors may also matter leading to some differences. Global guidelines indicate the need for vitamin D supplementation and suggest optimal supplementation doses for specific age and risk groups, with cholecalciferol being the first choice. Most guidelines also suggest an upper dose level and recommend that supplementation be monitored through serum 25(OH) D concentrations. Also, because of the lack of detailed data, many guidelines suggest that in some cases, such as prolonged therapy with steroids, doses be consistently increased two to three times. Those recommendations also apply to the pediatric population [23, 24].

This section will focus only on the most frequent representative diseases included in the whole group of JRDs. We aimed to present representative, but not exhaustive, data about possible associations between vitamin D and JRDs (Table 1).

Juvenile idiopathic arthritis

Juvenile idiopathic arthritis (JIA) is a heterogeneous group of chronic arthritides with clinical manifestation starting before the age of 16 years, comprising seven subtypes. The symptoms are predominantly related to inflammation of peripheral articulations but also can involve axial joints, as well as extra-articular structures such as the uvea, skin, entheses, bursae, and internal organs. The prevalence of JIA varies between 16 and 150 per 100,000 people, making the disease the most common JRD [61]. The pathogenesis of JIA remains under investigation, but it seems to be related to genetic susceptibility and environmental factors that destabilize immune harmony. JIA subtypes are associated with human leukocyte antigen (HLA) genes, similar to rheumatoid arthritis, but also with non-HLA-related genes [62]. Also, many immunological processes involved in JIA development promote aberrant activation of immune cells and increase production of proinflammatory mediators, mainly tumor necrosis factor alpha (TNF-α), IL-1, IL-6, IL-17, and CXCL9, enhancing synovitis and further bony erosions [63]. Despite the heterogeneity, different subsets of JIA patients are treated similarly. The first-line therapy includes nonsteroidal anti-inflammatory drugs, followed by DMARDs, with methotrexate (MTX) as the drug of first choice in almost all patients. In addition, the growing role of biological DMARDs should be highlighted. Treatment needs to begin as soon as possible to achieve remission or minimize disease activity [64].

Despite the effectiveness of the current treatment, some JIA patients do not achieve sustained remission, prompting the search for new therapeutic options. Also, treatment with MTX can further decrease 25(OH)D concentration, requiring adequate vitamin D supplementation [65]. Vitamin D deficiency has often been reported in children with JIA and may be associated with disease frequency and activity, although conflicting findings exist [62, 66, 67]. A study on sun exposure and JIA risk showed that higher UV radiation doses before diagnosis and sun exposure during pregnancy were associated with lower risk and frequency of JIA, potentially linked to dose-dependent vitamin D synthesis in the skin [68].

Instead, a study by Thorsen et al. reported no association between serum 25(OH)D concentration at birth and the risk of JIA later in life [69]. Similarly, a recent Mendelian randomization study by Clarke and colleagues showed no causal relationship between serum 25(OH)D and JIA [70]. Even so, considering the immunomodulatory properties and potential immune-restoring effects of vitamin D discussed earlier, we aim to explore how it affects JIA treatment and outcomes.

In a placebo-controlled RCT, Tang et al. found that supplementation with 2000 IU of cholecalciferol per day increased serum 25(OH)D concentration but did not significantly affect BMD or disease activity in JIA patients [71]. Observational studies by Nandi et al. and Sengler et al. reported negative correlations between 25(OH)D concentration and disease activity in JIA patients, as well as an increased risk of JIA-related uveitis [72, 73]. However, Çomak et al. found no difference in disease activity or 25(OH)D concentration between JIA patients with and without standard-dose supplementation [74]. Marini and colleagues observed suboptimal 25(OH)D concentration in a majority of JIA patients, with no significant improvement in

Table 1 Published data regarding the status of vitamin D and its therapeutic potential in selected rheumatic diseases in pediatric population

Ref.	Study design	Results
Juvenile idiopathic arthritis		
Tang et al. (2019) [71]	RCT	Supplementation with 2000 IU of cholecalciferol daily for 24 weeks significantly increased serum 25(OH)D levels in the study group compared with the control group. No differences according to BMD, and disease activity assessed with JADAS-27 were found between groups
Chiaroni-Clarke et al. (2019) [68]	Retrospective	Higher prediagnosis UVR exposure was associated with a lower risk of JIA, with a dose–response relationship. UVR exposure at 12 weeks of pregnancy was inversely linked to JIA. Lower UVR exposure may increase JIA risk
Thorsen et al. (2017) [69]	Case–control	No significant association was found between 25(OH)D levels and the risk of JIA. No evidence that 25(OH)D levels around birth are linked to later JIA risk
Clarke et al. (2023) [70]	Mendelian randomization	No evidence indicating a causal relationship between genetically predicted 25(OH)D levels and the incidence of JIA. Lack of evidence suggesting that genetically predicted JIA causally affects 25(OH)D levels
Nandi et al. (2022) [72]	Observational	A significant negative correlation between the JADAS-27 score and serum vitamin D was confirmed. The corrected Chi-square test showed a significant association between serum vitamin D status and disease activity groups
Sengler et al. (2018) [73]	Observational	~50% of the patients had inadequate 25(OH)D levels (< 20 ng/ml) in the initial serum sample, whereas 25% had inadequate levels in both samples. Inverse correlation between serum 25(OH)D, disease activity, and risk of developing JIA-associated uveitis
Çomak et al. (2014) [74]	Retrospective	Significant negative correlation between vitamin D levels and disease activity. Patients with 25(OH)D levels < 15 ng/ml had significantly higher mean JADAS-27 scores than patients with 25(OH)D levels > 15 ng/ml
Dağdeviren-Çakır et al. (2016) [76]	Cross-sectional	No significant difference in vitamin D levels between activation and remission periods in JIA patients. No significant association between disease activity and serum 25(OH)D. Significantly lower vitamin D levels in JIA and FMF children compared with healthy controls. Patients with JIA and FMF often showed vitamin D deficiency and insufficiency
Bouaddi et al. (2014) [77]	Cross-sectional	75% of patients exhibited hypovitaminosis D. Univariate analyses confirmed a negative correlation between 25(OH)D and DAS-28 scores in polyarticular and oligoarticular JIA. No significant association was found between 25(OH)D levels and BASDAI scores in juvenile spondyloarthropathy. Multivariate linear regression did not confirm any association between 25(OH)D levels and DAS-28 scores
Juvenile systemic lupus erythematosus		
Lima et al. (2016) [88]	RCT	Patients with JIA supplemented with a weekly dose of 50,000 IU of cholecalciferol for 24 weeks presented not only higher serum 25(OH)D levels but also a significant improvement in SLEDAI, ECLAM, and fatigue reduction compared with controls
Lima et al. (2018) [89]	RCT	Significantly higher trabecular number with a decrease in trabecular separation at the tibia site was observed in patients supplemented with 50,000 IU of cholecalciferol per week compared with controls
Abo-Shanab et al. (2021) [83]	Cross-sectional	jSLE patients showed significantly higher levels of IFN-γ and IL-17, and significantly lower levels of 25(OH)D than in controls. Negative correlation between 25(OH)D and both SLEDAI-2K and IFN-γ
Stagi et al. (2014) [84]	Cross-sectional	jSLE patients, especially with active disease, had lower 25(OH)D levels than controls. Moreover, reduced total calcium levels, increased phosphate levels, and higher BSAP and PTH were observed. jSLE patients had lower spine BMAD SDS values than controls, with higher values in patients with 25(OH)D sufficiency and insufficiency than in those with deficiency ($p < 0.001$)
Tabra et al. (2020) [85]	Cross-sectional	Significant differences in mean 25(OH)D concentrations between patients and controls, with significant differences between active and inactive patients. Significant negative correlations between serum 25(OH)D and SLEDAI, steroid dose, anti-dsDNA, 24-h proteinuria, and PTH. Significant positive correlations between 25(OH)D and C3, C4, serum calcium, and Z score, whereas nonsignificant correlations were found between 25(OH)D and serum phosphorus, disease duration, and steroid duration

Table 1 (continued)

