

Celiac disease and its serological pattern in Saudi Arabia: a systematic review

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Abstract

Aim: To analyze the status of Celiac Disease (CD) and its Serological Pattern in Saudi Arabia (SA).

Methods: Using a retrospective systematic literature review, the status of CD in SA was analyzed from various aspects. The related articles (74) were retrieved by database and journal search. Data were analyzed using the statistical package for social science (SPSS Inc).

Results: The retrieved studies mostly represent multi heterogeneity in terms of journals (42 journal), centers (23 center), mode (12 type), fields (21 discipline). Most publications were found in: Saudi Medical Journal (12 articles), King Saud University, Riyadh (21), cross sectional (18), retrospective (18), Case report (18), Diabetes mellitus (T1DM) (8); while down syndrome (DS), short status (SS), skeletal health and CD prevalence had 3, 5, 6 and 7 articles respectively. Female to male ratio was 1.95/1. Histological evaluation was introduced early 1980s followed by serology in 1990s. Biopsy showed the highest usage (in 57 studies), endomysial-antibody (EMA) (34), tissue-transglutaminase-antibodies (tTG-Ab) (29), anti-gluten-antibodies (AGA) (18), anti-reticulin- antibodies (ARA) (10). Publications started in 1990 with stable annual number (1-3) until it peaked (10 articles), in 2012, 2016 and 2017.

Conclusion: The current study represents the first and only Systematic Review concerning the status of CD in SA and its serological pattern. We found one review evaluating skeletal health in CD in SA and one Meta-analysis concerning polymorphism association with CD, but no meta-analysis were found concerning the relationship between CD and other conditions such as T1DM, SS, DS and CD prevalence in SA, which will be our plan for separate publications.

Introduction

Celiac disease (CD) was first described in the second century AD by Aretaeus of Cappadocia [1], who used the Greek word “koeliakos”, which means “suffering of the bowels”. Only in 1888 AD did Samuel Gee [2] give it the classical clinical description. Its cause was explained by the Dutch Pediatrician “Willem K. Dick” who recognized an association between the consumption of bread and cereals and the relapsing diarrhea [3] and that the health of celiac children dramatically improved when wheat, rye and barley were unavailable during the 2nd World War but relapsed at the end of the war when the consumption of wheat flour started afresh in the Netherlands [4].

At the Interlaken meeting of the European Society of Paediatric Gastroenterology and Nutrition (ESPGAN) society in 1969 [5], three diagnostic criteria for celiac disease were proposed, and were further enunciated at the second symposium on celiac disease in 1974 [6], namely:

- * Structurally abnormal jejunal mucosa by taking a gluten-containing diet.
- * Clear improvement of villous structure by a gluten-free diet.
- * Deterioration of the mucosa during challenge.

In 1971, Seah and coworkers observed binding of antibodies in CD patient sera with rodent liver and kidney sections and identified anti-reticulin antibodies (ARA) [7]. CD serology started initially in the 1970s and 1980s using anti-gluten antibodies (AGA) immunofluorescence followed by ELISA respectively [8,9]. Chorzelski and colleagues (in

1983) described the production of endomysial antibody (EMA) in patients with CD and dermatitis herpetiformis [10]. AGAs also exist in healthy individuals (up to 10%) and in nonceliac-enteropathies, thus, diagnostic guidelines have recommended that AGA tests should be abandoned for routine diagnosis [11].

In 1990, the ESPGAN revised criteria for diagnosis of celiac disease [12] considered the finding of the circulating antibodies (AGA-IgA, ARA, and EMA) during diagnosis and their disappearance during a gluten free diet (GFD) as valuable to the diagnosis, and emphasized on two diagnostic criteria with no need for further confirmation: firstly “on the appearance of flat small intestinal mucosa with the histological features of hyperplastic villous atrophy, while the patient is eating adequate amounts of gluten; and secondly on unequivocal and full clinical remission after withdrawal of gluten from the diet”.

In 1989, A simple and flexible approach for diagnosis of celiac disease was suggested by Guandalini S, *et al.* [13].

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In 1992, Marsh introduced a grading scheme to classify the morphologic spectrum of the mucosa of untreated CD patients [14]. Then, Marsh-Oberhuber classification [15] modified some of Marsh's parameters. In 1997, tissue transglutaminase tTG2 was identified as CD-specific autoantigen [16], which allowed the development of ELISA-based tTGA tests.

The prevalence of CD, which has been underestimated, is now considered one of the most common genetic disorders in the West with a prevalence of 1%-2.67% [17-19]. The literature regarding CD has expanded significantly in the Middle Eastern (ME) and North African (NA) countries during the last 30 years which are mostly epidemiological [20]. Many studies exist on celiac disease (CD) in Saudi Arabia [21-94], but data from these investigations have not yet been compiled. Here, studies on CD in SA were systematically analyzed, classified, characterized and their serological pattern was discussed to highlight the current status of CD in SA, with the aim that the results of this study will contribute in promotion of national guidelines for organized SD research and management.

Strategy for systematic search and study selection

As shown in the PRISMA flow-diagram (Figure 1); using "celiac disease in Saudi Arabia", "celiac disease in Saudi children" and "prevalence of celiac disease in Saudi Arabia" as key words, an electronic literature search was conducted via PubMed (US National Library of Medicine, with no specific period), Ovid, EBSCO and scholar Google. The retrieved studies (articles) were designed as twelve groups: three groups (according to the three key words) by PubMed search and three groups by EBSCO, three groups by Ovid and three groups by scholar Google. Additional group of articles were obtained through the library of King Fahd research centre of King Abdulaziz University. In addition, we obtained (with thanks) the publications (two articles and one meeting abstract) related to "celiac disease in Saudi Arabia" directly from the editorial department of two local journals (Saudi Journal of Internal Medicine and Journal of King Abdulaziz University Medical Science). All the retrieved articles were checked for matching (duplication) between groups and intra groups via their titles, author(s) and year of publication. The obtained pooled studies (after matching between groups and intra groups) were checked by reading their titles and abstracts, and the full texts for the possibly relevant publications. Articles that were concerned with celiac disease in Saudi Arabia were included. All forms of studies were included (original studies, reviews, guidelines, surveys, questionnaire, letter to the editor, comments and correction; pediatric, adult, both pediatric and adult). Global reviews with author(s) from Saudi centers were also included. The selected (included) articles were arranged in four groups: references of both adult and pediatric subjects, references of adult subjects, references of pediatric subjects and references of animal models. Data from each article of this classification (as four groups) was recorded using statistical package for social science (SPSS Inc), Version 20. Chicago. The recorded data from each article comprised: author(s), date of publication, journal, date of the study, duration, place of the study, single or multi centres, number of patients, female/male ratio, type of serology and whether with or without biopsy, type of study (cross sectional, retrospective, prospective, case report, letter to the editor, genetic, HLA, Case-control, meta-analysis, review, pilot prospective, animal experiment, correction to previous publication), pattern of study (general pattern, prevalence, genetic, association (with diabetes mellitus, with autoimmune disease(s), with short stature and association with small bowel (SB) damage), animal model, clinical and/or lab characterization (presentation), corrigendum to previous

publication, cardiac assessment, diet (GFD) assessment, skeletal assessment, assessment of knowledge, general assessment, effect of breast feeding on autistic CD and effect of thyroidism.

