Prevalence of coeliac disease in patients with rheumatoid arthritis and juvenile idiopathic arthritis: a systematic review and meta-analysis

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Abstract

Objective

The reported prevalence of coeliac disease (CD) in patients with rheumatoid arthritis (RA) and juvenile idiopathic arthritis (JIA) varies in previous studies. We aimed to examine the prevalence of CD in patients with RA and JIA.

Methods

We searched Medline, Embase, Cochrane and Web of Science Core Collection between 1 January 1990 and 31 October 2022. In our primary analysis, the prevalence of biopsy-confirmed CD in RA and JIA patients was investigated. In secondary analyses, the prevalence of serological markers for CD was examined. Pooled weighted prevalences of CD and serological markers with 95% confidence intervals (95%CI) were calculated and quality of included studies was assessed. Meta-regression analysis was performed on publication year, sample size, CD prevalence in the general population, proportion of females, and quality assessment score.

Results

In this systematic review, 14 publications were deemed relevant for RA and 22 for JIA, with nine and 18 included in the primary analyses of CD prevalence, respectively. Among a total of 754 RA patients and 2077 patients with JIA, the weighted pooled prevalence estimates of biopsy-confirmed CD were 0.4% (95%CI=0.0–1.2) and 1.4% (95%CI= 0.7–2.2), respectively. The pooled prevalence estimates of positive CD serology were 0.9% (95%CI=0.3–1.9) in RA and 5.4% (95%CI=2.5–9.2) in JIA.

Conclusion

In this meta-analysis, we found a pooled prevalence of biopsy-confirmed CD in patients with RA and JIA comparable to that in the general population. Routine screening for CD is not warranted in RA but could be considered in JIA patients with additional risk factors for CD.

Key words

coeliac disease, juvenile idiopathic arthritis, prevalence, rheumatoid arthritis, systematic review

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Introduction

Rheumatoid arthritis (RA) is a chronic autoimmune inflammatory disease characterised by symmetrical polyarthritis (1). RA affects about 0.5% of the global population (2). The autoimmune aetiology of RA has been associated with genetic susceptibility, and known risk factors are smoking, female sex, diet, and altered gut microbiota (3, 4). Arthritis with disease onset typically before the age of 16 years is classified as juvenile idiopathic arthritis (JIA) and includes all categories of idiopathic childhood long-lasting arthritis (5). The global prevalence of JIA is estimated to about 0.02% (6). RA and JIA have been associated with other autoimmune conditions, including coeliac disease (CD) (7, 8).

CD is an immune-mediated disease caused by an inflammatory response in the intestinal tract due to gluten intolerance (9). CD causes chronic diarrhoea, malabsorption, involuntary weight loss, and in children sometimes impaired growth (9). However, extraintestinal symptoms may also occur. CD is more common than RA and JIA with an estimated global prevalence of 0.5–2% (9). Some studies have found an increased prevalence of CD in patients with RA (10-12) and JIA (13-15) compared with the general population, while other studies (16-21) do not support such findings. RA and JIA patients also appear to have a higher prevalence of CD serological markers (16, 19, 22). At present, no major international gastroenterology or rheumatology society advocates screening for CD in RA and JIA patients. It is debated whether such may not be warranted, at least in JIA.

To our knowledge, no previous study has examined the prevalence of biopsy-confirmed CD in patients with RA and JIA through systematic review and meta-analysis. Hence, there is a need to investigate the pooled prevalence of CD in RA and JIA.

Material and methods

This review was planned and performed in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (23).

A prespecified protocol was used and registered in the PROSPERO database (Protocol ID: CRD42021289656).

Search

A search was conducted of Medline, Embase, Cochrane and Web of Science Core Collection from 1 January 1990 up to 28 October 2021 including the terms: "arthritis, rheumatoid" and "arthritis, juvenile", "rheumatoid factor" combined with "celiac disease", "non-tropical sprue", "glutens", "transglutaminases", "endomysium", and "villous atrophy". Complete search strategies for each database are presented in Supplementary Figure S1. We performed an updated search for the period 29 October 2021 to 31 October 2022. Search strategies were elaborated together with an experienced librarian at the library of Karolinska Institute (Stockholm, Sweden). We limited the search to English language publications. Review of search results was conducted independently by AF and AS. Disagreement between them about inclusion of publications in the study were resolved by discussion, and in unresolved cases by JFL. A total of 78 publications were screened in full text after initial review of titles and abstracts. The reference lists of these were searched for additional publications, but no additional publications eligible for full text screening were found. In all, 34 publications (10-22, 24-44) were included in the final analyses (Table I and Suppl. Fig. S1). Of these, the updated search yielded four publications.

Identification of patients

- Coeliac disease

For CD diagnosis, a small intestinal biopsy examination was required independent of serological CD markers (45). Only biopsy examinations that reported Marsh stages 2 or 3 were accepted as proof of CD diagnosis (46). When CD was reported as "biopsy-verified CD" or similarly, without explicit reference to Marsh stages, we assumed the biopsy represented Marsh stages 2 or 3. It is well known from previous studies that the prevalence of CD will increase when serology or Marsh stage 1 biopsies are accepted as proof of CD.

In a sub-analysis, the prevalence of CD was investigated based on the requirement of a Marsh stage 3 biopsy. We also investigated the prevalence of positive CD serology markers (available in the majority of studies) in RA and JIA patients. A positive CD serology was classified as a positive test for one of the two serological markers tissue transglutaminase antibodies (TTG) IgA/IgG and endomysial antibodies (EMA) IgA/IgG. In an additional analysis, we applied a wider definition and also included a positive test for anti-gliadin antibodies (AGA) IgA/IgG.

- Rheumatoid arthritis and juvenile idiopathic arthritis

For RA and JIA diagnoses we required a notation by the investigators that the international diagnostic guidelines for RA and JIA [*i.e.* American College of Rheumatology (ACR) (47), European Alliance of Associations for Rheumatology (EULAR) (48) or International League of Associations for Rheumatology (ILAR)] (49) were used in the study. We also included studies where patients were (i) diagnosed at specialised rheumatology clinics, (ii) treated with disease modifying anti-inflammatory drugs (DMARDs) or (iii) based on international classification of disease codes (ICD codes). Characteristics of included studies are presented in Table I.

Data items and risk of bias

We systematically extracted data on the following variables to a study specific form: (1) first author and year of publication, (2) country and region, (3) sample size (including proportion of males/females), (4) number of CD cases, (5) Marsh stage/villous atrophy (46), (6) diagnostic criteria for RA and JIA, (7) serological markers of CD, and (8) number of cases with positive CD serology (Table I).

The prevalence of CD in the general population differs between countries. For this reason, the prevalence of CD in RA and JIA was examined in relation to the underlying prevalence in each country (Table I) when data were available [Austria (we applied the European average) (50), Brazil (51, 52), Egypt (53), Finland (54), Germany (55), Iran (56. 57), Italy (58, 59), Mexico (60), Saudi Arabia (61), Spain (62), The Netherlands (63), Turkey (64), United Kingdom (65), and the United States (66).

The Newcastle-Ottawa quality assessment scale (67, 68) was used to grade the quality of included studies (Suppl. Table S1). Potential publication bias was examined through funnel plots and by applying the Egger's test.

Statistics

We used the "metaprop" STATA (StataCorp, College Station, TX, USA) command (69) for performing meta-analysis of binomial data. We choose metaprop because it implements specific procedures for binomial data and is appropriate for dealing with proportions close to or at the margins (0% and 100%). It also uses the Freeman-Tukey Double Arcsine Transformation to stabilise the variances. The heterogeneity between studies was estimated as I^2. We defined a $I^2 > 50\%$ as a substantial heterogeneity. We expected a high degree of heterogeneity among the studies of this meta-analysis and therefore used a random effects model to calculate the weighted pooled prevalence along with the 95% confidence intervals (CIs). The significance level was set to a *p*-value of <0.05.

We also performed subgroup analysis stratified by region, study size ($\leq$100 *vs.* >100) and Marsh stage 3 (yes/no). According to country of origin, studies were grouped in different regions (*Asia*: Egypt, Iran, Saudi Arabia; *Europe*: Austria, Italy, Netherlands, Spain, Turkey, UK; *North America*: Mexico and USA; *South America*: Brazil). Through meta-regression we also examined the association of CD prevalence in RA and JIA according to publication year, study sample size, CD prevalence in the general population, proportion of females, and quality assessment score. These study characteristics were chosen based on the assumption that they could explain potential variance of CD prevalence between studies. The meta-regression analysis was restricted to studies with biopsy-confirmed CD.

STATA version 17 (StatCorp, College Station, Texas) was used for all analyses. Microsoft Excel (v. 16.54, 2021, Microsoft Corporation, Washington, USA) was used for compiling and managing extracted data.

Ethics

This was a study of the existing literature, therefore no ethical permission was needed.

Results

We screened titles and abstracts for 2,965 publications published between 1 January 1990 and 31 October 2022 (Suppl. Fig. S1). A total of 78 publications were identified as potentially relevant for inclusion and read in full text. Of these, 44 were excluded due to insufficient definition of outcome or exposure (n=33) (7, 70-101); overlapping study populations (n=2) (102 103); not in English language (n=2) (104, 105) and duplicate (n=7) (106-111). The remaining 34 publications (10-22, 24-44) were inluded in this systematic review and consisted of 2,402 RA patients (studies, n=14) (10, 12, 16-18, 22, 24-26, 31, 34-36, 40) and 3,480 JIA patients (studies, n=22) (13-16, 19-22, 27-30, 32, 33, 37-39, 41-44). The study characteristics of included studies are reported in Table I.