Ref.	Study design	Results
Caetano et al. (2015) [86]	Observational	No significant difference in FMI, LMI, or ZBMI between measurements from the two-time points was found. Significant decrease in BMD in patients without vitamin D supplementation. Nearly half of the patients had altered nutritional status
Peracchi et al. (2014) [87]	Cross-sectional	Patients with JSLE exhibited significantly lower mean levels of calcium, albumin, and alkaline phosphatase compared to controls. Inadequate serum 25(OH)D concentrations were more often observed in jSLE patients than in controls. No associations were found with disease activity, PTH levels, alkaline phosphatase levels, medication use, or alterations in BMD
Behçet disease		
Can et al. (2012) [122]	Observational	BD patients commonly exhibited reduced levels of serum 25(OH)D. Vitamin D replacement had beneficial effects on endothelial function and led to a significant improvement in CIMT. Although FMD measurements also improved, the improvement did not reach statistical significance
Omar et al. (2022) [124]	Case–control	The study found that lower vitamin D levels in BD patients are associated with increased oxidative stress. Vitamin D levels were inversely correlated with disease activity, inflammation markers, and oxidative stress markers, while positively correlated with antioxidant levels
Güngör et al. (2016) [125]	Case–control	Vitamin D-deficient patients had significantly higher baseline plasma levels of ESMs compared to vitamin D sufficient patients, but there were no significant differences in baseline TLRs levels between the two groups. After vit D replacement, the mean plasma levels of ESMs significantly decreased, while the mean plasma levels of TLRs showed a decrease, but it was not significant. The active stage disease rate was slightly higher in the pre-treatment group compared to the post-treatment group, but the difference was not significant
Hamzaoui et al. (2010) [126]	Cross-sectional	Patients with active BD had lower vitamin D levels compared to both inactive BD patients and healthy controls. In active BD, vitamin D levels were found to be correlated with CRP and ESR levels. Additionally, serum vitamin D levels showed a positive correlation with the number of Treg cells. On the other hand, the Th1/Th2 ratio was inversely correlated with serum 25(OH)D levels
Zhong et al. (2021) [128]	Mendelian randomization	The analysis using inverse variance weighted estimate revealed that a genetically increased 25(OH)D level was linked to a higher risk of Behçet's disease
Periodic fever, aphthous stomatitis, pharyngitis and adenitis syndrome (PFAPA)		
Stagi et al. (2014) [135]	Interventional study	PFAPA patients displayed lower 25(OH)D levels compared to controls. Winter 25(OH)D levels were notably reduced compared to those measured in summer and were significantly lower than in healthy controls. Serum 25(OH)D levels showed correlations with both fever episodes and C-reactive protein values. Following repletion, PFAPA patients experienced a significant decrease in the number and duration of febrile episodes
Familial Mediterranean fever (FMF)		
Kazem et al. (2021) [138]	cross-sectional	Following a 6-month dietary intervention involving Curcumin, vitamin D, and flaxseed, FMF patients in the study group experienced significant improvements in clinical presentation, cognitive test results, and overall well-being. The intervention also led to a notable increase in serum 25(OH)D levels and a decrease in CRP levels

25(OH)D 25-hydroxyvitamin D, *anti-dsDNA* anti-double-stranded DNA, *BASDAI* Bath ankylosing spondylitis disease activity index, *BMAD SDS* bone mineral apparent density standard deviation score, *BMD* bone mineral density, *BSAP* bone-specific alkaline phosphatase, *CIMT* Carotid Intima-Media Thickness, *CRP* C-reactive protein, *ECLAM* European consensus lupus activity measurement, *ESM* Endothelial selectine molecules, *ESR* erythrocyte sedimentation rate, *FMD* brachial artery flow mediated dilatation, *FMF* Familial Mediterranean Fever, *FMI* fat mass index, *IFN-γ* gamma interferon, *IL-17* interleukin 17, *JIA* juvenile idiopathic arthritis, *jSLE* juvenile systemic lupus erythematosus, *LMI* lean mass index, *PTH* parathyroid hormone, *RCT* randomized controlled trial, *SLEDAI* systemic lupus erythematosus disease activity index, *TLR* toll-like receptor, *Treg* regulatory T lymphocytes, *ZBMI Z* score body mass index

25(OH)D concentration in those receiving supplementation. The researchers also identified associations among VDR polymorphisms and JIA susceptibility and serum 25(OH)D concentrations [75].

In a cross-sectional case–control study, Dağdeviren-Çakır et al. found significantly lower serum 25(OH)D concentration in JIA patients than in healthy controls, although no association with disease activity was observed [76]. Similarly, Bouaddi et al. reported a negative correlation between 25(OH)D and DAS-28 for certain JIA subtypes, but without statistical significance [77].

JIA patients often have vitamin D insufficiency or deficiency, and more well-designed RCTs are needed to confirm the potential associations. Rapid supplementation with regular monitoring and dosage adjustments, along with efforts to determine optimal supplementation doses and duration for children with JIA, is recommended.

Juvenile systemic lupus erythematosus

The prevalence of systemic lupus erythematosus (SLE) varies geographically, ranging from 29 to 210 per 100,000 people in Europe and from 48 to 366 per 100,000 people in North America [78]. Juvenile SLE (jSLE) is diagnosed in patients younger than 16 years, accounting for approximately 10%–20% of all SLE cases [79]. jSLE and adult SLE (aSLE) have similar symptomatology, pathophysiology, and treatment patterns, but jSLE often presents with a more acute and aggressive clinical course, with higher rates of systemic involvement, particularly in the kidneys, blood, and nervous system [80]. The disease course varies within the pediatric group, with rare cases in patients younger than 5 years, limited symptoms in prepubertal onset, and a peak incidence at age 12–14 years [81].

In jSLE, serological testing shows a higher occurrence of anti-double-stranded DNA antibodies and antibodies against cellular components than in aSLE. However, a larger percentage of jSLE patients do not exhibit antinuclear antibodies, particularly during the prepubertal period [79]. Pathophysiology of jSLE is characterized by increased activation of B and effector T lymphocytes, reduced regulatory T cells, elevated proinflammatory cytokines, and decreased immune-regulating cytokines. Although some mutations increase susceptibility to SLE, most cases of jSLE are not solely attributed to genetic factors, but pediatric patients may have a higher prevalence of gene variants associated with SLE risk [81].

Treating jSLE requires more immune-modulating medications, including glucocorticosteroids (GCS), than for aSLE, because jSLE exhibits higher disease activity measured by the SLE disease activity index [82]. Some studies suggest an inverse correlation between proinflammatory cytokines (IFN-γ and IL-17) and serum 25(OH)D concentration in jSLE patients [83]. Analysis of the literature indicates that jSLE patients are commonly vitamin D deficient [84, 85], and its potential role in treatment has been investigated. A cross-sectional study by Tabra et al. reported lower serum 25(OH)D concentration in jSLE patients, with significant correlations between 25(OH)D concentration and disease activity, steroid dose, and biomarkers [85]. Similar observations were made by Stagi et al., showing correlations between 25(OH)D concentration and various parameters, including BMD [84]. Caetano et al. studied female adolescents with jSLE and found a significant decrease in BMD over time, particularly in patients without vitamin D supplementation [86]. In contrast, Peracchi et al. did not find significant correlations between 25(OH)D concentration and disease activity, PTH, or BMD in jSLE patients, despite a lower concentration of 25(OH)D than in controls [87].

Two RCTs investigated vitamin D's influence on jSLE. In a double-blind, placebo-controlled trial, Lima et al. administered oral cholecalciferol supplementation (50,000 IU per week) to one group of 40 jSLE patients for 24 weeks [88]. The intervention group showed an increased 25(OH)D concentration and significant improvements in disease activity and fatigue in comparison with the controls. The second RCT from Lima et al. revealed significant improvement in bone microarchitecture, reflected in the increased trabecular number and decreased trabecular separation, after a weekly dose of 50,000 IU of cholecalciferol administered for 24 consecutive weeks compared to placebo [89].

Vitamin D deficiency is prevalent in jSLE patients and may contribute to the onset of the disease. Despite jSLE's more aggressive nature and the need for anti-inflammatory medications, including GCS, vitamin D supplementation is a reasonable addition to the treatment regimen. However, the reviewed studies used fixed doses of vitamin D and did not achieve adequate intake in all patients, complicating efforts to determine the optimal dosage for jSLE treatment. Certainly, further well-designed trials are needed to explore vitamin D's immunomodulatory role, because current data are limited.