Strategy for studies' grouping

Age wise, according to Al-Agha, *et al.* 2015 [33], puberty is defined with a cut-off level of 10 years in females, and 12 years in males; while the term "children and adolescent" denotes "aged one to 18 years" [33,39,40]. Thus, age wise, articles were divided into 3 groups: pediatric (<12 years in male, <10 years in female or male with females), adults with adolescents (>12 years) and pediatric with adults (and/or adolescents) (> 1 year (or 1-18 years)).

The reference section comprises the included articles [21-94] but not the excluded articles. The included references were serially arranged in two groups: the PubMed references (with PubMed numbers) followed by the non-PubMed references (without PubMed numbers). The PubMed references were further arranged in two subgroups: the "pediatric with adults (and/or adolescents)" group followed by references of "adult with adolescents", as no recorded pediatric references were found. The non-PubMed references were further arranged in three subgroups: "pediatric with adults (and/or adolescents)" group followed by references of "adult with adolescents" then the "pediatric" subgroup. References in each subgroup were arranged in descending chronological order.

According to PubMed classification, children are individuals aged 0-18 years, while adults are those above 18 years, other definitions of age-groups existed in which individuals aged 19-21 years have been included as children [95,96] indicating that the age group definitions were not always clear. Here, studies which clearly stated that they are concerned with children (without adolescents) or adults were considered accordingly, otherwise they were considered of both children and adults (and/or adolescents).

Statistical analysis

Analysis of data was performed using statistical package for social science (SPSS Inc), Version 20. Chicago. The results were illustrated in tabulated form and diagrams showing comparisons and frequencies of variables.

Results

I. Results of the selection process (inclusion/exclusion) of the pertinent Studies (Figure 1 and Table 1): By PubMed search, using "celiac disease in Saudi Arabia" as a key word, 93 references (articles) were retrieved and designed as general group; while by using "celiac disease in Saudi children" as a key word, a group of 52 references were obtained, of which only 8 references were pediatric while the rest 43 references were found among the general 93 references. By PubMed search, using "prevalence of celiac disease in Saudi Arabia" as a key word, a group of 35 references were obtained, of which only 6 references were not matching with the previous two groups of references.

By Ovid search, the results and the Search Strategy were as follows:

A- Search for Celiac disease in Saudi Arabia (1946-March, weak 3, 2018). We obtained 20 articles by using the following Search Strategy:

- 1- Celiac Disease/ (N=18464)
- 2- Saudi Arabia/(N=10586)
- 3- 1 and 2 (N=20); which were used,

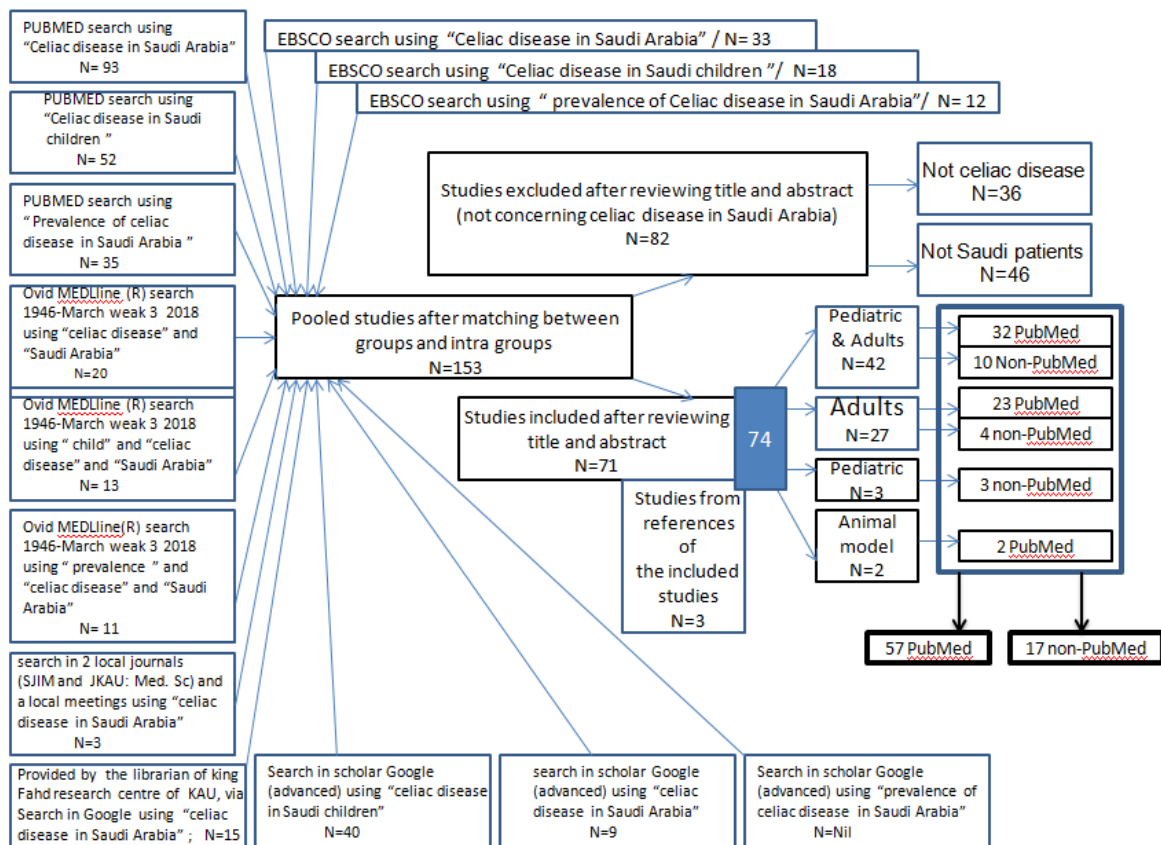


Figure 1. PRISMA flow-diagram showing the selection process (inclusion/exclusion) of the pertinent Studies

Table 1. Age pattern of selected (identified) studies on celiac disease (CD) in Saudi Arabia

		Pediatric & Adult (and/or adolescent) (One year and over)	Adult (and/or adolescent) (>12 years)	Pediatric <12 years/M <10 years/F)	Animal model	
Saudi*	Celiac^	42	27	3	2	74
	References	21-52	53-75	92-94	76-77	21-77 PubMed
	Not celiac^^	78-87	88-91			78-94 non-PubMed
	References					36 excluded
	Total					110
non-Saudi**	Total					46
	References					excluded
Total	(153 pooled+3 from the references of the pooled-included studies) 156					

*Saudi= articles concerned with Saudi patients or animal studies in Saudi Arabia .

** non-Saudi= articles concerned with non-Saudi patients or animal studies not in Saudi Arabia.

^celiac= articles concerned with celiac disease.

^^articles concerned with non-celiac disease(s).