Prevalence of coeliac disease in rheumathoid arthritis

In the main analysis of CD in patients with RA, we only included studies (n=9) reporting biopsy-confirmed CD (10, 12, 16-18, 22, 24, 36, 40). The mean study population for these studies was n=84 (range 15–161), with four studies having a population of 100 or more (12, 18, 24, 40). Four studies reported no CD cases (study population: n=15, n=55, n=85, n=100) (16, 17, 24, 36), and the remaining five reported prevalance estimates between 0.6% and 5.0%. Of a total of 754 patients with RA in the included studies, eight had CD, yielding an unweighted proportion of 1.1%. Two studies (12, 18) reported Marsh stage 3 biopsy-confirmed CD cases, yielding an unweighted prevalence proportion of 1.5% (total CD cases, n=4 in 261 patients).

The weighted pooled prevalence in the same nine studies was 0.4% (95%CI=0.0–1.2) (Fig. 1). The het-

Table I. Publications included in the meta-analysis on coeliac disease in rheumatoid arthritis and juvenile idiopathic arthritis.

Study	Country	Prevalence of CD in the general population* (%)	Patients n.	Female (%)	Age mean (range)	Mean disease duration years	Biopsy verified CD n. (%)	Biopsied[¥] n.	Villous atrophy[¥]	Antibodies	Seropositive n. (%)	Diagnostic criteria
RA (n=14)												
AlEnzi, 2020	Saudi Arabia	1.3	62	93.5	48.8 (NA)	NA	1 (1.6)	1	Yes	AGA/EMA/TTG	6 (9.7)	ACR
Atzeni, 2008	Italy	0.6	20	85.0	58.5 (28-80)	8.6	1 (5.0)	1	Yes	TTG	1 (5.0)	ACR
Bizzaro, 2003	Italy	0.6	100	NA	NA (NA)	NA	0 (0.0)	0	0	EMA/TTG	1 (1.0)	ACR
Caio, 2018	Italy	0.6	67	80.6	NA (18-84)	NA	-	-	-	AGA/EMA/TTG	2 (3.0)	ACR
Castillo-Ortiz, 2011	Mexico	2.7	85	87.1	49.1 (16-76)	11.2	-	-	-	AGA/TTG	29 (34.1)	ACR
Coaccioli, 2010	Italy	0.6	15	60.0	55.4 (32-76)	1.8	0 (0.0)	0	0	EMA/TTG	0 (0.0)	Clinical
Elhami, 2018	Iran	0.4	100	90.0	38.8 (32-47)	NA	3 (3.0)	3	Yes (Marsh 3)	TTG	3 (3.0)	ACR
Francis, 2002	UK	0.6	161	66.5	61 (20-84)	12	1 (0.6)	1	Yes (Marsh 3)	EMA	1 (0.6)	ACR
Goeldner, 2011	Brazil	0.3	156	88.5	51.3 (NA)	8.9	-	-	-	EMA	0 (0.0)	ACR
Liao, 2013	USA	0.7	1290	70.4	60.7 (NA)	NA	-	-	-	TTG	14 (1.1)	ACR
Luft, 2003	USA	0.7	50	NA	NA (NA)	NA	-	-	-	EMA/TTG	1 (2.0)	ACR
Moghtaderi, 2016	Iran	0.4	55	72.7	46.4 (20-75)	15.2	0 (0.0)	5	0	TTG	6 (10.9)	Clinical
Nisihara, 2007	Brazil	0.4	85	87.1	47.0 (23-71)	NA	0 (0.0)	0	0	EMA	0 (0.0)	ACR
Zayeni, 2014	Iran	0.4	156	87.8	NA (NA)	NA	2 (1.3)	2	Unspecified	TTG	2 (1.3)	ACR
JIA (n=22)												
Al-Mayouf, 2003	Saudi Arabia	1.3	42	57.1	NA (5-15)	NA	1 (2.4)	16	Yes	AGA/EMA	18 (42.9)	ACR
AlEnzi, 2020	Saudi Arabia	1.3	73	61.6	10.0 (NA)	NA	1 (1.4)	1	Yes	AGA/EMA/TTG	8 (11.0)	ILAR
Chang, 2018	UK	0.6	127	NA	NA (NA)	NA	1 (0.8)	3	Unspecified	EMA	3 (2.4)	Clinical
George, 1996	Netherlands	0.5	62	58.1	9.8 (3-16)	NA	1 (1.6)	5	Yes (Marsh 3)	AGA/EMA	6 (9.7)	EULAR
Gheita, 2012	Egypt	1.0	30	73.3	11.9 (NA)	6.5	-	-	-	TTG	16 (53.3)	Clinical
Gheith, 2017	Egypt	1.0	44	77.3	12.5 (NA)	5.0	-	-	-	TTG	19 (43.2)	ILAR
Lepore, 1993	Italy	1.1	53	66.0	11.4 (2-16)	NA	0 (0.0)	8	0	AGA	18 (34.0)	Clinical
Lepore, 1996	Italy	1.1	119	73.1	11.5 (2-16)	NA	3 (2.5)	4	Yes (Marsh 3)	EMA	4 (3.4)	EULAR
Moghtaderi, 2016	Iran	0.6	53	49.1	15.6 (1-16)	3.5	0 (0.0)	1	0	TTG	1 (1.9)	Clinical
Naddei, 2022	Italy	1.1	329	74.8	NA (NA)	NA	6 (1.8)	6	Yes (Marsh 3)	EMA/TTG	8 (2.4)	ILAR
Nisihara, 2017	Brazil	0.4	45	64.4	NA (3-16)	NA	0 (0.0)	0	0	EMA/TTG	4 (8.9)	Clinical
Pellegrini, 1991	Italy	1.1	70	62.9	8.3 (1-17)	NA	0 (0.0)	3	0	AGA	5 (7.1)	EULAR
Pohjankoski, 2010	Finland	1.0	417	67.9	NA (NA)	NA	3 (0.7)	3	Yes (Marsh 2-3)	-	-	ILAR
Robazzi, 2013	Brazil	0.4	53	47.2	10.4 (2-17)	3.4	1 (1.9)	1	Yes (Marsh 3)	TTG	1 (1.9)	ILAR
Sadeghi, 2021	Iran	0.6	78	66.7	7.9 (1-16)	2.8	1 (1.3)	1	Yes (Marsh 3)	TTG	3 (3.8)	ILAR
Sahin, 2019	Turkey	0.9	96	58.3	11.6 (NA)	NA	0 (0.0)	0	0	EMA/TTG	0 (0.0)	ILAR
Schulz, 2022	Germany	0.7	499	66.7	NA (NA)	NA	-	-	-	TTG	4 (0.4)	ILAR
Skrabl-Baumgartner, 2017	Austria	0.8	95	69.5	12.3 (2-17)	NA	4 (4.2)	4	Yes (Marsh 2-3)	EMA/TTG	4 (4.2)	ILAR
Stagi, 2005	Italy	1.1	151	79.5	NA (2-16)	NA	10 (6.6)	10	Unspecified	AGA/EMA/TTG	10 (6.6)	ILAR
Taneja, 2017	USA	0.7	830	NA	NA (3-21)	NA	-	-	-	TTG	7 (0.8)	ILAR
Torres-Fernandez, 2022	Spain	0.5	135	NA	NA (NA)	NA	3 (2.2)	3	Unspecified	EMA/TTG	4 (3.0)	ILAR
Tronconi, 2017	Italy	1.1	79	64.6	NA (2-21)	NA	3 (3.8)	3	Unspecified	TTG	NA	ILAR

ACR: American College of Rheumatology; AGA: anti-gliadin antibodies; CD: coeliac disease; EMA: endomysial antibodies; EULAR: European Alliance of Associations for Rheumatology; ILAR: International League of Associations for Rheumatology; JIA: juvenile idiopathic artrhritis; NA: data not available; RA: rheumatoid arthritis; TTG: tissue transglutaminase antibodies. *General population prevalence, for sources see main text.

[¥] "-" = studies only including antibodies; "0" = no cases of biopsy-confirmed CD; "Yes" = when stated in the study that biopsy-confirmed cases showed villous atrophy (and in some cases Marsh stage 3).

erogeneity between studies was low (I^2=1.2%, p=0.42). Stratified by sample size ≤100 (n=7) (10, 12, 16, 17, 22, 24, 36) *vs*. >100 (n=2) (18, 40), the weighted pooled prevalence was 0.3% (95%CI=0.0–1.7) compared to 0.9% (95%CI=0.1–2.4) (p=0.94). Comparing studies reporting Marsh stage 3 biopsy-confirmed CD (n=2) (12, 18) and studies without explicit reference to Marsh stage 3 (n=7) (10, 16, 17, 22, 24, 36, 40) yielded weighted CD prevalence estimates of 1.3% (95%CI=0.2–3.2) and 0.1% (95%CI=0.0–1.0), respectively (p=0.44). In comparison by region, Asia (n=4) (12, 16, 22, 40) showed a higher weighted pooled estimate (1.3%:95%CI=0.3–3.0) than Europe (n=4; 0.0%:95%CI=0.0–1.1) (10, 17, 18, 24) (p=0.30). South America was represented by one study (36) which reported no CD cases.