Juvenile systemic scleroderma

Juvenile systemic scleroderma (jSSc) is an inflammatory connective tissue disorder with various degrees of multisystemic involvement diagnosed in children younger than 16 years. According to the most recent data, the prevalence of jSSc is estimated at 3 cases per million children [90], and the incidence is approximately 0.27 cases per million children. Moreover, less than 10% of all systemic

scleroderma cases begin in childhood or adolescence [91]. The pathogenesis is multifactorial and not fully understood. However, both adult-onset and jSSc are believed to share the same underlying mechanisms. The disease arises from dysregulation of both the innate and adaptive immune systems, leading to an imbalance favoring proinflammatory cells and resulting in the overproduction of proinflammatory and profibrotic cytokines, including IL-6, IL-4, IL-1, transforming growth factor beta, and autoantibodies. A significant reduction in T regulatory cells also occurs. Those inflammatory processes affect the microvasculature, promoting vasoconstriction and leading to vascular damage and remodeling. Furthermore, fibroblasts transform into secretory subtypes that produce more collagen and profibrotic cytokines [92–94]. Some studies have identified genetic and environmental factors that may increase susceptibility to the disease [95]. The autoantibody patterns differ between types of SSc. Lower prevalence of antinuclear antibody and anti-topoisomerase I antibody (anti-Scl-70) has been found in jSSc, whereas anticentromere and anti-RNA polymerase III may be more prevalent [96].

Clinical manifestations of jSSc involve the skin (especially the face and hands) and peripheral circulatory disorders such as Raynaud's phenomenon. Musculoskeletal involvement is common, with symptoms such as joint stiffness and muscle weakness but gastrointestinal, pulmonary, and cardiovascular systems also can be affected [97, 98]. Three main subtypes of jSSc are distinguished: diffuse cutaneous, limited cutaneous, and overlapping [99].

Several studies have highlighted notable differences in progression between juvenile- and adult-onset SSc. According to Adrovic et al., adult patients exhibit a significantly higher frequency of interstitial lung disease than their juvenile counterparts [100]. Although no significant differences were observed regarding renal, gastrointestinal, and cardiac involvement, a significantly higher incidence of arterial hypertension was reported among adults. Conversely, jSSc patients presented a significantly higher incidence of arthralgia and arthritis, but no disparities were observed in other musculoskeletal symptoms. Also, the predominant disease subtype varied significantly, with juvenile patients more commonly diagnosed with the diffuse cutaneous subset of SSc, whereas the limited cutaneous SSc subset was more prevalent among adult patients. Foeldevari and colleagues [101] reported similar findings. Research has shown that adults with diffuse cutaneous SSc have lower levels of serum 25(OH)D than patients with limited cutaneous SSc [102]. Moreover, vitamin D-deficient diffuse SSc patients experience reduced quality of life [103]. Those findings collectively highlight the importance of focusing on jSSc patients and their vitamin D levels.

Distinct treatment patterns were observed between jSSc and adult-onset SSc. MTX and GCS were more often used in jSSc than in adult-onset SSc, whereas no significant differences were noted regarding the use of other DMARDs. Conversely, adult patients more often required calcium channel blockers and angiotensin-converting enzyme inhibitors, potentially due to the higher incidence of organ involvement, including those affecting the cardiovascular system [100, 101, 104].

Although available data confirm that jSSc patients are at risk of vitamin D deficiency [105], no trials investigating the role of vitamin D supplementation in jSSc could be found. The identified studies discussed only cholecalciferol's theoretical influence on disease progression. Importantly, there are no significant contraindications to administering vitamin D in jSSc, although well-designed RCTs are necessary to determine vitamin D's potential efficacy in the treatment regimen. Considering the prevalence of vitamin D deficiency in both the general population and, particularly, among patients with these chronic diseases, consistent vitamin D supplementation appears to be a reasonable measure for all patients with jSSc.

Juvenile idiopathic inflammatory myopathies

Juvenile idiopathic inflammatory myopathies (JIIMs) are rare autoimmune disorders affecting children and adolescents. JIIMs result from a complex interplay of genetic predisposition, environmental triggers, and immune dysregulation. Persistent muscle inflammation occurs as a result of autoimmune reactions, involving T-cell activation and release of proinflammatory molecules [106, 107]. Genetic factors, including variations in HLA genes, and environmental triggers contribute to susceptibility [106–108]. Ongoing inflammation leads to muscle damage, causing weakness and functional impairment. The exact mechanisms of muscle damage are still under investigation but probably involve immune-mediated destruction and impaired muscle regeneration [109].

Juvenile dermatomyositis (JDM) is the primary form of JIIM, making up about 80% of cases. The annual incidence of JDM in children younger than 16 years ranges from 2.28 to 3.17 per million [106, 110]. Pathogenesis of JDM involves upregulated type I interferon-dependent genes [111]. Anti-p155/140 and anti-MJ antibodies are commonly observed in JDM [106]. JDM patients should be wary of excessive sun exposure because of the aggravating effects of UV radiation. That effect can result in decreased levels of serum 25(OH)D, which correlates with disease activity score as reported by Robinson et al. [112]. Therefore, we advise considering appropriate doses of vitamin D to prevent deficiency in JDM patients.

Overlap myositis, the second-most-common phenotype in JIIM, involves patients with an additional autoimmune disease. The phenotype is observed in approximately

6%–11% of JIIM patients [113]. Those overlapping diseases have been associated with lower 25(OH)D concentration.

Juvenile polymyositis (JPM) occurs in about 4–8% of JIIM cases. It typically presents during adolescence, causing weakness in both proximal and distal muscles, frequent falling episodes, muscle pain (myalgias), and elevated creatine kinase levels. JPM has a more severe onset than JDM, with about 35% of JPM patients experiencing cardiac involvement. Weight loss and Raynaud's phenomenon also are commonly observed. Distinctive pathological features, including endomysial infiltrates, are seen in affected muscles [106, 113].

Our literature research, conducted based on previously described criteria, found no trials concerning vitamin D supplementation in the pediatric population with idiopathic inflammatory myopathies. Nonetheless, most patients with idiopathic inflammatory myopathies, both adults and children, exhibit low serum 25(OH)D concentrations, which could play a role in developing adult myositis, just similar to certain other autoimmune disorders [112, 114]. By contrast, an in vitro study by Di Luigi et al. revealed that some VDR agonists exhibited strong efficacy in reducing the secretion of CXCL10 protein induced by IFN-γ/TNF-α, showing their potent inhibitory effects [115]. In addition, they targeted the signaling pathways downstream of TNF-α in those cells. The knowledge about immune and nonimmune pathways related to the development of this complex group of diseases is continually growing. Well-designed in vitro and in vivo research is required to shed light on vitamin D's potential complementary role in treating JIIMs.

Behçet disease

Behçet's disease (BD) is a systemic vasculitis that affects both the arteries and veins, presenting with a relapsing and remitting nature and having a complex pathogenesis [116, 117]. Typical manifestations include recurrent fever, oral and genital aphthae, alongside other features involving joints, eyes, gastrointestinal, and nervous systems [116, 118]. The clinical presentation varies slightly between adult and pediatric patients [119], with male patients experiencing a more severe course [120]. While not common in the pediatric population, specific diagnostic criteria for pediatric BD have been published, requiring full clinical manifestation below the age of 16 years [117]. Originally occurring along the "Silk Road" area, BD is now observed worldwide, primarily due to migrations, whereas the estimated prevalence in children is 1 per 600,000 [121].

Treatment depends on organ involvement and includes colchicine, immunosuppressives, and biologic drugs [119]. Data regarding the status of vitamin D in BD patients are primarily acquired from adult or mixed populations and remain limited. Some authors confirm lower 25(OH)D concentration in BD patients compared to controls [122], while others report opposite results, noting a significant decrease in serum 25(OH)D during active BD [122, 123]. Potential associations between vitamin D and laboratory and clinical features of BD have been largely investigated. For instance, Omar et al. found that decreased vitamin D levels in BD patients were associated with higher concentrations of oxidative stress markers compared to healthy controls [124]. Additionally, Güngör et al. revealed that BD patients with vitamin D deficiency exhibited higher concentrations of endothelial selectin molecules, playing an important role in the disease's pathogenesis. Interestingly, these patients showed significant improvement after 3-month-long vitamin D supplementation [125]. This could, at least partly, support another observation by Can et al. who demonstrated that supplementation with a daily dose of 1000 IUvitamin D for 3 months significantly improved carotid intima-media thickness [122]. Another observational study showed that insufficient levels of vitamin D were associated with the promotion of Th1 lymphocytes, and a decrease in Treg cells [126]. Similarly, Tian et al. confirmed that vitamin D significantly inhibited the differentiation of Th17 cells in BD patients [127].

Contrary to all of the aforementioned studies, the latest Mendelian randomization study by Zhong et al. revealed a potential link between lifelong higher 25(OH) D concentrations and an increased risk of BD [128]. These findings warrant further research, to elucidate real associations in the specific disease. Unfortunately, no RCTs regarding the therapeutic role of vitamin D in the pediatric BD population have been published so far. More studies in this field are still required to clarify whether vitamin D can play a supplementary role in the treatment of BD in children.