B- Search for Celiac disease in Saudi Children (1946-March weak 3 2018). We obtained 13 articles by using the following Search Strategy:

- 1- Child / (N=1544508)
- 2- Celiac Disease/ (N=18464)
- 3- Saudi Arabia/(N=10586)
- 4- 1 and 2 and 3 (N=13) which were used,

C- Search for Prevalence of celiac disease in Saudi Arabia (1946-March weak 3 2018). We obtained 11 articles by using the following Search Strategy:

- 1- Prevalence/ (N=246629)
- 2- Celiac Disease/ (N=18476)
- 3- Saudi Arabia/(N=10601)
- 4- 1 and 2 and 3 (N=11) which were used,

By EBSCO search using:

- “Celiac disease in Saudi Arabia” (N= 33).
- “Celiac disease in Saudi children” (N=18).
- “prevalence of Celiac disease in Saudi Arabia” (N= 12)

All the EBSCO articles were also PubMed, that match with the previous PubMed articles.

By search in scholar Google (advanced) using:

- “celiac disease in Saudi children” (N=40)
- “celiac disease in Saudi Arabia” (N=9)
- “prevalence of celiac disease in Saudi Arabia”/ N=Nil

Only eight studies were new non-PubMed articles

Fifteen articles were obtained through the library of king Fahd research centre of King Abdulaziz University. Two articles and one meeting abstract, related to “celiac disease in Saudi Arabia”, were obtained directly from the editorial department of two local journals (Saudi Journal of Internal Medicine and Journal of King Abdulaziz University Medical Science).

All the retrieved references (articles) were checked for matching intra and between groups via their titles, author(s) and year of publication. Following the matching process, 153 pooled articles were obtained. 82 articles were excluded that were not concerned with celiac disease in Saudi Arabia; they were 36 not celiac articles and 46 articles not related to Saudi Arabia. Three additional non-PubMed studies were obtained from the references of the included articles: Two pediatric and one adult.

The sum of the included articles were 74 references (see references). The 74 references (articles) [21-94] comprised of two groups: 57 PubMed references [21-77] and 17 non-PubMed references [78-94]. The 57 PubMed references comprised three subgroups: 32 references of “pediatric and adult (and/or adolescents)” [21-52], 23 references of “adult with adolescents” [53-75] and 2 animal references [76,77]. The 17 non-PubMed references comprised of three subgroups: 10 “pediatric with adults (and/or adolescents)” [78-87], 4 “adult with adolescents” [88-91] and three “pediatric” [92-94]. References in each subgroup were arranged (in the reference section) in a descending chronological order.

II. Female to male ratio: Gender information was found in 53 articles, while missing [not specified (NS) or not applicable (NA)] in

Table 2. Classification and characterization of identified studies on celiac disease (CD) in Saudi Arabia, with their serological/biopsy pattern

Reference number	journal*	Type**	Author(s)/Date	Prevalence	F/M Ratio (Age Y)	Cohort (Age Year)	Center*** (Multi-#)	Period	serology/biopsy pattern
Case report = 17 articles									
35	34	4	Al-Hussaini A, etal/2013	Not applicable	1/0 (11)	one patient case study	12(2)	case study	TTG-IgA, and biopsy
49	46	4	Al Hemidan AI, etal/2006	Not applicable	1/0 (3)	one patient case study	13(3)	case study	TTG-IgA, EMA-IgA, and biopsy
50	43	4	Al Furaikh S, etal/2005	Not applicable	2/1 (25,30,42)	3patients case study	16(1)	case study	TTG-IgA, and biopsy
55	20	4	Tarabzouni S, AlKhairallah T/2017	Not applicable	1/0 (44)	one case report	7(1)	NS	EMA-IgA, and biopsy
57	23	4	Lihabi AA/2016	Not applicable	1/0 (22)	a case of 22-year-old Saudi female	8(1)	Not applicable	Two years ago, diagnosed with CD (No details of the used lab tests)
60	2	4	Hasanato RM, Almomen AM/2015	Not applicable	1/0 (39)	one case study	2(1)	case study	CD patient on GFD
62	25	4	Al-Judaibi B etal/2015	Not applicable	1/0 (68)	one case study	2(2)	case study	TTG and biopsy
65	38	4	Masoodi I etal/2012	Not applicable	0/1 (27)	one patient case study	12(1)	case study	TTG-IgA, and biopsy
68	2.	4	Azzam NA etal/2006	Not applicable	1/0 (30)	one patient case study	13(1)	case study	TTG-IgA, EMA-IgA, and biopsy
69	47	4	Al-Gahtani HA/2005	Not applicable	2/0 (28,32)	2 cases	1(1)	case study	email to author
70	4	4	Yasawy MI etal/2004	Not applicable	2/1 (25,30,42)	3 cases	19(1)	case study	EMA, AGA (ARA in 2), and biopsy in 3
73	6	4	Al-Humaidi MA/2001	Not applicable	1/0 (22)	one patient case report	20(1)	case study	IgG and IgA AGA and biopsy
74	2	4	Ahluwalia M etal/1996	Not applicable	1/0 (25)	one patient case study	21(2)	case study	AGA,ARA and biopsy
75	15	4	Nazer HM etal/1991	Not applicable	2/1 (11,15,4)	3 lymphangereadectasia masq	13(1)	case study	biopsy and GFD no improvement
88	50	4	Alahdal AM/2017	Not applicable	0/1 (44)	one case	1(1)	case study	TTG-IgA, and biopsy
89	53	4	Ahmed M-E K etal/2014	Not applicable	0/1 (70)	one case	20(1)	case study	AGA, EMA-IgA, and biopsy
91	6	1	Zawawi TH et al/1996	Not applicable	5/1 (19-54)	6	30(2)	1988-1994	EMA.AGA , ARA , and biopsy