In meta-regression analyses of the relationship between the prevalence of CD in RA and publication year (p=0.56), study sample size (p=0.56), CD prevalence in the general population (p=0.80), proportion of females (p=0.22), and quality assessment score (p=0.59), no significant associations were found. (Suppl. Fig. S2 A-E)

Prevalence of coeliac disease in juvenile idiopathic arthritis

Consistent with the definition of CD in RA, we restricted the main analysis of CD in patients with JIA to studies (n=18) reporting biopsy-confirmed CD (11, 13-16, 19-22, 27, 28, 32, 33, 37, 38, 41, 42, 44). For these studies, the mean study population was 115 (range 42–417), with six studies having a population of 100 or more (13, 27, 33, 37, 42, 44). Five studies reported no CD cases (study population n=45, n=53, n=53, n=70, and n=96) (16, 19-21, 32), and the remaining 13 studies reported prevalance estimates between 0.7% and 6.6%. Of 2,077 patients with JIA in the included studies, 38 had biopsy-confirmed CD, yielding an unweighted prevalence proportion of 1.8%. For studies (n=6) (14, 28, 33, 38, 41, 42) reporting positive Marsh stage 3 biopsy-confirmed CD, the unweighted proportion of CD was 2.2% (total CD cases, n=16 in 736 JIA patients). One

study (42) reported CD according to the updated diagnostic guidelines of the European Society of Paediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN), that do not require an intestinal biopsy for CD diagnosis (112). To be consistent with our definition of biopsy-confirmed CD, we recategorised two positive CD cases to non-CD (n=6, instead of n=8).

The weighted pooled prevalence in the 18 studies reporting biopsy-confirmed CD in JIA was 1.4% (95%CI=0.7–2.2) (Fig. 2). The heterogeneity was comparably low (I^2=37%, p=0.08). Stratified by sample size ≤100 (n=12) (11, 14-16, 19-22, 28, 32, 38, 41) *vs.* >100 (n=6) (13, 27, 33, 37, 42, 44) the weighted pooled prevalence was 1.0% (95%CI=0.3–2.0) compared with 2.0% (95%CI=0.8–3.8) (p=0.47). For studies reporting Marsh stage 3 biopsy-confirmed CD (n=6) (14, 28, 33, 38, 41, 42) the weighted pooled CD prevalence was 2.0% (95%CI=1.0–3.2), and for studies without an explicit reference to Marsh 3 (n=12) (11, 13, 15, 16, 19-22, 27, 32, 37, 44), it was 1.0% (95%CI=0.2–2.2) (p=0.27). The weighted pooled estimates of CD by region were: Asia (n=4) 1.0% (95%CI=0.0–3.0) (11, 16, 22, 41), Europe (n=12) 1.6% (95%CI=0.7–2.8) (13-15, 20, 21, 27, 28, 32, 33, 37, 42, 44), and South America (n=2) 0.7% (95%CI=0.0–4.0) (19, 3)8 (p=0.91).

In meta-regression analyses, publication year (p=0.92), study sample size (p=0.79) and CD prevalence in the general population (p=0.33), and quality assessment scores (p=0.06), were not associated with a higher CD prevalence in JIA. However, we found a positive association between a high proportion of females in included studies and a higher prevalence of CD (p=0.046) (Suppl. Fig. S3 A-E). Two studies that lacked sufficient data on the proportion of females were not inluded in this analysis (27, 44).

Prevalence of coeliac disease antibodies in patients with RA and JIA

We also performed a meta-analysis of the prevalence of serological CD markers (EMA and TTG antibodies). Of included studies, all but two (15, 37) reported frequency of serological markers

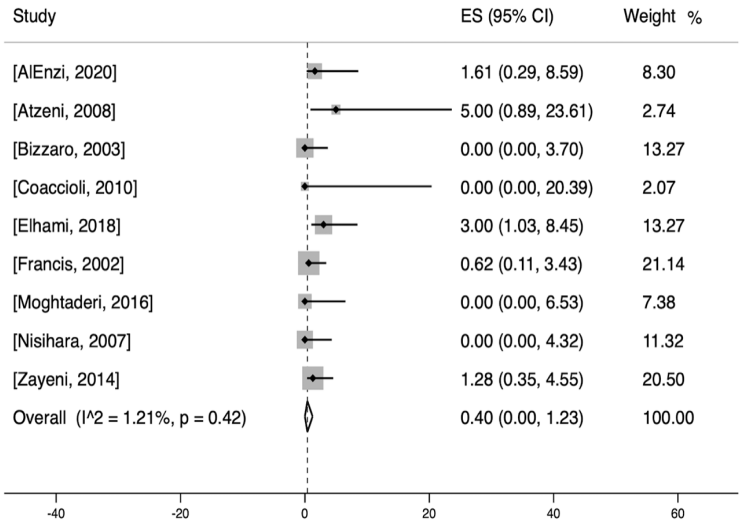

Fig. 1. Prevalence of biopsy-confirmed coeliac disease in rheumatoid arthritis. CI: confidence interval.

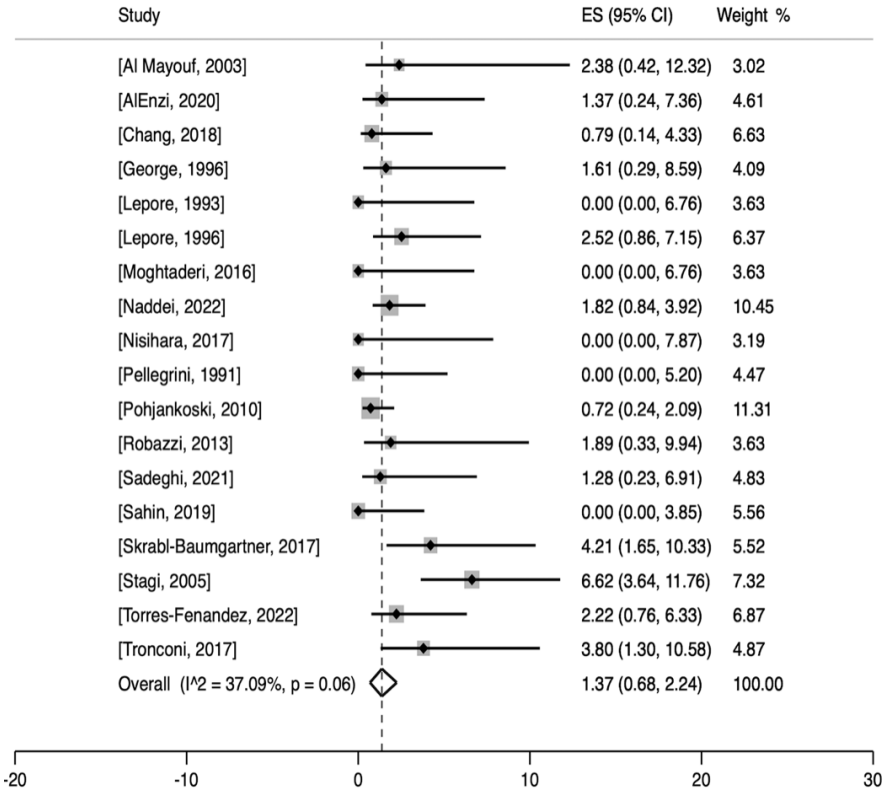

Fig. 2. Prevalence of biopsy-confirmed coeliac disease in juvenile idiopathic arthritis. CI: confidence interval.

(Table I). The crude prevalence of any of the serological CD markers EMA or TTG in RA patients was 1.3% (32 serology positives in 2402 RA patients from 14 studies), and the weighted pooled prevalence was 0.9% (95%CI=0.3–1.9; I^2=43%; p=0.04) (Suppl. Fig. S4). Corresponding percentages for JIA were 3.3% (87 serology positive in 2,637 JIA patients from 16 studies [seropositivity for EMA or TTG was not possible to distinguish from AGA in two studies (10, 13)] and 5.4% (95%CI=2.5-9.2; I^2=91%; p<0.001) for the crude and weighted pooled prevalence, respectively (Suppl. Fig. S5). Three studies reported prevalences >15% (11, 29, 30). When excluding

these studies the weighted pooled prevalence in JIA was 2.1% (95%CI=1.0–3.4; I^2=67%; p<0.001).

With a wider definition of a CD positive serology, including a positive test for any of EMA, TTG or AGA, the pooled prevalence was 3.0% (95%CI=0.7–6.3; I^2=89%; p<0.001) for RA and 7.8% (95%CI=4.2–12.3; I^2=93%; p<0.001) for JIA (Suppl. Fig. S6-S7).

Discussion

In this systematic review and meta-analysis of 754 patients with RA and 2077 patients with JIA, the pooled weighted prevalence estimates of biopsy-confirmed CD in RA and JIA were 0.4% and 1.4%, respectively. This is approximately equivalent to one in 250 RA patients, and one in 71 JIA patients. Our prevalence estimates for RA and JIA are comparable to that in the general population (50). To our knowledge, this meta-analysis is the first to report the pooled weighted prevalence of CD in patients with RA and JIA.