Juvenile periodic fever syndromes

Autoinflammatory diseases (AIDs) encompass a diverse group of conditions triggered by the activation of the innate immune system [129]. Unlike autoimmune disorders, AIDs are not associated with autoantibodies or antigen-specific T cells. Many of these diseases are linked to inborn errors of innate immunity, affecting the function of immune cells. While most AIDs are caused by monogenic mutations inherited in an autosomal dominant or recessive pattern, some remain unexplained by mutations in known periodic syndrome-related genes. The exact underlying causes vary and require further investigation, but they often involve specific endogenous or exogenous stimuli [130].

Clinical presentations of most AIDs include recurring episodes of fever, accompanied by increased inflammatory markers, followed by periods of general well-being, with the onset typically in childhood [130]. Among the common pediatric autoinflammatory diseases are periodic fever, aphthous stomatitis, pharyngitis, and adenitis syndrome (PFAPA), familial Mediterranean fever (FMF), tumor necrosis factor (TNF)-receptor-associated periodic syndrome (TRAPS), hyper-IgD syndrome (HIDS), as well as the cryopyrin-associated periodic syndromes (CAPS), and systemic undifferentiated recurrent fever (SURF) [131].

Not only the diagnostics but also the treatment of these rare and underestimated conditions have posed many challenges for physicians, with a revolutionary role of biological treatment blocking specific cytokines, which are oversecreted in AIDs [132].

Periodic fever, aphthous stomatitis, pharyngitis and adenitis syndrome

Evidence is limited although some investigators, e.g. Mahamid et al. or Nalbantoğlu et al. reported a notable association between PFAPA outcome and vitamin D deficiency [133, 134]. Furthermore, Stagi et al. demonstrated lower serum 25(OH)D concentrations in patients with PFAPA compared to healthy controls, particularly during the winter months. Moreover, their study showed that daily supplementation of 400 IU of cholecalciferol led to a reduction in the frequency and duration of febrile episodes [135].

Familial Mediterranean fever

Previous studies have reported lower levels of vitamin D in children with FMF [136, 137]. Moreover, an interesting study by Dağdeviren-Çakır confirmed that during attack periods in FMF patients, serum 25(OH)D concentration was significantly lower [76]. An interventional study conducted by Kazem et al. demonstrated that a 6-month dietary supplementation regimen, consisting of flaxseed, curcumin, and 4000 IU of daily vitamin D, significantly improved cognitive functions and the course of FMF in terms of attack frequency, severity, and duration among the patient group. However, the study did not assess the effects of the specific supplements individually [138]. Thus, generalizable conclusions regarding the beneficial role of vitamin D in FMF should be drawn and discussed carefully.

Our review did not determine published studies investigating the status or potential role of vitamin D in HIDS, TRAPS, CAPS syndrome, and SURF. The available data examining the relationship between recurrent fever syndromes and vitamin D are scarce, indeed, due to the low prevalence. These conditions are considered to be rare, and—importantly—have a relatively short history of research. Given the limited data availability, the field remains open for future research, particularly in prospective cohorts, and also regarding dose–response studies.

Summary and conclusions

Vitamin D exhibits a broad range of beneficial effects on various human cells. Its pleiotropic impact includes regulating the immune system and modulating autoimmune disorders, including pediatric rheumatic conditions, as shown by in vitro and in vivo studies. Several investigations have shown an inverse relationship between vitamin D deficiency and disease severity or outcomes in those conditions, although some reports indicate limited effects. Although JRDs are relatively uncommon, they significantly affect the pediatric population's health and can have long-term negative consequences on quality of life, even into adulthood.

Despite inconsistent evidence, vitamin D is believed to have a positive influence on people with various diseases, including rheumatic conditions. However, published data are scarce regarding vitamin D's modifying or complementary role in pediatric rheumatology. That lack may be attributed to methodological issues and the flawed design of previous studies, which often resembled drug trials rather than investigations into nutrient effects. Classical skeletal health outcomes related to serum 25(OH)D concentration may be variable and may often be strongly dependent on the initial level i.e. adequacy or deficiency, however, the threshold required to activate all the extraskeletal effects, particularly those related to autoimmune regulation, remains uncertain. Furthermore, most RCTs used the same vitamin D dosage for all participants, without ensuring its efficacy in achieving sufficient serum 25(OH)D concentrations for each individual. Although the data gathered for our review are promising, the findings are insufficient to confirm vitamin D's supplementary role in treating JRDs.

Therefore, further well-designed interventional studies, especially RCTs, are needed to establish definitive conclusions and develop specific recommendations. Dose–response studies in the field of pediatric rheumatology may be particularly useful. Considering the high prevalence and the growing incidence of vitamin D deficiency, even in the healthy population, we advise encouraging children and adolescents to follow current recommendations for vitamin D supplementation.

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Data availability Not applicable to this article as no datasets were generated during the current study.

Declarations

Conflict of interest The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Consent to participate All authors agreed with the content of the revised version of the manuscript, take full responsibility for the integrity of all aspects of the work and gave explicit consent to submit the manuscript.

Consent for publication The authors declare that this review or its part has not been copied or published before in whole or in part and that it is not under consideration for publication anywhere else.

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Prevalence of Vitamin D Deficiency in Patients Treated for Juvenile Idiopathic Arthritis and Potential Role of Methotrexate: A Preliminary Study

Maciej K. Stawicki [1], Paweł Abramowicz [1,*], Adrian Góralczyk [2], Justyna Młyńczyk [1], Anna Kondratiuk [1] and Jerzy Konstantynowicz [1]

[1] Department of Pediatrics, Rheumatology, Immunology, and Metabolic Bone Diseases, Medical University of Bialystok, Waszyngtona Street 17, 15274 Bialystok, Poland; maciej.stawicki@umb.edu.pl (M.K.S.); justyna.mlynczyk@umb.edu.pl (J.M.); an.kondratiuk@gmail.com (A.K.); jurekonstant@o2.pl (J.K.)

[2] Department of Orthopaedics and Traumatology, Hospital of Ministry of Administration and Internal Affairs in Bialystok, Fabryczna Street 27, 15471 Bialystok, Poland; adriangoralczyk1@yahoo.com

* Correspondence: pawel.abramowicz@umb.edu.pl; Tel.: +48-857-450-622; Fax: +48-857-450-644

Abstract: Background: Vitamin D deficiency is reported in rheumatological diseases in adults. The aim was to evaluate the prevalence of vitamin D deficiency in children with juvenile idiopathic arthritis (JIA) and to investigate potential correlations between vitamin D status and clinical factors, laboratory traits, and medical treatment, including methotrexate (MTX) and glucocorticoids (GCs). Methods: In 189 patients aged 3–17.7 years, with JIA in the stable stage of the disease, anthropometry, clinical status, serum 25-hydroxyvitamin D [25(OH)D], calcium (Ca), phosphate (PO_4), total alkaline phosphatase (ALP), erythrocyte sedimentation rate (ESR), and C-reactive protein (CRP) were assessed. Results: Median 25(OH)D level was 15.00 ng/mL, interquartile range (IQR) 12.00 ng/mL. Vitamin D deficiency was found in 67.2% and was independent of sex, disease manifestation, and CRP, ESR, ALP, or PO_4 levels. Higher doses of MTX corresponded with lower 25(OH)D levels using both univariate and multivariate models ($p < 0.05$). No such trend was found for GCs treatment. Serum Ca was lower in patients treated with GCs ($p = 0.004$), MTX ($p = 0.03$), and combined GCs/MTX ($p = 0.034$). Conclusions: JIA patients are vitamin D depleted independently of disease activity or inflammatory markers. MTX therapy may be an iatrogenic factor leading to inadequate 25(OH)D levels. Vitamin D supplementation should be considered in all children with JIA, particularly those receiving long-term MTX therapy.

Keywords: juvenile idiopathic arthritis; vitamin D; calcium/phosphate metabolism; methotrexate; children

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1. Introduction

Juvenile idiopathic arthritis (JIA) is a heterogenic group of chronic autoimmune disorders with a large spectrum of clinical manifestations and varying severity [1]. The causes of the disease are yet to be discovered. It is suggested that immunogenic mechanisms secondary to genetic and environmental factors are the background of the disease, while infections together with stress and trauma are suspected to be the most possible etiological agents for JIA [2].

As the incidence of JIA has been reported to increase worldwide, the management of this condition has become an important issue in pediatric care [3,4]. The complex autoimmune, inflammatory, and destructive processes, which are key pathogenic mechanisms in the disease, may lead to disability early in childhood and adolescence and may either persist to adulthood or confer a risk of later significant rheumatologic conditions including rheumatoid arthritis (RA).