Association with diabetes mellitus = 8 articles									
27	6	1	Al-Hakami AM/2016	by serology (21/202=10.4%)	13/8 (1-21)	202 T1DM patients	20(1)	March 2013 to June 2014.	EMA and TTG
33	6	1	Al-Agha AE etal/2015	By serology and biopsy ??/228= 19.7%	NS (1-18)	228 children	1(1)	January 2013 to January 2014	TTG-IgA and biopsy
37	35	1	Al-Hussaini A, etal/2012	-By serology (19/106= 17.9%) -Biopsy proven CD 12/106= (11.3%)	11/1 (8m-15.5)	106 children	12(1)	prospective; 208-2010	TTG-IgA, EMA-IgA, and biopsy
39	6	2	Saadah OI, etal/2012	-By serology (91/430= 21.2%) -Biopsy proven CD 48/430= (11.2%)	NS (1.1-18)	430 children	1(1)	retrospective hospital record-based study of all children and adolescents with T1DM who were screened for CD	TTG-IgA and biopsy
51	6	1	Al-Ashwal AA, etal/2003	-By serology (10/123= 8.1%) -Biopsy proven CD 6/123= 4.9%	2/8 (2-33)	123 patients (10 with CD)	1(1)	between 1995 and 1996	AGA,ARA IgA, and biopsy
78	56	2	Alghamdi RA, etal/2018	By serology 19/268= 7.1%	11/8 (2-23)	268 (19 with CD)	4(3)	NS	TTG
83	55	1	Alshareef MA, etal/2016	-By serology (16/218= 7.3%) -Biopsy proven CD 10/218= 4.6 %	12/4 (12-50)	218 (16 with CD)	28(1)	between January 2008 and June 2009	TTG and biopsy
87	60	2	Saadah OI ,etal/2004	-By serology (23/110= 21%) -Biopsy proven CD 11/110= 10%	NS (1-18)	110 diabetic children and adolescents (1-18 Y)	1(1)	Retrospectively	AGA,TTG,biopsy
Prevalence =7 articles									
23	7	1	Al-Hussaini A, etal/2017	-By serology (221/7930= 2.78%) -Biopsy and/or ESPHAN criteria (119/7930= 1.5%)	81/38 (6-15)	7930 (6-15Y)	7(3)	January 2014 to June 2016	TTG-IgA, EMA-IgA, and biopsy
26	25	2	Al-Hakami AM/2016	By serology (58/315= 18.4% of at-risk subjects) -Biopsy proven CD (22/315= 6.9%)	40/18 (1-79Y)	315 at-risk subjects (176F) (1-79Y) (40 had endoscopy)	6(1)	2009 to-2012 At- risk subjects	TTG-IgA, EMA-IgA, and biopsy
28	4	5	Al-Mendalawi MD/2016	Not applicable	Not applicable (comment)	Not applicable	9(1)	Not applicable	None/comments
29	4	5	Almadi MA, Aljebreen AM/2016	Not applicable	Not applicable (comment)	Not applicable	2(2)	Not applicable	None/comments
30	4	1	Al Hatlani MM/2015	3% by-tTG 1% by biopsy	6/4 (6-18)	1141 participants	10(1)	Between 2012 and 2014	IgA-TTG) and IgG-TTG. biopsy was offered to all
63	1	3	Aljebreen AM, etal/2013	By serology(26/1167=2.2 %)	17/9 (16-18)	1167 students	2(3)	December 2007 - January 2008	EMA-IgA and EMA-IgG
64	4	11	Khayyat YM/2012	By serology(3/204=1.5%)	1/2 (mean 35)	204 blood donors	26(1)	NS	TTG-IgA
CD and skeletal conditions = 6 articles									
36	2	2	Assiri A, etal/2013	10/26 (38.4%) CD in rickets	8/2 (1-15)	26	2(1)	2000 to 2010 (10Y)	TTG-IgA, EMA-IgA, and biopsy
38	36	10	Fouda MA, eta/2012	Global literature review	Not applicable (review)	Literature review	2(1)	Literature review (1996-2010)	None/review
42	10	2	Al Jurayyan NA, etal/2012	6.17% Rickets du to CD	5/0 (2-18)	81	2(1)	january1990 to December 2009	EMA,AGA,ARA an biopsy
61	6	1	Assiri AM, etal/2015	Physicians' survey	Not applicable (Adults)	109 physicians completed the survey	2(3)	January 2013 - January 2104	None/survey
84	52	8	Jouhari O/2013	43% of IBD had Low BMD	38/34 (3-18)	72 IBD (61% Croh's and 39% CD)	1(1)	NS	No details of serology or histology
90	51	3	Othman HI and Ouda SA/2012	70% of CD had low BMD	24/36 (22- 46)	60	1(1)	NS	No details of serology or histology
Genetic=5 articles									
31	28	8	Saadah O,I etal/2015	Not applicable	51/46 (57 adolescent and 40 child)	97 unrelated patients and 123 controls	1(3)	case control study	AGA,TTG-IgA, EMA-IgA, and biopsy

54	19	8	Al-Aama JY, etal/2017	Not applicable	56/45 (21-19)	100 patients and 100 controls	1(1)	NS	TTG-IgA, EMA-IgA, and biopsy
56	21	6	Banaganapalli B, etal/2017	Not applicable	NS (P&Adolscents)	15 patients after remission and 15 controls	1(1)	NS	CD proven
58	9	9	Khan S, etal/2016	Not applicable	Not applicapble	Meta-analysis	5(3)	Not applicable	meta analysis of 11 case control studies Polymorphism is Associated with CD
59	49	2	Al-Ajlan AS/2016	1.9% of controls and 9.6% of IBD	32/23 (20-60)	482 controls and 498 IBD	2(1)	January 2012 to January 2013	TTG-IgA, EMA-IgA, and biopsy
Association with short stature = 5 articles									
41	10	2	Al-Jurayyan N NA, etal/2012	Biopsy proven (3/110=2.59%)	NS (2.5-14)	110	2(1)	January 1990 and December 2009	celiac screening and biopsy
45	41	3	Assiri AM/2010	-Seropositive (15/91=16.5%) - biopsy proven 10/91 (10.9%) -potential CD (4.3%)	9/6 (4.5-12)	91	2(1)	August 2002 to December 2008	TTG-IgA, EMA-IgA, and biopsy
47	40	1	Al-Ruhaily AD, Malabu UH/2009.	Serology and biopsy proven(4/104=4%)	NS for CD (12-21)	104 subjects	14(1)	January 1997 to December 2006.	EMA and biopsy
86	60	2	Saadah OI, etal/2004	24% (15/ 63) serologically; 9.5% (6/63) biopsy proven	Not applicable (1.37-17.6)	63 children and adolescents with short stature	1(1)	retrospectively	AGA,TTG,biopsy
92	58	1	Al-Jurayyan NAM, etal/2013	Biopsy proven (5/110=4.5%)	NS (2.5-14)	110	8(2)	January 1990 - December 2009	EMA and biopsy
Clinical and/or lab characterization (presentation)=5 articles									
21	4	1	Fouda MA/2017.	86.9%	149/69 (1-75)	218(90 children and 128 adults)	2(1)	2003 and 2012.	TTG-IgA, EMA-IgA, and biopsy
22	6	2	Saeed A, etal/2017	20.1% of biopsies	30/29 (1-18)	64/318(20.1%)	2(1)	January 2009 to January 2015	TTG-IgA, and biopsy
71	2	8	Al Attas RA/2002	By biopsy :4.0% in CD; By EMA: 7.6% in CD.	64/81 (0.9-36)	145 CD, 100 healthy blood donors controls	15(1)	prospective	EMA and ARA
72	6	2.	Qari FA/2002	Not applicable	14/2 (mean37.5)	16	1(1)	5 years from 1998-2002	Biopsy and improvment by GFD
93	6	2	Abdullah AMA /1990	Not applicable	NS (20-60)	19	2(1)	retrospectively	Biopsy and improvement by GFD
Association with autoimmune disease(s)=3 articles									
44	6	2	Bin-Abbas BS/2010	1/20 (CD in APS-1)	1/0 (16)	20 (APS-1) 1Fem/with CD	13(1)	January 2000 to December	AGA,ARA,EMA,TTGA,biopsy
52	1	3	Al-Mayouf SM/2011	42.8% (18/42) Sero+ in JRA	10/8 (5-15)	42 Juvenile RA(JRA)	13(1)	NS	AGA-IgA,AGA-IgG, ARA and EMA-IgA and biopsy
76	19	12	Vangone A/2014	Not applicable	Not applicable (Mouse model)	mouse model	11(3)	anti-idio type Ab structure related to CD (mouse model)	animal model
Association with Down syndrome=3 articles									
40	6	2	Saadah OI, etal/2012	2/51=4%by ttg and 1/51=2% by biopsy	0/1 (0.5-16.6)	51	1(1)	January 2007 - August 2011	TTG-IgA and biopsy
82	59	2	AlRuwayli F, etal/2017	27/84 = 32.14 % AGA-IgA+ve 9/84= 10.9% biopsy confirmed 10.7%	Not applicapble (1-18)	84	13(1)	retrospectively	EMA,TTG,AGA,biopsy