The pooled prevalence of 0.4% for biopsy-confirmed CD (Marsh stages 2 or 3) in patients with RA in our study do not differ significantly from the global CD prevalence of 1% in the general adult population (50). The CD prevalence ranged from 0% to 5% in the studies included in our meta-analysis. For two of these studies (12, 18) where CD diagnosis was confirmed with a Marsh stage 3 biopsy, the prevalence was 0.6% and 3.0%.

The global prevalence of paediatric CD is estimated to around 0.5-2.0% (9), which is similar to the the 1.4% found in our study. Restricted to studies reporting Marsh stage 3 biopsy-confirmed CD (n=6) (14, 28, 33, 38, 41, 42) the weighted pooled CD prevalence (2.0%, 95%CI=1.0–3.2) is also similar to the global estimate. Among included studies, a recent Italian study reported a CD prevalence of 2.4% in 329 JIA patients (42). However, CD was diagnosed either by histological findings or according to the updated ESPGHAN diagnostic criteria that do not require a confirmatory duodenal/jejunal biopsy (112). Restricting their result to biopsy-confirmed CD yielded a prevalence of 1.8%, which is similar to our result.

It is important to note that in some studies included in our meta-analysis not all patients with elevated levels of CD serological markers underwent biopsy. This may lead to underestimation of the true prevalence of CD. A temporal relationship with RA and JIA diagnosis before CD diagnosis was found in the majority of studies and imply that patients with CD may have been asymptomatic at the time of RA and JIA diagnosis, thus more likely to have a normal intestinal biopsy. Notably, this could indicate a need for increased awareness of signs and symptoms of CD in this group of patients, especially since rheumatologic diseases can manifest with gastrointestinal symptoms. Additional to that, some studies excluded patients with known CD diagnosis (41). We excluded studies that included and counted patients already diagnosed with CD as cases in their results (70, 98). Few studies reported testing the study participants for IgA deficiency. Presence of IgA deficiency is known to lead to lower diagnostic sensitivity of CD serological screening tests (112, 113). This is of particular importance in JIA since it has been suggested that IgA deficiency is more common in JIA than the general paediatric population (44, 114, 115). In the case of RA, the distinction between rheumatoid factor or anti-citrullinated protein antibodies (ACPA) seropositive and seronegative RA could not be made in our study due to lack of data in included studies. Such distinction could be important for the interpretation of our results. Seropositive RA seems to be a rather well-defined pathophysiological entity of RA, with evidence of a strong genetic association, and the hypothesis that autoimmunity is generated at the mucosal surfaces where inflammation leads to citrullination that induces pathogenic autoantibodies in genetically susceptible hosts (116). While for seronegative RA patients, a common opinion is that this is not the case. It is suggested that these patients instead represent different subsets of RA where different pathophysiolocigal mechanisms are in play (116). The seronegative group consists of around one third of all RA patients. We cannot exclude that a stronger link between CD and RA exists within a subset of seronegative patients that was not captured in our meta-analysis.

The prevalence of CD varies in patients with different autoimmune and chronic inflammatory diseases. For example, a systematic review and meta-analysis of CD in autoimmune thyroid disease (117) showed a pooled prevalence of 1.6% (95%CI=1.3–1.9), and a multicentre study (118) of patients with Sjögren's syndrome (n=354) reported a prevalence of 6.8% (95%CI=4.6–9.9). These differences indicate that disease-specific immunopathogenic factors are potentially associated with the variation in CD prevalence between different autoimmune diseases.

Notably, there were substantial differences between the studies included in our meta-analysis, such as differences in type and methods for detecting CD serological markers, frequency of autoimmune comorbidity, genetics, region and ethnicity of the study population, and ongoing treatment for RA and JIA where only a few studies reported data on immunosuppressive therapies.

We explored potential publication bias through funnel plots and Egger's test. No major publication bias could be identified in funnel plots (Fig. 3-4) or in Egger's test (RA, p=0.61; JIA, p=0.95). To explore the heterogeneity between studies, we also performed a series of meta-regression analyses. For RA, we found no associations with CD prevalence, while for JIA a higher proportion of females was associated with increasing prevalence of CD. This finding may be explained by the female predominance in both CD and JIA (50).

We investigated the prevalence of CD serological markers in patients with RA and JIA. A previous meta-analysis found a prevalence of CD serological markers of 1.4% in the general population (50). Previous studies have shown a higher occurrence of CD serological markers in patients with autoimmune diseases (13, 19, 22). Our pooled estimates of 0.9% for RA and 5.4% for JIA are higher than our prevalence estimates for biopsy-confirmed CD, and substantially higher than in the general population for JIA. However, the studies included in the meta-analysis of

positive CD serology in JIA show high heterogeneity (I^2=91%). Additionally, some studies showed unexpectedly high prevalences (three JIA studies reported prevalences of >15%). After exclusion of these high prevalence studies, the prevalences were 0.5% in RA and 2.1% in JIA. Included studies also span over a long period of time (1991 to 2022) when different methods for detecting positive CD serology were applied. Furthermore, studies also differ substantially in sample size and study design. The results should therefore be interpreted with caution.

At present, no major international gastroenterology society recommends screening for CD in RA and JIA. Although, some authors have suggested screening for CD in JIA could be warranted (42, 119). For JIA patients, our pooled estimate of 1.4% may not alone be convincing enough to strongly advocate routine screening for CD. However, as already commented, there are several reasons to believe our pooled estimates could underestimate the true prevalence of CD in both RA and JIA. First, several of the included studies did not perfom duodenal/jejunal biopsies of all patients positive for serological CD markers. Second, IgA deficiency testing was not performed in all included studies, thus yielding lower reliability of CD serological screening tests. Third, the majority of patients included in the studies in our meta-analysis were asymptomatic and therefore less likely to present with a positive CD serological screening test and villous atrophy in a subsequent biopsy. Fourth, the prevalence of serological CD markers in JIA was 5.4% (and 2.1% when excluding studies with reported prevalences of >15%) in our study, compared to 1.4% in the general population (50). This could indicate that JIA patients are at higher risk of developing CD and might be less symptomatic than CD patients in the general population. For RA, no such difference in the seroprevalence of CD markers was observed compared with the general population.

In all, there is reason to believe that the true prevalence of CD in RA and JIA patients might be higher than the pooled prevalence of our meta-analysis. Regardless of this, we believe our results do not support routine screening for CD in patients with RA. However, systematic serological screening and subsequent biopsy in JIA patients could be warranted in patients with known risk factors for CD, but also in the presence of clinical suspicion of CD. The exact diagnostic workup algorithm for such systematic screening remains to be elaborated.

This study has some strengths, such as a large pool of identified studies drawn from four major databases (Medline, Embase, Cochrane and Web of Science Core Collection). The comparably large number of studies included allowed us to restrict the analysis to histologically confirmed diagnosis of CD instead of diagnosis based solely on serological markers. The latter diagnostic approach is likely to overestimate the true prevalence of CD. Furthermore, we performed a meta-analysis of serological markers of CD in RA and JIA to contrast our findings based on histological findings.

We acknowledge some limitations. First, we lacked data on CD from large

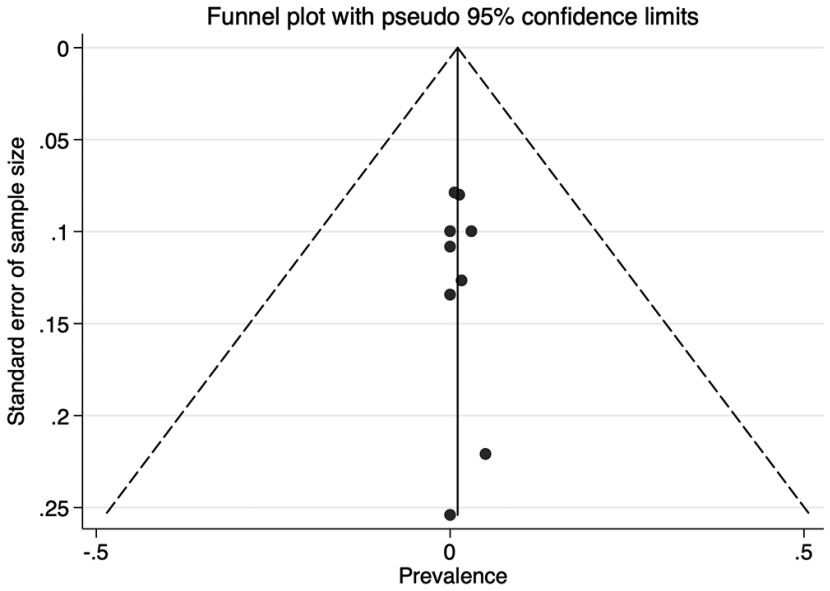

Fig. 3. Funnel plot of studies investigating biopsy-confirmed coeliac disease in patients with rheumatoid arthritis.