Vitamin D is a fat-soluble vitamin and an important hormone involved in many physiological processes in the human body, such as bone mineralization, insulin regulation,

and immune regulation [5–7]. Vitamin D is affecting the tissues by specific vitamin D receptors (VDR) inducing its biological activities. VDR is widely expressed in different cells, i.e., immune cells. There are many polymorphic variants of the VDR gene that possibly affect the functionality of the receptor [8].

Recent research focused on vitamin D in relation to a variety of inflammatory disorders revealed several controversial results. Furthermore, a large body of evidence was published within the last decade to demonstrate a vast range of vitamin D deficits in general, otherwise healthy, populations worldwide [9–14]. The role of vitamin D, being mainly a well-known regulator of calcium/phosphate metabolism, has been extensively investigated in adult rheumatoid diseases, demonstrating a potential beneficial effect on the disease course and activity; however, some studies did not support such associations [15].

Available reports show that vitamin D may have a significant influence on pathogenesis [16] and the outcome of JIA, i.e., a lower level of 25-hydroxyvitamin D [25(OH)D] was found in JIA patients compared with healthy children [17,18]. At present, there is a strongly held general view, based also on prospective studies, that vitamin D has pleiotropic multidimensional effects on human metabolism and may interact in situ with specific tissues and, therefore, demonstrates some preventive potential including anti-proliferative, anti-inflammatory, and immunomodulatory actions. On the other hand, the long-lasting vitamin D deficiency, reflected by decreased 25(OH)D concentrations, can deteriorate immune-mediated mechanisms or even exacerbate the course of the disease [19].

Assuming that vitamin D in pediatric rheumatoid diseases may be of importance and that several questions regarding vitamin D deficit remain unanswered, we attempted to investigate correlations between vitamin D status, clinical manifestation, and medical treatment of JIA. This study aimed to determine the prevalence of vitamin D deficiency and to evaluate potential risk factors of decreased serum 25-hydroxyvitamin D levels in children diagnosed with JIA.

2. Material and Methods

In this cross-sectional study, 189 Caucasian individuals (both in- and outpatients) treated for juvenile idiopathic arthritis were examined. The diagnosis of JIA was ascertained using standard classification criteria [20]. Clinical assessment, anthropometric measurements using standardized methods, and laboratory tests were performed. Blood samples were collected at the beginning of hospitalization. Clinical assessment, based on physical examination and functional tests, was performed during scheduled hospital admission. Juvenile arthritis disease activity score (JADAS27) was used to determine disease activity status [21]. Anthropometric measurements were carried out with standardized methods, compliant with WHO guidelines [22], and included body weight using an electronic scale (Seca^{TM} 799, Hamburg, Germany) and standing height obtained with a wall-mounted stadiometer (Seca^{TM} 216, Hamburg, Germany). Body Mass Index (BMI) was calculated with a standard formula.

Vitamin D status was determined by measuring serum 25(OH)D concentration using the automatic immunoenzyme method using Immulite®2000 Immunoassay System (Siemens AG, Munich, Germany). Vitamin D deficiency was defined as serum 25(OH)D level < 20 ng/mL, consistently with the Institute of Medicine recommendations and the updated guidelines for Central Europe [5,10]. To assess inflammation activity, erythrocyte sedimentation rate (ESR), and C-reactive protein (CRP) concentration were measured. Calcium (Ca) and phosphate (PO_4) serum concentrations and total alkaline phosphatase (ALP) activity were also tested and referred to age-specific normative values to check basic bone mineral metabolism.

All procedures were approved by the Ethical Committee of the Medical University of Bialystok upon informed consent obtained from all participants and/or their legal guardians according to the Declaration of Helsinki and its later amendments.

The statistical analyses were performed with the STATISTICA software (version 13.3, Tibco Software Inc., Palo Alto, CA, USA) and statsmodels.org (version 0.13.2). To evaluate the normality of data distribution, Shapiro–Wilk test was used. Variables distributed normally were expressed as mean and standard deviation, whereas for those with skewed

distribution, median and IQR were used as a method of result presentation. According to the data distribution, Student's *t*-test or, the Mann–Whitney *U* test was applied. Subsequently, Spearman rank correlation was used to test the relation between pairs of factors. Furthermore, multinomial logistic regression was used to investigate associations between 25(OH)D concentration and body weight, BMI, MTX dose, GCs dose, CRP, ESR, Ca, P, and ALP, which were incorporated as covariates in the models.

3. Results

A total of 189 children and adolescents (113 girls and 76 boys), aged 3–17.7 years (median 13.12, IQR 6.23) were included; all were Caucasian, living at a similar latitude, none of the participants had been diagnosed with comorbidities potentially affecting vitamin D or bone metabolism, and none had been supplemented with vitamin D at the time of the recruitment to the study.

Among the whole studied group, 49% had oligoarticular manifestation, 44% presented polyarticular manifestation, and 7% had systemic-onset JIA (Table 1). All of them were in a stable stage of the disease (remission or minimal disease activity) according to the JADAS27 scoring [21].

Table 1. Basic characteristics of the study group (* Median and IQR value are shown when applicable).

	Total (*n* = 189)
Age (years) *	13.12 (6.23)
Male-to-female	76/113
Weight (kg) *	48.50 (24.00)
Height (cm) *	155.00 (28.00)
BMI (kg/m^2) *	19.58 (5.26)
Polyarticular JIA (*n*; %)	83 (43.90%)
Oligoarticular JIA (*n*; %)	93 (49.20%)
Systemic-onset JIA (*n*; %)	13 (6.90%)
Treated with GCs (*n*; %)	73 (38.60%)
Treated with MTX (*n*; %)	84 (44.40%)

Methotrexate at a weekly dose of 10–20 mg per m^2, administered orally or subcutaneously, was the only conventional synthetic disease-modifying anti-rheumatic drug (csDMARD) used in these patients, whereas no other DMARDs combination was introduced. In addition, some patients required interim GCs as a bridging therapy, in rare cases given by intra-articular injections.

The median 25(OH)D serum concentration was 15.00 ng/mL, and the IQR was 12.00 in the whole studied group. Vitamin D deficiency was found in 127 patients of both sexes (67.2% of the examined population). Comparisons between the groups in relation to serum 25(OH)D concentration based on the cut-off level of 20 ng/mL are shown in Table 2.

Vitamin D status in children with JIA was independent of sex, age, clinical manifestation, disease activity, or inflammatory markers. Serum 25(OH)D was inversely associated with BMI ($r = -0.19$), i.e., overweight JIA patients had lower vitamin D levels. Additionally, a weak yet significant correlation between 25(OH)D and serum Ca ($r = 0.19$) was found. An association was observed between vitamin D status and pharmacological therapy used in children with JIA. Furthermore, the treatment option affected calcium/phosphate metabolism in both boys and girls. Weekly MTX dose was found to be significantly higher in patients with vitamin D deficiency than in those with serum 25(OH)D > 20 ng/mL (Table 2). This association was consistent with Pearson's correlation coefficient, indicating an inverse relationship between the dose of MTX and 25(OH)D concentration ($r = -0.34$, $p < 0.05$). There was a significant negative correlation between MTX dose and Ca and PO_4 levels but not with serum ALP. Furthermore, the GCs dose had no significant effect on serum 25(OH)D concentration in children with JIA, whereas the daily dose of GCs was

inversely associated with ALP activity, Ca, and PO_4 levels. Significant correlations between the two treatment options are shown in Table 3.

Table 2. Characteristics of the patients with JIA in relation to their serum 25(OH)D concentration below and above 20 ng/mL (* mean ± SD or ** median and IQR are given).

	Low 25(OH)D Level <20 ng/mL	**Normal 25(OH)D Level ≥20 ng/mL**	***p* Value**
Patients (N; %)	127 (67.2%)	62 (32.8%)	
Age (years) **	13.34; (5.18)	11.84 (8.32)	0.19
Weight (kg) **	50.00 (22.00)	45.35 (33.00)	0.14
Height (kg) **	156.50 (25.00)	148.00 (37.50)	0.15
BMI (kg/m^2) **	19.81 (4.88)	19.06 (6.10)	0.17
GCs (mg) ** *daily dose*	5.00 (5.00)	5.00 (5.00)	0.29
MTX (mg) ** *weekly dose per m^2*	15.00 (7.50)	12.5 (7.50)	0.02
CRP (mg/L) **	1.00 (3.70)	1.60 (12.0)	0.23
25(OH)D (ng/mL) **	12.00 (8.00)	25.5 (6.0)	<0.001
Ca (mmol/L) *	2.48 ± 0.09	2.52 ± 0.12	0.01
P (mg/dL) *	4.50 ± 0.63	4.54 ± 0.72	0.76
ALP (U/L) **	165.00 (138.00)	172.00 (124.00)	0.70
ESR (mm/h) **	11.50 (22.00)	19.00 (30.00)	0.05
JADAS27 score **	1.50 (0.70)	1.50 (0.50)	0.64

Table 3. Univariate correlations for methotrexate (MTX), glucocorticoids (GCs), and serum calcium/phosphate parameters in children with JIA.