85	45	2	AL Mehadib, et al/2011	45/91 = 49.45 % seropositive 9/91= 9.8% by biopsy confirmed	8/1(1.3-17.6)	91	13(1)	retrospectively	Ema,TTG,AGA,ARA,Biopsy
Pattern of celiac disease in adolescent and/or children=3 articles									
43	2	2	Saadah OI/2011	Not applicable	44/36(0.5-18)	80	1(1)	September 2002 -July 2007	TTG and biopsy
48	43	1	Assiri AM, etal/2008	Not applicable	NS in abstract (0.3 m-14Y)	62/first year	2(1)	retrospectively 10 years	EMA. AGA ARA , and biopsy
94	2	2	Nazer HM, etal/1990	Not applicable	NS(0.9-16y)	22	13(1)	1987-1988	Biopsy and improvement by GFD
Diet=2 articles									
32	24.	1.00	Sarkhy AA etal/2015	Not applicable	71/42 (≥18)	113	2(3)	November 2013- January 2014	children with biopsy
25	24.	1.00	Sarkhy A eta/2016	Not applicable	71/42 (≥18)	113	2(3)	Not applicable	children with biopsy
Corrigendum to previous publication=1 article									
53	7	1	Fouda MA, etal/2017	1.5%	Not applicable (correction)	Not applicable (correction)	7(1)	Not applicable (correction to reference 38)	None/correction
Aassociation with cardiac conditions=1 article									
24	4	8	Fathy A, etal/2016	Not applicable	12/8 (8.2 ± 2.7)	20 CD children and 20 healthy controls	8(1)	Prospective; February and march 2015	TTG-IgA, EMA-IgA, and biopsy
General review=1 article									
34	33	10	Guandalini S1, Assiri A/2014	Not applicable	Not applicable (review)	review	2(1)	review	review
Breast feeding and CD and autistic=1 article									
77	1	12	Selim ME, Al-Ayadhi LY/2013	Not applicable	Not applicable (Female rats)	animal model	2(1)	animal model	animal model20
Effect of thyroidism =1 article									
67	44	4	Alzahrani AS, Al Sheef M/2008	Not applicable	1/0 (24)	one patient case study	13(1)	case study	CD proven by serological screen and biopsy
CD and pregnancy =1 article									
66	12	4	Jammah AA/2012	Not applicable	1/0 (25)	one patient case study	2(1)	case study	TTG-IgA, EMA-IgA, and biopsy
Genetic and dental =1 article									
46	42	8	Ouda S, etal/2010	Not applicable	32/18 (10-18)	50 CD and 50 controls	1(1)	prospective	CD proven by biopsy
Psycatric=1 article									
81	54	1	Alharbi KL, etal/2017	43.1% depression	91/18 (<15->45)	109	27(1)	June and July 2017	CD proven by serological screen and biopsy
Extraabdominal conditions pattern =1 article									
80	57	1	Albrady ö, etal/2018	14.8% have osteoporosis	502/167 (18-50)	669 responses.	27(3)	28 February 2017 until 8 July 2017	online questionnaire.
Quality of life in CD 29=1 article									
79	57	1	Al-Qefari SA, etal/2018	Not applicable	192/72(5-64)	264	27(1)	NS	survey (SF-36) questionnaire

***Journals(Total 42):** 1=World J Gastroenterol, 2=Ann Saudi Med, 4=Saudi J Gastroenterol, 6= Saudi Med J, 9=J Pediatr Gastroenterol Nutr,10=Sci Rep,12=Sudan J Paediatr,15=Osteoporos Int,16=Ann Trop Paediatr,19= Can J Gastroenterol Hepatol, 20=PLoS One, 21=J Mov Disord, 23=J Cell Biochem, 24=Case Rep Gastroentero, 25=Pediatr Gastroenterol Hepatol Nutr, 28=Arab J Gastroenterol, 33=Dis Markers, 34=JAMA Pediat, 35=Ann Hepatol, 36=BMC Gastroenterol, 38=Can J Gastroenterol, 40=Eur J Gastroenterol Hepatol, 41=Niger J Med, 42=Pediatr Rep, 43=J Clin Pediatr Dent, 44=Trop Gastroenterol, 45=Endocr Pract, 46=J Gastroenterol Hepatol, 47=Eur J Ophthalmol, 48=Neurosciences (Riyadh),49=J Biol Sci, 50=Saudi J Intern Med, 51=JKAU: Med. Sci, 52=9th Applied Medical Sciences Students' Annual Meeting; February 19, 2013; King Abdulaziz University, 53=American Journal of Medicine and Medical Sciences, 54=Annals of Medical and Health Sciences Research, 54=Int J Diabetes Metab Disord, 55=IOSR Journal of Pharmacy and Biological Sciences (IOSR-JPBS), 56=Ann Med Health Sci Res, 57=Journal of Taibah University Medical Sciences, 59=International Journal of Pediatrics and Adolescent Medicine, 60=Journal of Pediatric Gastroenterology and Nutrition.

** **Type of study:** 1=Cross sectional, 2=Retrospective, 3=Prospective, 4=Case report, 5=Letter to the editor, 6=Genetic, 8=Case-control, 9=Meta analysis, 10=Review, 11=Pilot prospective, 12=animal experiment, 13=Corrigendum to previous publication.

*****Centers:** 1=KAU-jedda; 2= King Saud University, Riyadh; 3=not Saudi; 4=29= King Fahd Hospital, Al-Baha, Saudi Arabia; 5=University of Ha'il; 6= King Khalid University; 7= Alfaisal University, Riyadh; 8= Taibah University, Madinah; 9= Baghdad University; 10= King Abdullah International Medical Research Center-Riyadh; 11= King Abdullah University of Science and Technology, Thuwal; 12= King Fahad Medical City, Riyadh; 13= King Faisal Specialist Hospital and Research Center-Riyadh; 14= The Townsville Hospital, Australia; 15= Regional Laboratory and Blood Bank, Ministry of Health, Dammam; 16=King Fahad National Guard Hospital, Saudi Arabia.; 17= Abdul-Aziz Medical City, Jeddah; 18=Good Hope Hospital NHS - Sutton - UK; 19= King Fahad Hospital of the University, Al-Khobar, Saudi Arabia; 20= King Khalid University, Abha; 21= Al Mana General Hospital, Al Khobar; 22= Queen Rania Alabdullah Hospital of Pediatrics, King Hussein Center, Amman, Jordan; 23= Alkadra Teaching Hospital, Tripoli, Libya; 24= Alkadra Teaching Hospital, Tripoli, Libya; 25= Shaheed Beheshti University, Tehran, Iran;26Umm AlQura University; 27= Qassim University; 28= King Fahad Armed Forces Hospital, Jeddah; 30= King Khalid National Guard Hospital,Jeddah.