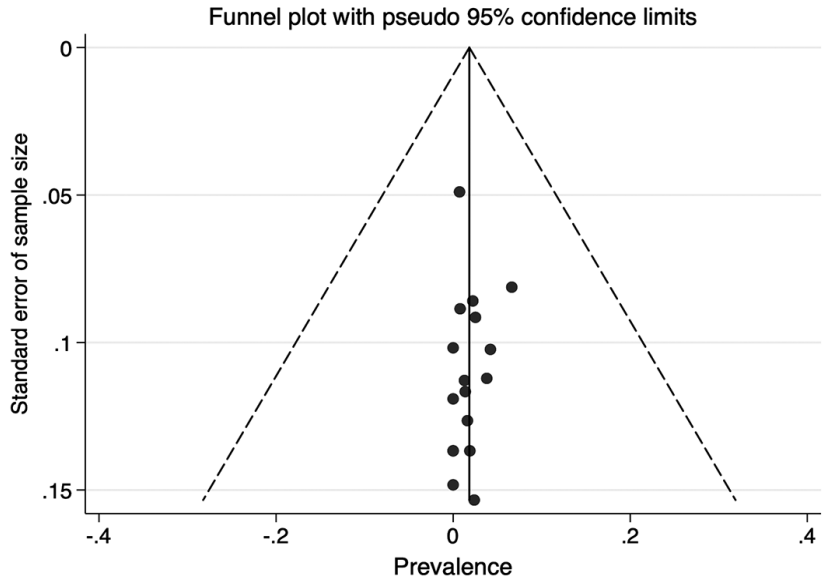

Fig. 4. Funnel plot of studies investigating biopsy-confirmed coeliac disease in patients with juvenile idiopathic arthritis.

parts of the world, such as Sub-Saharan Africa and East Asia, and we also lacked data on the ethnicity of included study participants. Second, the included studies did not allow a meaningful analysis of biopsy-negative CD in RA and JIA. Third, since several studies did not confirm all CD cases with a positive serology with a biopsy, our estimates are likely to underestimate the true prevalence of CD. Fourth, the lack of data on immunosuppressive therapies of patients is a limitation and should be considered when interpreting the results.

In conclusion, through systematic review and meta-analysis we found a prevalence of biopsy-confirmed CD in patients with RA and JIA comparable to that in the general population. At present, no major gastroenterology or rheumatology society advocates routine screening for CD in RA and JIA. Our findings do not support routine screening of RA patients but screening could be considered in JIA patients with additional risk factors for CD.

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References

1. SMOLEN JS, ALETAHA D, BARTON A *et al*.: Rheumatoid arthritis. *Nat Rev Dis Primers* 2018; 4: 18001. https://doi.org/10.1038/nrdp.2018.1
2. ALMUTAIRI K, NOSSENT J, PREEN D, KEEN H, INDERJEETH C: The global prevalence of rheumatoid arthritis: a meta-analysis based on a systematic review. *Rheumatol Int* 2021; 41(5): 863-77. https://doi.org/10.1007/s00296-020-04731-0
3. MACGREGOR AJ, SNIEDER H, RIGBY AS *et al*.: Characterizing the quantitative genetic contribution to rheumatoid arthritis using data from twins. *Arthritis Rheum* 2000; 43(1): 30-7. https://doi.org/10.1002/1529-0131(200001)43:1%3C30::aid-anr5%3E3.0.co;2-b
4. DEANE KD, DEMORUELLE MK, KELMENSON LB, KUHN KA, NORRIS JM, HOLERS VM: Genetic and environmental risk factors for rheumatoid arthritis. *Best Pract Res Clin Rheumatol* 2017; 31(1): 3-18. https://doi.org/10.1016/j.berh.2017.08.003
5. PRAKKEN B, ALBANI S, MARTINI A: Juvenile idiopathic arthritis. *Lancet* 2011; 377(9783): 2138-49. https://doi.org/10.1016/s0140-6736(11)60244-4
6. THIERRY S, FAUTREL B, LEMELLE I, GUILLEMIN F: Prevalence and incidence of juvenile idiopathic arthritis: a systematic review. *Joint Bone Spine* 2014; 81(2): 112-7. https://doi.org/10.1016/j.jbspin.2013.09.003
7. SIMON TA, HARIKRISHNAN GP, KAWABATA H, SINGHAL S, BRUNNER HI, LOVELL DJ: Prevalence of co-existing autoimmune disease in juvenile idiopathic arthritis: a cross-sectional study. *Pediatr Rheumatol Online J* 2020; 18(1): 43. https://doi.org/10.1186/s12969-020-00426-9
8. DOYLE JB, LEBWOHL B, ASKLING J *et al*.: Risk of juvenile idiopathic arthritis and rheumatoid arthritis in patients with celiac disease: a population-based cohort study. *Am J Gastroenterol* 2022; 117(12): 1971-81. https://doi.org/10.14309/ajg.0000000000002014
9. CATASSI C, VERDU EF, BAI JC, LIONETTI E: Coeliac disease. *Lancet* 2022; 399(10344): 2413-26. https://doi.org/10.1016/s0140-6736(22)00794-2
10. ATZENI F, DORIA A, GHIRARDELLO A *et al*.: Organ-specific autoantibodies in patients with rheumatoid arthritis treated with adalimumab: a prospective long-term follow-up. *Autoimmunity* 2008; 41(1): 87-91. https://doi.org/10.1080/08916930701620050
11. AL-MAYOUF SM, AL-MEHAIDIB AI, ALKAFF MA: The significance of elevated serologic markers of celiac disease in children with juvenile rheumatoid arthritis. *Saudi J Gastroenterol* 2003; 9(2): 75-8.
12. ELHAMI E, ZAKERI Z, SADEGHI A, ROSTAMI-NEJAD M, VOLTA U, ZALI MR: Prevalence of celiac disease in Iranian patients with rheumatologic disorders. *Gastroenterol Hepatology Bed Bench* 2018; 11(3): 239-43.
13. STAGI S, GIANI T, SIMONINI G, FALCINI F: Thyroid function, autoimmune thyroiditis and coeliac disease in juvenile idiopathic arthritis. *Rheumatology* (Oxford) 2005; 44(4): 517-20. https://doi.org/10.1093/rheumatology/keh531
14. SKRABL-BAUMGARTNER A, CHRISTINE HAUER A, ERWA W, JAHNEL J: HLA genotyping as first-line screening tool for coeliac disease in children with juvenile idiopathic arthritis. *Arch Dis Child* 2017; 102(7): 607-11. https://doi.org/10.1136/archdischild-2016-311544
15. TRONCONI E, MINIACI A, PESSION A: The autoimmune burden in juvenile idiopathic arthritis. *Ital J Pediatr* 2017; 43(1): 56. https://doi.org/10.1186/s13052-017-0373-9
16. MOGHTADERI M, FARJADIAN S, AFLAKI E, HONAR N, ALYASIN S, BABAEI M: Screening of patients with juvenile idiopathic arthritis and those with rheumatoid arthritis for celiac disease in southwestern Iran. *Turk J Gastroenterol* 2016; 27(6): 521-24. https://doi.org/10.5152/tjg.2016.16354
17. COACCIOLI S, LANDUCCI P, FATATI G, DEL GIORNO R, PAPINI M, PUXEDDU A: Prevalence of coeliac disease in rheumatoid and psoriatic arthritis and in psoriasis. *Med J Nutrition Metab* 2010; 3(1): 61-64. https://doi.org/10.1007/s12349-009-0063-2
18. FRANCIS J, CARTY JE, SCOTT BB: The prevalence of coeliac disease in rheumatoid arthritis. *Eur J Gastroenterol Hepatol* 2002;14(12):1355-6. https://doi.org/10.1097/00042737-200212000-00011
19. NISIHARA R, SKARE T, JARDIM AC, UTIYAMA SR: Celiac disease autoantibodies in juvenile idiopathic arthritis. *Rheumatol Int* 2017; 37(2): 323-24. https://doi.org/10.1007/s00296-016-3581-5
20. SAHIN Y, SAHIN S, BARUT K *et al*.: Serological screening for coeliac disease in patients with juvenile idiopathic arthritis. *Arab J Gastroenterol* 2019; 20(2): 95-98. https://doi.org/10.1016/j.ajg.2019.05.005
21. PELLEGRINI G, SCOTTA MS, SOARDO S *et al*.: Elevated IgA anti-gliadin antibodies in juvenile chronic arthritis. *Clin Exp Rheumatol* 1991; 9(6): 653-6.
22. ALENZI F, YATEEM M, SHAIKH M *et al*.: The value of screening for celiac disease in systemic lupus erythematosus: a single experience of a tertiary medical center. *Rheumatol Ther* 2020; 7(3): 649-56. https://doi.org/10.1007/s40744-020-00223-6
23. PAGE MJ, MCKENZIE JE, BOSSUYT PM *et al*.: The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. *Syst Rev* 2021; 10(1): 89. https://doi.org/10.1186/s13643-021-01626-4
24. BIZZARO N, VILLALTA D, TONUTTI E *et al*.: IgA and IgG tissue transglutaminase antibody prevalence and clinical significance in connective tissue diseases, inflammatory bowel disease, and primary biliary cirrhosis. *Dig Dis Sci* 2003; 48(12): 2360-65. https://doi.org/10.1023/b:ddas.0000007875.72256.e8
25. CAIO G, DE GIORGIO R, URSINI F, FANARO S, VOLTA U: Prevalence of celiac disease serological markers in a cohort of Italian rheumatological patients. *Gastroenterol Hepatol Bed Bench* 2018; 11(3): 244-49.
26. CASTILLO-ORTIZ JD, DURÁN-BARRAGÁN S, SÁNCHEZ-ORTÍZ A, RAMOS-REMUS C: [Anti-transglutaminase, antigladin and ultra purified anti-gladin antibodies in patients with a diagnosis of rheumatoid arthritis]. *Reumatol Clin* 2011; 7(1): 27-29. https://doi.org/10.1016/j.reuma.2010.03.006
27. CHANG RS, MCMILLAN R, EDGERTON J *et al*.: Evolving coeliac disease and thyroid disease in children with juvenile idiopathic arthritis: reason for annual screening? *Rheumatology* 2018; 57 (Suppl. 8) [Abstract P38]. https://doi/10.1093/rheumatology/key273.040
28. GEORGE EK, HERTZBERGER-TEN CATE R, VAN SUIJLEKOM-SMIT LW *et al*.: Juvenile chronic arthritis and coeliac disease in The Netherlands. *Clin Exp Rheumatol* 1996; 14(5): 571-5.
29. GHEITA TA, FAWZY SM, NOUR EL-DIN AM, GOMAA HE: Asymptomatic celiac sprue in juvenile rheumatic diseases children. *Int J Rheum Dis* 2012; 15(2): 220-6. https://doi.org/10.1111/j.1756-185x.2011.01681.x
30. GHEITH RE, EL GAZZAR, II, BAHGAT DMR, NOUR EL-DIN AM: Elevated tissue transglutaminase antibodies in juvenile idiopathic arthritis children: Relation to neutrophil-to-lymphocyte ratio and disease activity. *Egypt Rheumatol* 2017; 39(4): 233-37. https://doi.org/10.1016/j.ejr.2017.03.001
31. GOELDNER I, SKARE TL, DE MESSIAS REASON IT, NISIHARA RM, SILVA MB, DA ROSA UTIYAMA SR: Autoantibodies for gastrointestinal organ-specific autoimmune