	MTX ***weekly dose per m^2***	**GCs** ***daily dose***
25(OH)D	r = −0.33; p = 0.003	r = −0.08; p = 0.26
Calcium	r = −0.31; p = 0.01	r = −0.23; p = 0.01
Phosphate	r = −0.42; p = 0.03	r = −0.27; p = 0.004
ALP	r = −0.14; p = 0.17	r = −0.79; p = 0.004

Multinomial logistic regression analysis showed that, out of all factors introduced in the model, only the weekly MTX dose per m^2 was inversely associated with serum 25(OH)D concentration. The calculated coefficient was 1.79 for MTX/week/m^2 (95% confidence interval [CI]: 0.33–3.24), whereas no other variables were significantly associated with vitamin D concentration. The results of the multivariate analysis are presented in Table 4.

Table 4. Results of multinomial logistic regression performed to investigate multivariate analysis of factors associated with 25(OH)D concentration.

	Coefficient	**Standard Error**	**95% CI**		***p* Value**
Body weight	0.09	0.40	−0.69	0.87	0.82
BMI	−0.08	0.32	−0.70	0.54	0.80
GCs *daily dose*	0.18	0.21	−0.24	0.60	0.41
MTX *weekly dose per m^2*	1.79	0.74	0.33	3.24	0.02
CRP (mg/L)	−0.29	0.23	−0.74	0.17	0.21
ESR (mm/h)	−0.72	0.23	−0.51	0.37	0.75
Ca (mmol/L)	−0.13	0.19	−0.51	0.24	0.48
P (mg/dL)	0.32	0.21	−0.10	0.73	0.13
ALP (U/L)	0.01	0.20	−0.37	0.40	0.94

4. Discussion

Vitamin D deficiency is common in the general population during growth, according to the available supportive evidence [9–11]. This observation has been extended by the present study demonstrating a disease-specific deficiency in patients with juvenile idiopathic arthritis. Several studies have reported suboptimal vitamin D status in children with rheumatic diseases resulting from multifactorial mechanisms associated with the autoimmunity and/or iatrogenic effects [4,15]. The main finding of our study was an association between long-term methotrexate therapy in children with JIA and a deteriorated vitamin D status. Due to the cross-sectional design of this study, causal pathways may not be clearly elucidated; however, the unfavorable effect of the MTX therapy on 25-hydroxyvitamin D may indicate a role of this particular medication in an increased risk of deficiency.

Presumably, the above-mentioned treatment essentially affected the vitamin D status and calcium/phosphate metabolism, as it was found to interfere at most with vitamin D deficiency, among other variables analyzed in this study. Noteworthy, the strategies of therapeutic management are similar in RA and JIA, excluding current therapies with a single drug, e.g., biologics. Effective recommendations include the proposal of subsuming a sequential application of non-steroidal anti-inflammatory drugs (NSAIDs), GCs, and non-biological/biological DMARDs in the treatment of RA depending on disease activity and severity [23]. Similarly, the currently binding approach to the complex medication of children with juvenile arthritis is based on analogous recommendations [24]. Methotrexate—out of all non-biological DMARDs—appears the most effective and preferably applicable agent due to its well-known effectiveness for restricting autoimmune and inflammatory processes. Moreover, recent studies have shown that MTX is also an inhibitor of osteoclastogenesis by impeding RANKL-induced calcium influx into osteoclast progenitor cells [25]. Kanagawa et al. postulated that MTX would have a protective role against osteoporosis and joint destruction via some of the above-mentioned specific mechanisms [25]. In the light of the multivariate approach, the results of our study suggest a different view, showing that MTX use may be associated with a decreased 25(OH)D level. Initial univariate analyses also showed a dose-dependent effect, i.e., the weekly dose of MTX is negatively associated with serum calcium and phosphate, although multivariate analyses failed to support those results. The influence of MTX on calcium/phosphate metabolism can be direct or indirect—just by affecting vitamin D metabolism. Assuming these causal effects may be true, a question arises: During which transformation phase of vitamin D precursors does this drug interfere? Possible interaction may occur at intestinal absorption, during which methotrexate may deteriorate vitamin D bioavailability from nutrients. Furthermore, it can also considerably downregulate hepatic hydroxylation of calciferol (due to its fully understood liver toxicity), or it can even affect skin synthesis of vitamin D.

These associations have not yet been probably reported in the literature concerning rheumatoid diseases, i.e., JIA or RA. Methotrexate may be regarded as a risk factor for secondary osteoporosis in adults, even if the available data are inconsistent [26,27]. Nevertheless, there is a need for further relevant investigation to determine if long-term MTX use is an independent factor of bone loss in children with rheumatoid conditions. Moreover, a workout of a molecular mechanism through which MTX affects vitamin D metabolism is necessary to prevent the negative effects of MTX treatment on the growing skeleton.

Surprisingly, the prolonged use of GCs in our patients was not associated with a decrease in 25(OH)D concentration despite an evident inverse relationship between GCs and calcium or phosphate metabolism. Some studies support our results by demonstrating clearly that the use of systemic steroids does not influence 25(OH)D levels [28]. Other reports show, by contrast, that GCs may have a specific regulatory effect on vitamin D metabolism [19,29]. Our finding seems even more interesting considering an insight into the molecular mechanism of actions of GCs, reflecting "anti-vitamin D effects". Possible explanations include that glucocorticoids increase calcium and phosphate renal excretion, being antagonists of $1,25(OH)_2D$, while not influencing its serum concentration. Furthermore, there was a strong negative association between the GCs dose and total alkaline

phosphatase activity. It has been reported that the decreased serum Ca and PO_4 levels, as well as reduced ALP activity, may be a compelling contribution to reduced bone mineral apparent density (BMAD) concomitant with long-term GCs treatment in children with JIA [30]. The causal relationship between exposure to GCs and suboptimal bone mineral acquisition during growth, including glucocorticoid-induced osteoporosis, has been widely documented, although not all mechanisms have been clarified.

Disease activity, duration, and active inflammation play an important role in the deterioration of mineral and bone metabolism in the course of chronic rheumatologic conditions [15]. We point out that the inflammatory process is supposed to be another risk factor for vitamin D deficiency in children with confirmed JIA. Several published reports are attempting to elucidate this association, but the results are inconsistent and provide ambiguous information [31]. To optimize the usefulness of our study, the JADAS27 scale was applied for disease activity assessment. All studied patients were in remission or had minimal activity of JIA based on the JADAS criteria [21]. These characteristics allowed us to minimize the effect of the confounder, i.e., the impact of disease activity and severity on the results. Based on large cohort studies, there was an inverse relationship between vitamin D intake and RA disease risk [32]. However, the data are different when comparing RA and JIA, while results vary across published studies. More recent reports showed that vitamin D level was significantly reduced in patients with active RA [33–36]. In those studies, the scores DAS28, JADAS-27, and inflammatory markers (ESR, CRP, fibrinogen serum concentration) were used to assess disease activity. Some investigators reported that the prevalence of vitamin D deficiency or insufficiency was high in juvenile idiopathic arthritis; however, it was unassociated with either intensity of inflammation [37–39] or the genotypes of the vitamin D receptor [8]. Other studies revealed the relationship between the inflammatory process and reduced 25(OH)D [40–42]. Active forms of vitamin D have been shown to diminish the inflammatory process through the inhibition of interleukin-6 which is a key cytokine involved in joint destruction [43]. Finally, more profound and corrected analyses may detect true associations. There are published studies in which univariate analyses indicating significant correlation have been essentially altered by multivariate analyses [44]. Our study supports the view that 25(OH)D is independent of disease activity, despite a slight negative correlation between ESR and vitamin D levels. We believe that inflammatory markers alone may not be specific enough to assess disease activity categorically, as both clinical manifestation and the severity of JIA are determined by a multiplicity of factors. If so, it was difficult to find or confirm associations between biochemical markers of inflammation and 25(OH)D serum concentration in this study. Some reports showed an association between a clinical manifestation of RA or JIA and the overall disturbance of the metabolism [45]. Interestingly, in the present study, no differences were observed in vitamin D status between individuals with polyarthritis and systemic-onset JIA even after adjustment for age and sex as possible confounding effects.