#Multi : 1=author(s) is (are) from one center; 2= authors are from two centers; 3= authors are from multi-centers

Table 3. Female to male pattern

	Number of Studies	Minimum count	Maximum count	Sum	Mean	Std. Deviation	Female /male ratio
Female	53	0	502	1731	33.88	75.88	1731/884=1.95
Male	53	0	167	884	17.31	29.50	

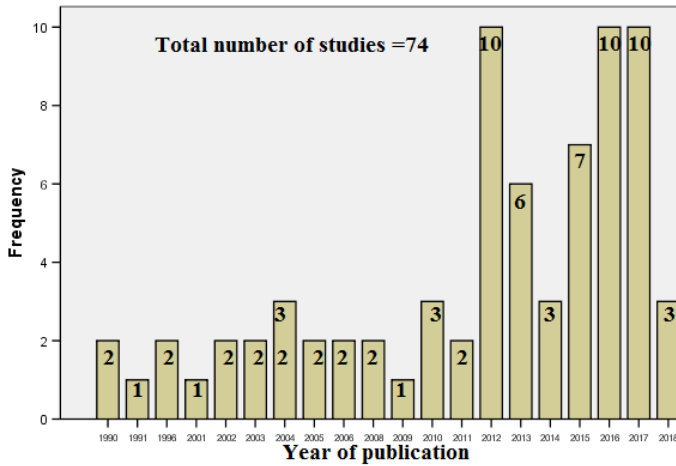


Figure 2. Distribution of studies (Total 74) according to the year of publication

21 articles (Table 2). Articles with “female more than male” were five time (45/8) those with “male more than female” (Table 2). The ratio of the total female (1731) over the total male (884) was 1.95 /1 (Table 3).

III. **Duration span:** Publications concerning CD in SA started in 1990 (Figure 2) with stable annual number (1-3) until it peaked (10 articles) in 2012, 2016 and 2017. The two earliest studies of 1990 [93,94] covered the retrospective period from 1978.

IV. **Cohort:** In this study, cohort is meant to be the number of human subjects that were involved in each study whether patients of CD (for different evaluations) or of other conditions (for CD association), normal subjects (for CD prevalence), normal controls (in the case control studies) and participants in surveys.

Information about cohort were found in 66 articles, while missing [not specified (NS) or not applicable (NA)] in 8 articles (2 animal model, 2 comments, 1 correction, 2 reviews, 1 meta-analysis) (Table 2). The 66 articles with cohorts’ information included: 14 articles of one case studies [35,49,57,55,60,62,65,67,66,68,73,74,88,89], one article of two case studies [69], three articles of three case studies [50,70,75] and 48 articles [21-34, 36-48, 51-54,56,58,59,61,63,64, 71,72, 76-87,90-94] with a range of 6 - 7930 subjects (Table 2).

V. **Journals:** The selected studies were published in 42 journals. Saudi Med J showed the highest (31 publications), followed by Saudi J Gastroenterol and Ann Saudi Med (7 publications each), World J Gastroenterol (3 publications), then Seven journals with two publications each and finally, thirty-one journals with one publication each (Figure 3).

VI. **Centers:** Studies were related to 23 centers representing almost the entire kingdom of SA. King Saud University, Riyadh, showed the highest number of studies (21), followed by KAU-Jeddah (14), King Faisal Specialist Hospital and Research Center-Riyadh (10), Alfaisal University, Riyadh (2), four centers with 3 studies each, and fourteen centers (with one study each) which included two centers from outside the kingdom: the Townsville Hospital [29], and Baghdad University [28] concerning comments on another article from SA (Figure 4).

VII. **Types versus fields (disciplines) of studies:** Twelve types were found. Most publications were found as cross sectional, retrospective and case report (18 each). Followed by case-control 6, prospective 4, review 2, letter to the editor 2, animal experiment 2, genetic 1, Meta-analysis 1, Pilot prospective 1, corrigendum to previous publication 1.

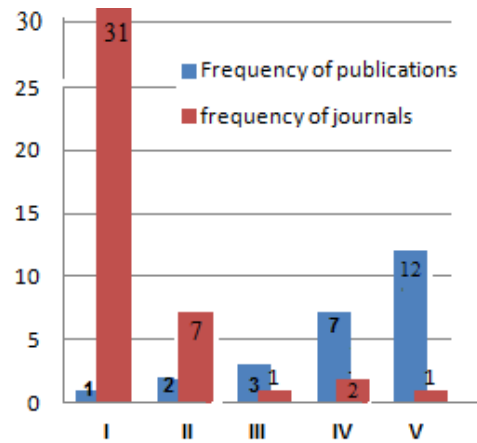


Figure 3. Frequency of journals (Total 42) versus frequency of publications (Total 74)

I=Thirty one journals with one publication each: J Pediatr Gastroenterol Nutr, Sci Rep,Osteoporos Int, Ann Trop Paediatr, Can J Gastroenterol Hepatol, J Mov Disord, J Cell Biochem, Case Rep Gastroentero, Dis Markers, JAMA Pediatr, Ann Hepatol, BMC Gastroenterol, Can J Gastroenterol, Eur J Gastroenterol Hepatol, Niger J Med, Pediatr Rep, J Clin Pediatr Dent, Endocr Pract, J Gastroenterol Hepatol, Eur J Ophthalmol, Neurosciences (Riyadh), J Biol Sci, Saudi J Intern Med, JKAU: Med. Sci, 9th Applied Medical Sciences Students’ Annual Meeting; February 19, 2013; King bdulaziz University, American Journal of Medicine and Medical Sciences, Annals of Medical and Health Sciences Research, Int J Diabetes Metab Disord, IOSR Journal of Pharmacy and Biological Sciences (IOSR-JPBS), Journal of Taibah University Medical Sciences, International Journal of Pediatrics and Adolescent Medicine,

II=Seven journals with two publications each: PLoS One, Pediatr Gastroenterol Hepatol Nutr, Arab J Gastroenterol, Trop Gastroenterol, Sudan J Paediatr, Journal of Pediatric Gastroenterology and Nutrition, Ann Med Health Sci Res.

III= One journal with three publications: World J Gastroenterol

IV=Two journals with seven publications each: Ann Saudi Med and Saudi J Gastroenterol

V=One journal with twelve publications: Saudi Med J

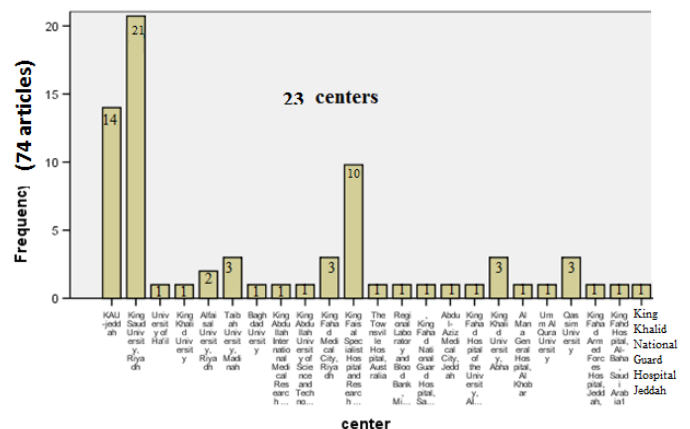


Figure 4. Distribution of articles (Total 74) according to centres (Total 23)

- Fourteen centers with one study each
- One center with two studies
- Four centers with three studies each
- One center with ten studies
- One center with fourteen studies
- One center with twenty-one studies
- Descriptive Statistics