diseases in rheumatoid arthritis patients and their relatives. *Clin Rheumatol* 2011; 30(1): 99-102. https://doi.org/10.1007/s10067-010-1540-1
32. LEPORE L, PENNESI M, VENTURA A *et al*.: Anti-alpha-gliadin antibodies are not predictive of celiac disease in juvenile chronic arthritis. *Acta Paediatr* 1993; 82(6-7): 569-73. https://doi.org/10.1111/j.1651-2227.1993.tb12756.x
33. LEPORE L, MARTELOSSI S, PENNESI M *et al*.: Prevalence of celiac disease in patients with juvenile chronic arthritis. *J Pediatr* 1996; 129(2): 311-3. https://doi.org/10.1016/s0022-3476(96)70262-7
34. LIAO KP, KURREEMAN F, LI G *et al*.: Associations of autoantibodies, autoimmune risk alleles, and clinical diagnoses from the electronic medical records in rheumatoid arthritis cases and non-rheumatoid arthritis controls. *Arthritis Rheum* 2013; 65(3): 571-81. https://doi.org/10.1002/art.37801
35. LUFT LM, BARR SG, MARTIN LO, CHAN EK, FRITZLER MJ: Autoantibodies to tissue transglutaminase in Sjogren's syndrome and related rheumatic diseases. *J Rheumatol* 2003; 30(12): 2613-9.
36. NISIHARA RM, SKARE TL, SILVA MB, UTIYAMA SR: Rheumatoid arthritis and anti-endomysial antibodies. *Acta Reumatol Port* 2007; 32(2): 163-67.
37. POHJANKOSKI H, KAUTIAINEN H, KOTANIEMI K, KORPPI M, SAVOLAINEN A: Autoimmune diseases in children with juvenile idiopathic arthritis. *Scand J Rheumatol* 2010; 39(5): 435-6. https://doi.org/10.3109/03009741003685608
38. ROBAZZI TC, ADAN LF, PIMENTEL K *et al*.: Autoimmune endocrine disorders and coeliac disease in children and adolescents with juvenile idiopathic arthritis and rheumatic fever. *Clin Exp Rheumatol* 2013; 31(2): 310-7.
39. TANEJA A, PRAHALAD S, HERSH AO *et al*.: Prevalence of celiac antibodies and IgA deficiency in juvenile idiopathic arthritis [Abstract 13]. *Arthritis Rheumatol* 2017; 69 (Suppl 4): 22-23.
40. ZAYENI H, SHAFAGHI A, POUR AG *et al*.: Celiac disease in rheumatoid arthritis: across-sectional study in Iran. *Indian J Rheumatol* 2014; 9(4): 220-21. https://doi.org/10.1016/j.injr.2014.05.002
41. SADEGHI P, SALARI K, ZIAEE V, REZAEI N, EFTEKHARI K: Serological screening of celiac disease in patients with juvenile idiopathic arthritis. *Arch Iran Med* 2021; 24(10): 783-85. https://doi.org/10.34172/aim.2021.116
42. NADDEI R, DI GENNARO S, GUARINO A, TRONCONE R, ALESSIO M, DISCEPOLO V: In a large Juvenile Idiopathic Arthritis (JIA) cohort, concomitant celiac disease is associated with family history of autoimmunity and a more severe JIA course: a retrospective study. *Pediatr Rheumatol Online J* 2022; 20(1): 31. https://doi.org/10.1186/s12969-022-00689-4
43. SCHULZ C, FUEHNER S, SCHLÜTER B *et al*.: Prevalence of autoantibodies in patients with juvenile idiopathic arthritis: results from the German inception cohort ICON-JIA. *Pedr Rheumatol* 2022; 20: 8. https://doi.org/10.1186/s12969-022-00668-9
44. TORRES-FERNANDEZ D, PEREZ-HERAS I, FERNANDEZ-MANSO B, GALÁN DEL RÍO P, GONZALEZ-GRANADO LI, DE INOCENCIO J: IgA deficiency and autoimmune comorbidities in juvenile idiopathic arthritis. *An Pediatr* (Engl Ed) 2022; 97(3): 172-78. https://doi.org/10.1016/j.anpede.2022.03.004
45. LUDVIGSSON JF, LEFFLER DA, BAI JC *et al*.: The Oslo definitions for coeliac disease and related terms. *Gut* 2013; 62(1): 43-52. https://doi.org/10.1136/gutjnl-2011-301346
46. MARSH MN: Gluten, major histocompatibility complex, and the small intestine. A molecular and immunobiologic approach to the spectrum of gluten sensitivity ('celiac sprue'). *Gastroenterology* 1992; 102(1): 330-54.
47. ARNETT FC, EDWORTHY SM, BLOCH DA *et al*.: The American Rheumatism Association 1987 revised criteria for the classification of rheumatoid arthritis. *Arthritis Rheum* 1988; 31(3): 315-24. https://doi.org/10.1002/art.1780310302.
48. ALETAHA D, NEOGI T, SILMAN AJ *et al*.: 2010 Rheumatoid arthritis classification criteria: an American College of Rheumatology/European League Against Rheumatism collaborative initiative. *Arthritis Rheum* 2010; 62(9): 2569-81. https://doi.org/10.1002/art.27584
49. PETTY RE, SOUTHWOOD TR, MANNERS P *et al*.: International League of Associations for Rheumatology classification of juvenile idiopathic arthritis: second revision. *J Rheumatol* 2004; 31(2): 390-2.
50. SINGH P, ARORA A, STRAND TA *et al*.: global prevalence of celiac disease: systematic review and meta-analysis. *Clin Gastroenterol Hepatol* 2018; 16(6): 823-36 e2. https://doi.org/10.1016/j.cgh.2017.06.037
51. ALENCAR ML, ORTIZ-AGOSTINHO CL, NISHITOKUKADO L *et al*.: Prevalence of celiac disease among blood donors in Sao Paulo: the most populated city in Brazil. *Clinics* (Sao Paolo) 2012; 67(9): 1013-18. https://doi.org/10.6061/clinics/2012(09)05
52. PRATESI R, GANDOLFI L, GARCIA SG *et al*.: Prevalence of coeliac disease: unexplained age-related variation in the same population. *Scand J Gastroenterol* 2003; 38(7): 747-50. https://doi.org/10.1080/00365520310003255
53. ABU-ZEKRY M, KRYSZAK D, DIAB M, CATASSI C, FASANO A: Prevalence of celiac disease in Egyptian children disputes the east-west agriculture-dependent spread of the disease. *J Pediatr Gastroenterol Nutr* 2008; 47(2): 136-40. https://doi.org/10.1097/mpg.0b013e31815ce5d1
54. MAKI M, MUSTALAHTI K, KOKKONEN J *et al*.: Prevalence of celiac disease among children in Finland. *N Engl J Med* 2003; 348(25): 2517-24. https://doi.org/10.1056/nejmoa021687
55. LAASS MW, SCHMITZ R, UHLIG HH, ZIMMER KP, THAMM M, KOLETZKO S: The prevalence of celiac disease in children and adolescents in Germany. *Dtsch Arztebl Int* 2015; 112(33-34): 553-60. https://doi.org/10.3238/arztebl.2015.0553
56. DEHGHANI SM, HAGHIGHAT M, MOBAYEN A, REZAIANZADEH A, GERAMIZADEH B: Prevalence of celiac disease in healthy Iranian school children. *Ann Saudi Med* 2013; 33(2): 159-61. https://doi.org/10.5144/0256-4947.2013.159
57. BAHARI A, KARIMI M, SANEI-MOGHADDAM I, FIROUZI F, HASHEMI M: Prevalence of celiac disease among blood donors in Sistan and Balouchestan Province, Southeastern Iran. *Arch Iran Med* 2010; 13(4): 301-5.
58. FABIANI E, PERUZZI E, MANDOLESI A *et al*.: Anti-human versus anti-guinea pig tissue transglutaminase antibodies as the first-level serological screening test for coeliac disease in the general population. *Dig Liver Dis* 2004; 36(10): 671-6. https://doi.org/10.1016/j.dld.2004.05.008
59. BONAMICO M, NENNA R, MONTUORI M *et al*.: First salivary screening of celiac disease by detection of anti-transglutaminase autoantibody radioimmunoassay in 5000 Italian primary schoolchildren. *J Pediatr Gastroenterol Nutr* 2011; 52(1): 17-20. https://doi.org/10.1097/mpg.0b013e3181e6f2d0
60. REMES-TROCHE JM, RAMIREZ-IGLESIAS MT, RUBIO-TAPIA A, ALONSO-RAMOS A, VELAZQUEZ A, USCANGA LF: Celiac disease could be a frequent disease in Mexico: prevalence of tissue transglutaminase antibody in healthy blood donors. *J Clin Gastroenterol* 2006; 40(8): 697-700. https://doi.org/10.1097/00004836-200609000-00007
61. AL-HUSSAINI A, TRONCONE R, KHORMI M *et al*.: Mass screening for celiac disease among school-aged children: toward exploring celiac iceberg in Saudi Arabia. *J Pediatr Gastroenterol Nutr* 2017; 65(6): 646-51. https://doi.org/10.1097/mpg.0000000000001681
62. MARINE M, FARRE C, ALSINA M *et al*.: The prevalence of coeliac disease is significantly higher in children compared with adults. *Aliment Pharmacol Ther* 2011; 33(4): 477-86. https://doi.org/10.1111/j.1365-2036.2010.04543.x
63. CSIZMADIA CG, MEARIN ML, VON BLOMBERG BM, BRAND R, VERLOOVE-VANHORICK SP: An iceberg of childhood coeliac disease in the Netherlands. *Lancet* 1999; 353(9155): 813-14. https://doi.org/10.1016/s0140-6736(99)00243-3
64. DEMIRCEKEN FG, KANSU A, KULOGLU Z, GIRGIN N, GÜRIZ H, ENSARI A: Human tissue transglutaminase antibody screening by immunochromatographic line immunoassay for early diagnosis of celiac disease in Turkish children. *Turk J Gastroenterol* 2008; 19(1): 14-21.
65. EL-HADI S, TUTHILL D, LEWIS E *et al*.: Unrecognised coeliac disease is common in healthcare students. *Arch Dis Child* 2004; 89(9): 842. https://doi.org/10.1136/adc.2003.041459
66. RUBIO-TAPIA A, LUDVIGSSON JF, BRANTNER TL, MURRAY JA, EVERHART JE: The prevalence of celiac disease in the United States. *Am J Gastroenterol* 2012; 107(10): 1538-44; quiz 37, 45. https://doi.org/10.1038/ajg.2012.219
67. WELLS GA SB, O'CONNELL D, PETERSON