In summary, our preliminary study showed that methotrexate may have a general negative influence on vitamin D status in children with JIA. This confers a possible risk of deteriorated bone density and impaired skeletal accrual during growth. There is always a need for supplementation of vitamin D and calcium to be considered in these patients accordingly to the general guidelines. The maintenance of the optimal vitamin D status can be useful in reducing pain symptoms and improving the quality of life in these children, as it was proven in patients with RA [46], considering particular pleiotropic effects of calcitriol, including anti-inflammatory, immunomodulatory, and cell-protecting features. Though there are still some controversial findings in the literature suggesting that vitamin D supply, although effective, does not sufficiently enhance bone health. For example, Hillman et al. proved that vitamin D_3 treatment with 2000 IU/day plus calcium increased 25(OH)D concentration and allowed maintaining the $1,25(OH)_2D$ level but did not improve BMD accretion [47].

We are aware that our study has some relevant limitations, and the cross-sectional design does not allow establishing firm conclusions concerning causal effects. Accessibility

to relevant solid data was limited, specifically related to the duration of GCs, and MTX therapy was ineffective. The difficulty resulted from the study design, as the treatment courses were established individually for each patient and were subsequently adjusted depending on clinical manifestation and course of the disease. Because of essential technical issues, it was not possible to assess skeletal status by measuring bone mineral density.

5. Conclusions

The majority of children with juvenile idiopathic arthritis have significantly decreased 25-hydroxyvitamin D serum concentrations independent of clinical manifestations, disease activity, age, sex, or inflammatory markers. Iatrogenic factors play an important role in the development of vitamin D deficiency in JIA. According to our study, long-term methotrexate therapy appears to be the factor associated with reduced 25(OH)D levels. Although glucocorticoids used in JIA essentially affect calcium/phosphate metabolism, indicators of their influence on vitamin D status were not found. Our findings suggest the necessity of extensive vitamin D supplementation in children with JIA, particularly those treated with methotrexate. There is a need for further studies on the effects of methotrexate on vitamin D status in this population with special regard to the underlying molecular mechanism.

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7. Wnioski

Przeprowadzone badania oryginalne oraz analiza aktualnej literatury fachowej pozwoliły na sformułowanie następujących wniosków:

1. U większości pacjentów leczonych z powodu młodzieńczego idiopatycznego zapalenia stawów (MIZS) stwierdza się niedobór witaminy D, niezależny od postaci klinicznej, aktywności choroby, płci, wieku oraz wybranych wskaźników zapalnych.

2. Długotrwałe leczenie metotreksatem – najczęściej stosowanym klasycznym lekiem modyfikującym przebieg choroby – stanowi potencjalny czynnik ryzyka niedoboru witaminy D u dzieci i młodzieży z MIZS. Stosowanie metotreksatu może prowadzić do upośledzonego wchłaniania jelitowego witaminy D, zaś hepatotoksyczne działanie metotreksatu może zaburzać szlak syntezy witaminy D ograniczając hydroksylację kalcyferolu w wątrobie. Możliwy jest również niekorzystny wpływ metotreksatu na przebieg skórnej syntezy witaminy D.

3. Ponieważ pacjenci leczeni z powodu MIZS, szczególnie z użyciem metrotreksatu, należą do grupy ryzyka niedoboru witaminy D, uzasadnione jest zalecenie regularnej systematycznej suplementacji witaminy D w tej grupie, przy czym dawka powinna być modyfikowana w zależności od aktualnego stężenia 25(OH)D w krwi.

4. Stosowanie pomostowej steroidoterapii w MIZS wydaje się nie mieć wpływu na stężenie witaminy D, ale może mieć wpływ na gospodarkę wapniowo-fosforanową, jednakże przekrojowy charakter przeprowadzonego badania oraz zbyt mała grupa badana dyktują ostrożność w interpretacji tych powiązań.

5. Immunomodulujące działanie witaminy D oraz jej regulacyjny wpływ na procesy zapalne może mieć istotny wpływ na przebieg chorób reumatycznych wieku dziecięcego, ale wymaga potwierdzenia w przyszłych, dobrze zaprojektowanych badaniach naukowych. Podobnie udział witaminy D w terapii MIZS, a także innych chorób reumatycznych okresu rozwojowego, ma wiele korzystnych aspektów, ale lecznicza rola witaminy D nie może być na obecnym etapie wiedzy usankcjonowana.

8. Streszczenie w języku polskim

Niedobór witaminy D stanowi istotny problem kliniczny w populacji ogólnej i może dotyczyć szacunkowo ponad miliarda osób na całym świecie. Według dostępnych badań dotyka on w sposób szczególny pacjentów obciążonych chorobami przewlekłymi, w tym chorobami reumatycznymi. Znaczenie chorób z tej grupy systematycznie rośnie, znajdując odzwierciedlenie w obserwacjach klinicznych i danych epidemiologicznych, wiążąc się jednocześnie z dynamicznym rozwojem dziedziny jaką jest reumatologia dziecięca. Plejotropowe działanie witaminy D, poza klasycznie rozumianym regulowaniem gospodarki wapniowej, przejawia się również m.in. opisywanym w licznych doniesieniach naukowych immunomodulującym wpływem na procesy zapalne. Obserwacje poczynione zarówno w badaniach in vitro, jak i in vivo skłaniają do poszukiwania potencjalnej roli witaminy D oraz jej prawidłowego stężenia w patogenezie i ewolucji chorób reumatycznych. Aktualnie dostępne dane z tego zakresu dotyczą w przeważającej części populacji dorosłej.

Celem niniejszej pracy była ocena częstości występowania niedoboru witaminy D wśród pacjentów z młodzieńczym, idiopatycznym zapaleniem stawów (MIZS). Dodatkowo poszukiwano związku między stężeniem witaminy D oraz parametrów zapalnych, parametrów gospodarki wapniowo-fosforanowej, przebiegiem klinicznym oraz stosowanym leczeniem MIZS.

Badaniem objęto 189 pacjentów z rozpoznanym na podstawie standardowych kryteriów MIZS. Oceny klinicznej dokonywano w oparciu o badanie przedmiotowe. Wszyscy pacjenci w momencie kwalifikacji do badania byli w stabilnej fazie choroby, ocenianej według skali JADAS27. Jednym z elementów oceny były pomiary antropometryczne obejmujące masę ciała, wzrost, BMI wykonywane przy użyciu metod zgodnych z wytycznymi WHO. Zbadano stężenie 25(OH)D, CRP, OB, wapnia, fosforanów, ALP. Niedobór witaminy D definiowano jako stężenie 25(OH)D <20 ng/ml. Uzyskane wyniki poddano analizie statystycznej przy użyciu powszechnie dostępnego oprogramowania.

Mediana stężenia 25(OH)D w badanej populacji wyniosła 15,00 ng/ml (IQR 12,00 ng/ml). Niedobór witaminy D potwierdzono u 67,2% badanych. Stężenie witaminy D nie korelowało z płcią, postacią kliniczną, stężeniem CRP, OB, ALP, fosforanów. Wykazano natomiast odwrotną korelację stężenia 25(OH)D z BMI (r=-0,19) oraz dodatnią korelację

stężenia 25(OH)D ze stężeniem wapnia (r=0,19). Stosowana dawka MTX była istotnie statystycznie wyższa u pacjentów z niższym stężeniem 25(OH)D, zarówno w analizie jedno jak i wieloczynnikowej ($p<0,05$). Odmiennie stosowanie w leczeniu GKS nie korespondowało w istotny sposób ze stężeniem 25(OH)D ($p>0,05$). Wykazano natomiast negatywną korelację stężenia wapnia ze stosowaniem zarówno GKS, MTX jak i terapii łączonej ($p<0,05$).

Podsumowując, niedobór witaminy D stanowił istotny problem w badanej populacji pacjentów z MIZS. Stężenie 25(OH)D nie było związane z płcią, wiekiem, stopniem aktywności choroby ani parametrami zapalnymi. Leczenie MTX należy rozpatrywać jako możliwy jatrogenny czynnik ryzyka niedoboru witaminy D. Stosowanie GKS nie wpływa na stężenie witaminy D u pacjentów, jednak jest istotnie związane ze stężeniem wapnia i fosforanów. Suplementacja witaminy D, zgodna z aktualnie obowiązującymi wytycznymi dla populacji ogólnej powinna być rekomendowana pacjentom leczonym z powodu MIZS, szczególnie tym długotrwale stosującym metotreksat.