Table 4. Type of study versus Field of study

Field	Type of study												Total (%)
	cross sectional	retrospective	prospective	Case report	Letter to the editor	genetic	Case-control	Meta-analysis	Review	Pilot prospective	animal experiment	Corrigendum to previous publication	
prevalence	2(28.56) [11.11]	1(14.28) [5.55]	1(14.28) [25]		2(28.56) [100]					1(14.28) [100]			7(100.00) {9.45}
Genetic		1(20.00) [5.55]				1(20.00) [100]	2(40.00) [33.33]	1(20.00) [100]					5(100.00) {6.75}
association with diabetes mellitus	5(6.94) [27.75]	3(4.22) [15.65]											8(100.00) {10.8}
association with autoimmune disease(s))		1(33.33) [5.55]	1(33.33) [25]								1(33.33) [50]		3(100.00) {4.05}
association with short stature	2(40.00) [11.11]	2(40.00) [11.11]	1(20.00) [25]										5(100.00) {6.75}
clinical and/or lab characterization (presentation)	1(25.00) [5.55]	3 (50.00) [15.65]					1(25.00) [16.66]						5(100.00) {6.75}
case report	1(5.89) [5.55]			16(94.11) [88.88]									17(100.00) {22.95}
Corrigendum to previous publication												1(100.00) [100]	1(100.00) {1.35}
association with cardiac							1(100.00) [16.66]						1(100.00) {1.35}
Diet	2(100.00) [11.11]												2(100.00) {2.7}
CD and skeletal	1(16.66) [5.55]	2(33.36) [11.11]	1(16.66) [25]				1(16.66) [16.66]		1(16.66) [50]				6(100.00) {8.1}
General									1(100.00) [50]				1(100.00) {1.35}
Breast fed and CD and autistic											1(100.00) [50]		1(100.00) {1.35}
prevalence in Down syndrome		3(100.00) [15.65]											3(100.00) {4.05}
Pattern of CD (1 questionnaire)	1(33.33) [5.55]	2(66.66) [11.11]											3(100.00) {4.05}
effect of thyroidism				1(100.00) [5.56]									1(100.00) {1.35}
CD and pregnancy				1(100.00) [5.56]									1(100.00) {1.35}
genetic and dental							1(100.00) [16.66]						1(100.00) {1.35}
Psychiatric	1(100.00) [5.55]												1(100.00) {1.35}
Extraabdominal conditions pattern	1(100.00) [5.55]												1(100.00) {1.35}
Quality of life questionnaire	1(100.00) [5.55]												1(100.00) {1.35}
Total	18 (24.3) [100]	18 (24.3) [100]	4(5.4) [100]	18(24.3) [100]	2(2.7) [100]	1(1.35) [100]	6(8.1) [100]	1(1.35) [100]	2(2.7) [100]	1(1.35) [100]	2(2.7) [100]	1(1.35) [100]	74(100.00)

The 74 studies involved 21 disciplines: case report (in 17 articles), association with diabetes mellitus (8), prevalence (7), CD and skeletal (6), genetic (5), association with short stature (5), clinical and/or lab characterization (presentation) (5), association with autoimmune disease(s) (3), prevalence in Down syndrome (3), pattern of CD (1 questionnaire) (3), Diet (2). One article for each of the following ten disciplines: general, Breast fed and CD and autistic, association with cardiac, corrigendum to previous publication, effect of thyroidism, CD and pregnancy, genetic and dental, psychiatric, Extra-abdominal conditions pattern, quality of life (questionnaire).

Distribution of types versus fields (disciplines) and articles are shown in Table 2 & 4.

IIX. Results of histology and serology

- Commencing date

Histological evaluation was introduced early in 1980s [93,94] followed by serology in 1990s for EMA, ARA and AGA [91] and in 2004 for tTG-Ab [86,87] (Table 5).

- Frequency of usage whether as single or combined.

Biopsy showed the highest usage (in 57 studies), tissue-transglutaminase- antibodies (tTG-Ab) (34), endomysial-antibody (EMA) (29), anti-gluten-antibodies (AGA) (18), anti-reticulin-antibodies (ARA) (11) (Table 6).

Mode of double combination between different serological tests: tTG-Ab with EMA (in 18 studies), AGA with EMA (12), AGA with ARA (10), ARA with EMA (8), tTG-Ab with AGA (8), tTG-Ab with ARA (2) (Table 7).

Mode of combination between histology and serology in each article: Different patterns of cooperation between biopsy and serology in each article are shown in Table 8. The concerned information was found in 63 articles, while missing in 11 articles (2 animal models, 4 review and questionnaire, 2 comments, one survey, one correction and one with no details). Biopsy was used in 57 studies according to the following pattern of serological cooperation: eleven articles [22,30,33,35,39,40,50,62,65,83,88] of tTG-IgA and biopsy; eleven articles [21,

Table 5. Commencing date of different serology and histology

	AGA	ARA	EMA	TTG	Histology
Year	1996	1996	1996	2004	1990

Table 6. Frequency of different serological tests whether as single or combined

		tTG	EMA	AGA	ARA	Biopsy
Valid	Yes	34	29	18	11	53
	No	19	24	35	42	12
	CD proven	10	10	10	10	3
	biopsy and improvement by GFD	3	3	3	3	
	biopsy and no improvement by GFD	1	1	1	1	
	animal model	2	2	2	2	2
	no details	1	1	1	1	1
	Review and questionnaire	4	4	4	4	4
	Total	74	74	74	74	74

Table 7. Cross-tabulation between different serological tests

Test		AGA			ARA			EMA		
		Yes	NO	Total	Yes	NO	Total	Yes	NO	Total
tTG	yes	8	26	34	2	32	34	18	16	34
	no	10	9	19	8	11	19	11	8	19
	Total	18	35	53	10	43	53	29	24	53
AGA	yes				10	8	18	12	6	18
	no				1	34	35	17	18	35
	Total				11	42	53	29	24	53
ARA	yes	10	1	11				8	2	10
	no	8	34	42				21	22	43
	Total	18	35	53				29	24	53

23,24,26,36,37,45,49,59,66,68] of tTG-IgA, EMA-IgA and biopsy; ten articles [25,32,41,46,56,57,58,67,81,90] of CD proven by biopsy; five articles [42,48,52,70,91] of AGA,ARA,EMA and biopsy; three articles [31,54,82] of EMA, tTG Ab,AGA and biopsy; three articles [47,55,92] of EMA and Biopsy, three articles [43,86,87] of AGA, tTG Ab and biopsy; three articles [72,93,94] of Biopsy and improvement by GFD; two articles [44,85] of EMA, tTG Ab, AGA, ARA and Biopsy; two articles [69,73] of AGA and biopsy; one article [89] of AGA, EMA-IgA, and biopsy; two articles [51,74] of AGA,ARA and biopsy; one article [75] of AGA, EMA-IgA, and biopsy; one article [89] of biopsy and no improvement by GFD. Biopsy was not used in 7 studies according to the following pattern of serological cooperation: two articles [64,78] of tTG-Ab, one article [43] of EMA, one article [71] of EMA and ARA, one article [27] of EMA and tTG Ab, one article [51] of AGA and ARA, one article [60] of EMA, tTG Ab, AGA, ARA. The maximum usage (54%) was for tTG-Ab (30 with biopsy and 4 without) either alone or in combination with other serological markers; followed by 16% for CD proven by biopsy, 20% for markers without tTG-Ab [EMA,ARA,AGA with different combinations] (10 with biopsy and 3 without), 6% for Biopsy and GFD (3 improved with GFD and 1 no improvement); the minimum usage (4%) was for AGA-Ab without tTG-Ab (2 with biopsy and EMA or ARA, one with ARA, but never alone). (Table 8)