J, WELCH V, LOSOS M, TUGWELL P: The Newcastle-Ottawa Scale (NOS) for assessing the quality if nonrandomized studies in meta-analyses. The Ottawa Hospital Research Institute, 2009. https://www.ohri.ca/Programs/clinical_epidemiology/oxford.asp (Cited December 6, 2022)

68. STANG A: Critical evaluation of the Newcastle-Ottawa scale for the assessment of the quality of nonrandomized studies in meta-analyses. *Eur J Epidemiol* 2010; 25(9): 603-5. https://doi.org/10.1007/s10654-010-9491-z
69. NYAGA VN, ARBYN M, AERTS M: Metaprop: a Stata command to perform meta-analysis of binomial data. *Arch Public Health* 2014; 72(1): 39. https://doi.org/10.1186/2049-3258-72-39
70. ALPIGIANI MG, SALVATI P, VANNATI M *et al*.: Outcome of children with coeliac disease (CD) and juvenile idiopathic arthritis (JIA). *Clin Exp Rheumatol* 2011; 29(2): 410. http://dx.doi.org/10.1080/08916930701620050
71. BERTHOLD E, DAHLBERG A, MÅNSSON B *et al*.: Comorbidities in juvenile idiopathic arthritis-important to evaluate patient mental health. Pediatr Rheumatol 2020;18(Suppl 2). http://dx.doi.org/10.1186/s12969-020-00470-5
72. CHEN Y, LIU X, MA W *et al*.: Increased risk of celiac disease in Southern China. *Gastroenterology* 2020; 158: S-1120 [Abstract Tu1470]. https://doi.org/10.1016/S0016-5085(20)33470-3
73. CIVITELLI F, FERRARI F, BRUNO G *et al*.: Looking beyond joints: Gastrointestinal involvement in children and adolescents with juvenile idiopathic arthritis. *J Pediatr Gastroenterol Nutr* 2022; 74(2): 509. http://dx.doi.org/10.1097/mpg.0000000000003446
74. DAVIS TE, ONG MS, MILOJEVIC D, RAMAKRISHNA J, MD NATTER: Food allergy and celiac disease in children with juvenile idiopathic arthritis. *Arthritis Rheumatol* 2014; 66: S996. http://dx.doi.org/10.1002/art.38914
75. DIZDAREVIC AO, SELMANOVIC V, CENGIC A, SABANOVIC S, MUJIC M: Associated autoimmune diseases in children with juvenile idiopathic arthritis. *Pediatr Rheumatol* 2017; 15:138. http://dx.doi.org/10.1186/s12969-017-0186-9
76. EATON WW, ROSE NR, KALAYDJIAN A PEDERSEN, MG, MORTENSEN PB: Epidemiology of autoimmune diseases in Denmark. *J Autoimmun* 2007; 29(1): 1-9. https://doi.org/10.1016/j.jaut.2007.05.002
77. EATON WW, PEDERSEN MG, ATLADOTTÍR HÓ, GREGORY PE, ROSE NR, MORTENSEN PB: The prevalence of 30 ICD-10 autoimmune diseases in Denmark. *Immunol Res* 2010; 47(1-3): 228-31. https://doi.org/10.1007/s12026-009-8153-2
78. FEIGHERY L, COLLINS C, FEIGHERY C *et al*.: Anti-transglutaminase antibodies and the serological diagnosis of coeliac disease. *Br J Biomed* 2003; 60(1): 14-8. https://doi.org/10.1080/09674845.2003.11783671
79. GONZALEZ T, MALAGON C, GUARNIZO P, MOSQUERA AC, CHILA-MORENO L, ROMERO-SÁNCHEZ C: Autoantibodies and gastrointestinal symptoms in Colombian children with juvenile idiopathic arthritis. *Curr Rheumatol Rev* 2018; 14(2): 163-71. https://dx.doi.org/10.2174/1573397114666180108110429
80. HASSAN E, MAGDY N: Study of celiac disease antibodies in patients with juvenile onset rheumatological disorders. *Ann Rheum Dis* 2019; 78: 1572. http://dx.doi.org/10.1136/annrheumdis-2019-eular.848
81. KOEHNE VdB, BAHIA M, LANNA CCD, PINTO MRDC, BAMBIRRA EA, DA CUNHA AS: Prevalence of serological markers for celiac disease (IgA and IgG class antigliadin antibodies and IgA class antiendomysium antibodies) in patients with autoimmune rheumatologic diseases in Belo Horizonte, MG, Brazil. *Arq Gastroenterol* 2010; 47(3): 250-6. https://doi.org/10.1590/s0004-28032010000300008
82. KOSZARNY A, MAJDAN M, DRYGLEWSKA M, TABARKIEWICZ J: Prevalence of selected organ-specific autoantibodies in rheumatoid arthritis and primary Sjögren's syndrome patients. *Reumatologia* 2015; 53(2): 61-8. https://dx.doi.org/10.5114/reum.2015.51504
83. MINDEN K, BETENSTEHL N, KLOTSCHE J *et al*.: Frequency of comorbidities in JIA patients-results of an observational cohort study. *Ann Rheum Dis* 2017; 76: 195. http://dx.doi.org/10.1136/annrheumdis-2017-eular.5858
84. MISSOUM H, ALAMI M, BACHIR F e*t al*.: Prevalence of autoimmune diseases and clinical significance of autoantibody profile: data from National Institute of Hygiene in Rabat, Morocco. *Hum Immunol* 2019; 80(7): 523-32. https://dx.doi.org/10.1016/j.humimm.2019.02.012
85. NUNEZ E, GALINDO R, LOPEZ E, DIAZ G, VICIOSO MI, SIERRA C: Coeliac disease and intestinal inflammation in juvenil idiopathic arthritis. *Pediatr Rheumatol* 2011; 9. https://doi.org/10.1186/1546-0096-9-S1-P168
86. PAIMELA L, KURKI P, LEIRISALO-REPO M, PIIRAINEN H: Gliadin immune reactivity in patients with rheumatoid arthritis. *Clin Exp Rheumatol* 1995;13(5):603-7.
87. PAGNINI I, SCAVONE M, MACCORA I e*t al*.: The development of extra-articular manifestations in children with enthesitis-related arthritis: natural course or different disease entity? *Front Med* 2021; 8: 667305. https://dx.doi.org/10.3389/fmed.2021.667305
88. POHJANKOSKI H, KAUTIAINEN H, KOTANIEMI K, KORPPI M, SAVOLAINEN A: Diabetes, coeliac disease, multiple sclerosis and chronic arthritis in first-degree relatives of patients with juvenile idiopathic arthritis. *Acta Paediatr* 2012; 101(7): 767-71. https://dx.doi.org/10.1111/j.1651-2227.2012.02658.x
89. RIENTE L, CHIMENTI D, PRATESI F *et al*.: Antibodies to tissue transglutaminase and Saccharomyces cerevisiae in ankylosing spondylitis and psoriatic arthritis. *J Rheumatol* 2004; 31(5): 920-4.
90. REBANE K, TUOMI AK, KAUTIAINEN H, PELTONIEMI S, GLERUP M, AALTO K: Abdominal pain in Finnish young adults with juvenile idiopathic arthritis. *Scand J Gastro* 2022; 57(10): 1189-94. https://doi.org/10.1080/00365521.2022.2072691
91. RODRIGUEZ GR, ZAZZETTI F, DA REPRESENTAC AOS, LENCINA MV, BARREIRA JC: Frequency of antibodies for diagnosis of coeliac disease in patients with connective tissue diseases and inflammatory arthopathies [Abstract THU0377]. *Ann Rheum Dis* 2014; 73. http://dx.doi.org/10.1136/annrheumdis-2014-eular.2624
92. SHOR DB-A, ORBACH H, BOAZ M *et al*.: Gastrointestinal-associated autoantibodies in different autoimmune diseases. *Am J Clin Exp Immunol* 2012; 1(1): 49-55.
93. SIMON TA, KAWABATA H, RAY N, BAHETI A, SUISSA S, ESDAILE JM: Prevalence of coexisting autoimmune disease in rheumatoid arthritis: a cross-sectional study. *Adv Ther* 2017; 34(11): 2481-90. https://doi.org/10.1007/s12325-017-0627-3
94. SKRINER K, KONTHUR Z, ADOLPH K, BURMESTER PGR: Tissue transglutaminase in rheumatoid arthritis. *Ann Rheum Dis* 2006; 65: A17.
95. SMITH A, JOHNSON N, LUCA N, VEERAMREDDY D, SCHMELING H: Celiac disease in children diagnosed with juvenile idiopathic arthritis. *Arthritis Rheum* 2017; 69: 87-88. http://dx.doi.org/10.1002/art.v69.S4
96. STOLL ML, PATEL AS, CHRISTADOSS ML, PUNARO M, OLSEN NJ: IgA transglutaminase levels in children with juvenile idiopathic arthritis. *Ann Paediatr Rheum* 2012; 1(1): 31-35. https://doi.org/10.5455/apr.112220111551
97. YANG Y, DESHPANDE P, KRISHNA K *et al*.: Overlap of characteristic serological antibodies in rheumatoid arthritis and wheat-related disorders. *Dis Markers* 2019; 2019: 4089178. https://dx.doi.org/10.1155/2019/4089178
98. ÖMAN A, HANSON T, CARLSSON M, BERNTSON L: Evaluation of screening for coeliac disease in children with juvenile idiopathic arthritis. *Acta Paediatr* 2019; 108(4): 688-93. https://doi.org/10.1111/apa.14598
99. NATTER MD, ONG MS, MANDL KD, SCHANBERG L, KIMURA Y, ILOWITE N: Comorbidity patterns in children with juvenile idiopathic arthritis and systemic lupus erythematosus: The childhood arthritis and rheumatology research alliance registry. *Arthritis Rheumatol* 2014; 66: S576-S77. https://doi.org/10.1002/art.38914
100. ALPIGIANI MG, HAUPT R, PARODI S, CALCAGNO A, POGGI E, LORINI R: Coeliac disease in 108 patients with juvenile idiopathic arthritis: a 13-year follow-up study. *Clinic Exp Rheumatol* 2008;26(1):162.
101. ROTH EB, STENBERG P, BOOK C, SJÖBERG K: Antibodies against transglutaminases, peptidylarginine deiminase and citrulline in rheumatoid arthritis - new pathways to epitope spreading. *Clin Exp Rheumatol* 2006; 24(1): 12-18.
102. ÖMAN A, HANSSON T, CARLSSON M, BERNTSON L: A population based study on screening for celiac disease and levels of celiac-related antibodies in children with juvenile idiopathic arthritis (JIA). *Pediatr Rheumatol* 2017; 15: 137. http://dx.doi.org/10.1186/s12969-017-0186-9
103. BIZZARO N, VILLALTA D, TONUTTI E, TAMPOIA M, BASSETTI D, TOZZOLI R: Association of celiac disease with connective tissue diseases and autoimmune dis-