9. Streszczenie w języku angielskim

Vitamin D deficiency represents a significant clinical problem in the general population and may affect an estimated over one billion people worldwide. According to available research, it particularly affects patients burdened with chronic diseases, including rheumatic diseases. The importance of diseases from this group is steadily increasing, reflected in clinical observations and epidemiological data, while also being associated with the dynamic development of pediatric rheumatology.

According to multiple scientific data the pleiotropic action of vitamin D, beyond its classical role in regulating calcium homeostasis, includes the immunomodulatory effect on inflammatory processes. Observations made both in vitro and in vivo lead to the search for the potential role of vitamin D and its proper concentration in the pathogenesis and evolution of rheumatic diseases. Currently available data in this area are mainly focused on the adult population.

The aim of this study was to assess the frequency of vitamin D deficiency among patients treated for juvenile idiopathic arthritis (JIA). Additionally, the relationship between vitamin D levels and inflammatory parameters, calcium-phosphate metabolism parameters, clinical course, and treatment of JIA was investigated.

The study included 189 patients diagnosed with JIA based on standard criteria. Clinical assessment was based on physical examination. All patients at the time of study qualification were in a stable phase of the disease, ascertained by JADAS27 scale. Anthropometric measurements including body mass, height, and BMI were performed using standard techniques consistent with WHO guidelines. Serum / blood levels of 25(OH)D, CRP, ESR, calcium, phosphate, and ALP were determined. Vitamin D deficiency was defined as serum 25(OH)D concentration <20 ng/ml. These data were subsequently subjected to statistical analysis using commonly available software.

The median 25(OH)D concentration in the study population was 15.00 ng/ml (IQR 12.00 ng/ml). Vitamin D deficiency was confirmed in 67.2% of the JIA patients. Vitamin D levels did not correlate with gender, clinical presentation, CRP, ESR, ALP, or phosphate levels. However, an inverse correlation was found between 25(OH)D levels and BMI (r=-0.19), in addition to positive correlation between 25(OH)D levels and serum calcium calcium (r=0.19). The administered, weekly dose of MTX treatment was significantly

higher in patients with lower 25(OH)D levels, both in univariate and multivariate analysis ($p<0.05$). Contrary glucocorticoids (GCs) used in treatment did not significantly correspond to 25(OH)D levels ($p>0.05$). However, a negative correlation was shown between calcium levels and the use of either GCs or MTX, and combination therapy ($p<0.05$).

In summary, vitamin D deficiency was a significant problem in the studied population of JIA patients. 25(OH)D levels were not associated with gender, age, disease activity, or inflammatory parameters. MTX treatment should be considered a possible iatrogenic risk factor for vitamin D deficiency. The use of GCs did not affect vitamin D levels in JIA patients, but was significantly associated with calcium and phosphate levels. Vitamin D supplementation, following currently applicable guidelines for the general population, should be recommended for patients treated for JIA, especially those on long-term methotrexate therapy.

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11. Oświadczenia współautorów

lek. Maciej Stawicki

Klinika Pediatrii, Reumatologii, Immunologii
i Chorób Metabolicznych Kości
Uniwersytet Medyczny w Białymstoku

Białystok, 29.04.2024

Uniwersytet Medyczny w Białymstoku
ul. J. Kilińskiego 1
15-089 Białystok

Oświadczenie

Oświadczam, iż mój udział w przygotowaniu publikacji:

„Can vitamin D be an adjuvant therapy for juvenile rheumatic diseases?" autorstwa Macieja Konrada Stawickiego, Pawła Abramowicza, Gabrieli Sokołowskiej, Sebastiana Wołejszo, Williama B Granta, Jerzego Konstantynowicza, opublikowanej w Rheumatology International, wchodzącej w skład rozprawy doktorskiej *„Status witaminy D u dzieci z wybranymi chorobami reumatycznymi"* polegał na planowaniu i opracowaniu głównych założeń oraz optymalizacji metodologii badania, przeglądzie piśmiennictwa i pozyskiwaniu danych, analizie i interpretacji wyników, zredagowaniu pierwszej, oryginalnej wersji pracy.

Maciej Stawicki

dr n. med. Paweł Abramowicz

Białystok, 29.04.2024

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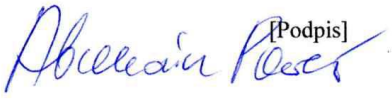
[Podpis]



lek. Gabriela Sokołowska
Tower Health
St. Christopher's Hospital for Children
in Philadelphia, PA

Białystok, 09.05.2024

Uniwersytet Medyczny w Białymstoku
ul. J. Kilińskiego 1
15-089 Białystok

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Gabriela Sokołowska

lek. Sebastian Wołejszo

Klinika Pediatrii, Reumatologii, Immunologii
i Chorób Metabolicznych Kości
Uniwersytet Medyczny w Białymstoku

Białystok, 29.04.2024

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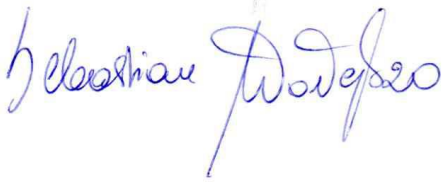

William B. Grant

Author's printed name and surname

San Francisco, USA, 6 May 2024

City, Country, Date

Sunlight, Nutrition and Health Research Center

Institution

Medical University of Białystok
J. Kilińskiego 1 Str.
15-089 Białystok
Poland

Declaration

I hereby declare that my participation in the preparation of the article entitled:
"Can vitamin D be an adjuvant therapy for juvenile rheumatic diseases?" authored by Maciej K Stawicki, Paweł Abramowicz, Gabriela Sokolowska, Sebastian Wołejszo, William B Grant, and Jerzy Konstantynowicz, published in *Rheumatology International* 2023; 43(11), which is part of the doctoral dissertation "Vitamin D status in children with selected rheumatic diseases", involved planning the concept of the study, literature data analysis, editing and critical evaluation of the manuscript.

I also give consent for Mr. Maciej Konrad Stawicki to use the publication in the process of obtaining a doctoral degree in medical sciences and health sciences in the discipline of medical science.

William B Grant

[Signature]

prof. dr hab. n. med. Jerzy Konstantynowicz

Klinika Pediatrii, Reumatologii, Immunologii
i Chorób Metabolicznych Kości
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lek. Maciej Konrad Stawicki
Klinika Pediatrii, Reumatologii, Immunologii
i Chorób Metabolicznych Kości
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Maciej Stawicki

dr n. med. Paweł Abramowicz
Klinika Pediatrii, Reumatologii, Immunologii
i Chorób Metabolicznych Kości
Uniwersytet Medyczny w Białymstoku

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lek. Adrian Góralczyk
Oddział Ortopedii i Traumatologii,
Szpital MSWiA
ul. Fabryczna 27 15-471 Białystok

Białystok, 29.04.2024

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Adrian Góralczyk

lek. Justyna Młyńczyk
Klinika Pediatrii, Reumatologii, Immunologii
i Chorób Metabolicznych Kości
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Justyna Młyńczyk

lek. Anna Kondratiuk
Klinika Pediatrii, Reumatologii, Immunologii
i Chorób Metabolicznych Kości
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Anna Kondratiuk

prof. dr hab. n. med. Jerzy Konstantynowicz
Klinika Pediatrii, Reumatologii, Immunologii
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12. Zgoda Komisji Bioetycznej

KOMISJA BIOETYCZNA
UNIWERSYTETU MEDYCZNEGO w BIAŁYMSTOKU
ul. Jana Kilińskiego 1
15-089 Białystok
tel. (085) 748 54 07, (085) 686 52 20, fax. (085) 748 55 08
prorektorkl@umb.edu.pl

Białystok, 27-06-2019

Uchwała nr: R-I-002/337/2019

Komisja Bioetyczna Uniwersytetu Medycznego w Białymstoku, po zapoznaniu się z projektem badania zgodnie z zasadami GCP/ Guidelines for Good Clinical Practice /- **w y r a ż a z g o d ę** na prowadzenie tematu badawczego: „Ocena statusu immunologicznego ze szczególnym uwzględnieniem stężenia podklas IgG u pacjentów z młodzieńczym idiopatycznym zapaleniem stawów przed i w trakcie leczenia immunosupresyjnego" przez dr n. med. Pawła Abramowicza wraz z zespołem badawczym z UMB.

Z-ca Przewodniczącej Komisji Bioetycznej UMB
dr n. farm. Krzysztof Chrzanowski