eases of the digestive tract. *Autoimmun Rev* 2003; 2(6): 358-63. https://doi.org/10.1016/S1568-9972(03)00055-7

104. KOCHBATI S, BOUSSEMA F, KILANI A *et al*.: [Antigliadin antibodies in rheumatoid arthritis]. *Tunis Med* 2002; 80(2): 65-9.
105. LIU XY, ZHOU WY, WU W *et al*.: [Serological screening and analysis of clinical characteristics for celiac disease in susceptible population in Southern China]. *Zhonghua Nei Ke Za Zhi* 2021; 60(6): 539-43. https://dx.doi.org/10.3760/cma.j.cn112138-20200715- 00671
106. ATZENI F, DORIA A, GHIRARDELLO A, VILLALTA D, CARRABBA M, SARZI-PUTTINI P: Anti-tissue transglutaminase and anti-thyroid antibodies in rheumatoid arthritis. *Ann Rheum Dis* 2007; 66: 163-63.
107. CIVITELLI F, ARDENTI MORINI F, SOSCIA F *et al*.: Looking beyond joints: gastrointestinal involvement in children and adolescents with juvenile idiopathic arthritis. *Pediatr Rheumatol* 2021; 19(Suppl 1) [Abstract]. https://doi.org/10.1186/s12969-021-00632-z
108. NADDEI R, DI GENNARO S, TRONCONE R *et al*.: A family history of autoimmunity is a risk factor for celiac disease and juvenile idiopathic arthritis co-occurrence. *J Pediatr Gastroenterol Nutr* 2021;72(Suppl 1):296. http://dx.doi.org/10.1097mpg.0000000000003177
109. SMITH A, JOHNSON N, LUCA N, VEERAMREDDY D, SCHMELING H: Celiac disease in children diagnosed with juvenile idiopathic arthritis-a case series. *J Rheumatol* 2017;44(6):945. http://dx.doi.org/10.3899/jrheum.170256
110. SAHIN Y, SAHIN S, BARUT K *et al*.: The frequency of the celiac disease in patients with juvenile idiopathic arthritis. *J Pediatr Gastroenterol and Nutr* 2017; 64: 222-23. http://dx.doi.org/10.1097/01.mpg.0000516381.25680.b4
111. STAGI S, GIANI T, SIMONINI G *et al*.: Thyroid function and autoantibodies, coeliac disease and absolute IgA deficiency in juvenile idiopathic arthritis. *Arthritis Rheum* 2003; 48(9): S102-S02. https://doi.org/10.1093/rheumatology/keh531
112. HUSBY S, KOLETZKO S, KORPONAY-SZABO I *et al*.: European Society Paediatric Gastroenterology, Hepatology and Nutrition Guidelines for Diagnosing Coeliac Disease 2020. *J Pediatr Gastroenterol Nutr* 2020;70(1):141-56. https://doi.org/10.1097/mpg.0000000000002497
113. NAZARIO E, LASA J, SCHILL A *et al*.: IgA deficiency is not systematically ruled out in patients undergoing celiac disease testing. *Dig Dis Sci* 2022; 67(4): 1238-43. https://doi.org/10.1007/s10620-021-06939-x
114. PELKONEN P, SAVILAHTI E, MAKELA AL: Persistent and transient IgA deficiency in juvenile rheumatoid arthritis. *Scand J Rheumatol* 1983; 12(3): 273-9. https://doi.org/10.3109/03009748309098549
115. ODINEAL DD, GERSHWIN ME: The epidemiology and clinical manifestations of autoimmunity in selective IgA deficiency. *Clin Rev Allergy Immunol* 2020; 58(1): 107-33. https://dx.doi.org/10.1007/s12016-019-08756-7
116. MALMSTROM V, CATARINA AI, KLARESKOG L: The immunopathogenesis of seropositive rheumatoid arthritis: from triggering to targeting. *Nat Rev Immunol* 2017; 17(1): 60-75. https://doi.org/10.1038/nri.2016.124
117. ROY A, LASZKOWSKA M, SUNDSTROM J *et al*.: Prevalence of celiac disease in patients with autoimmune thyroid disease: a meta-analysis. *Thyroid* 2016; 26(7): 880-90. https://doi.org/10.1089/thy.2016.0108
118. BARTOLONI E, BISTONI O, ALUNNO A *et al*.: Celiac disease prevalence is increased in primary Sjögren's syndrome and diffuse systemic sclerosis: lessons from a large multi-center study. *J Clin Med* 2019; 8(4): 540. https://doi.org/10.3390/jcm8040540
119. PODDIGHE D: Screening for celiac disease in juvenile idiopathic arthritis. *Pediatr Rheumatol Online J* 2022; 20(1): 36. https://doi.org/10.1186/s12969-022-00694-7