Chronological usage of serology and biopsy: The pattern of the chronological usage of serology and biopsy in SA is shown in Table 9 and Figure 5. The two earliest studies of 1990 [93,94] indicated that CD proven by histology (with improvement by GFD) was the mode of diagnosis in 1980s. The study of Zawawi TH, et al. [91], that covered

the period 1988-1994, indicated that all serology except tTG-Ab (EMA, AGA and ARA) were used during that period (1989-1994). Also, there was no mention for tTG-Ab in the publications of 2001,2002 and 2003 [73,71 and 51 respectively]. The first mention of tTG-Ab was found in 2004 [86,87] indicating its definite presence in 2004.

Discussion

The current study is a statistical evaluation of all relevant literature on CD in SA, published up to March 2018 with no retrospective date limit. It represents the first and only Systematic Review concerning the

Table 8. Mode of combination between histology and different serology in each article

Serology with/without histology	Frequency	Article's (reference) No
With biopsy=57	tTG-IgA, and biopsy	22,30,33,35,39,40,50,62,65,83,88
	tTG-IgA, EMA-IgA, and biopsy	21,23,24,26,36,37,45,49,59,66,68
	CD proven by biopsy	25,32,41,46,56,57,58,67,81,90
	AGA,ARA,EMA,biopsy	42,48,52,70,91
	EMA, tTG Ab,AGA and biopsy	31,54,82
	EMA and Biopsy	47,55,92
	AGA, tTG Ab and biopsy	43,86,87
	Biopsy and improvement by GFD	72,93,94
	EMA, tTG Ab, AGA, ARA,Biopsy	44,85
	AGA and biopsy	69,73
	AGA, EMA-IgA, and biopsy	89
	AGA,ARA and biopsy	74,51
	Biopsy and no improvement by GFD	75
Without biopsy=6	tTG Ab	64,78
	EMA	43
	EMA and ARA	71
	EMA and tTG Ab	27
	EMA, tTG Ab,AGA,ARA	60
Missing=11	Non	28,29,53,61
	Animal model	76,77
	Review and questionnaire	34,38,79,80,
	No details	84
Total	74	

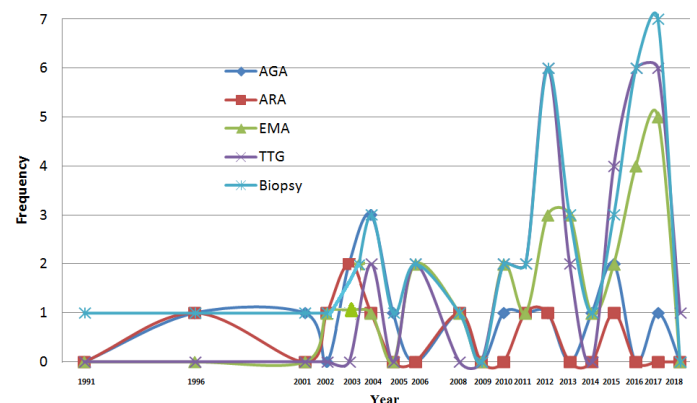


Figure 5. Chronological Pattern of Serology & Biopsy

Table 9. Chronological usage pattern of serology and biopsy

Year	19 90	19 91	1996	2001	2002	2003	2004	2005	2006	2008	2009	2010	2011	2012	2013	2014	2015	2015	2017	2018	Total
EMA	0	0	1	0	1	1	1	0	2	1	1	2	1	3	3	1	2	4	5	0	29
tTG-Ab	0	0	0	0	0	0	2	1	2	0	0	2	2	6	2	0	4	6	6	1	34
AGA	0	0	2	1	0	2	3	1	0	1	0	1	1	1	0	1	2	0	2	0	18
ARA	0	0	2	0	1	2	1	0	0	1	0	0	1	1	0	0	1	0	0	0	10
Histology	2	1	2	1	1	2	3	2	2	2	1	3	2	7	3	1	4	7	8	0	54

status of CD (and its serological pattern) in SA. However, we only found two studies from SA, analyzing the literature concerning specific fields of CD: one Meta-analysis of 11 global case-control studies concerning the genetic polymorphism association with CD [58], and one review (by literature electronic search using the MEDLINE and EMBASE databases) evaluating the global skeletal health (bone mineral density (BMD) and fracture risk) in CD from 1996 to 2010 [38], in addition to a general review about global CD, authored from SA [34].

In the 74 included articles, the ratio of the total female to total male was almost the double (1.95/1). Globally, CD is more common in female (double or triple) than in male, with a possible attribution to the higher frequency of the necessary HLA-DQ 2/ 8 alleles in female than male [97,98].

We found different rates of CD in different studies in SA. CD prevalence in SA is ranging from 1.5 % to 3% in four studies [23,30,63,64]. The global prevalence is 1% (with a range of 0.5-1.6%) [99-102], with a high prevalence (5.6%) among the "Saharawi refugees of Berber-Arabic origin" in North Africa [103]. One of the articles [26] studied the seroprevalence of celiac disease in at-risk subjects (T1DM, T1DM + Hypothyroidism, Hypothyroidism, Short stature, Failure to thrive, Abdominal pain, Chronic diarrhea, Anaemia, Others) which was 18.4%. Concerning the global at-risk groups (including Down and Turner syndromes, type 1 diabetes, and autoimmune thyroid disease) the prevalence is ranging from 5% to 10% [104].

Concerning the association of CD with other conditions, we found strongly variable rates of CD in different conditions in different studies. The prevalence of CD cases in patients with Rickets differed from 6.87% to 38.4% [42,36 respectively], while in patients with Low BMD differed from 43% to 70% [84,90 respectively]. Globally, low bone mineral density (BMD) at both the spine and hip in celiac patients was also reported [105-107]. It was also reported that celiac disease may cause rickets [108,109]; even, congenital rickets may be caused by untreated maternal CD [110]. In India, rickets rate within patients suffering of celiac and Type1 Diabetes Mellitus was reported to be 20.8% [111].

For CD with Diabetes Mellitus (T1DM) [27, 33,37,39,51,78,83,87], down syndrome (DS) [40,82,85] and short status (SS) [41,45,47,86,92]; the prevalence ranges were 7.3% -19.7%, 2-10.7% and 4%-19% respectively. The Global rates are 4-15% for Type 1 diabetes mellitus and 5-10% for Down's syndrome [112,113]. In Europe, the CD prevalence among children with short stature is approximately 0.05-0.56% [45], while it is 4.0% in western New York [114].

One article described a case of CD among 20 cases (5%) of APS type 1 [44], and one article described an association (42.8%) of CD and juvenile RA [52]. Cases of APS type 2 which were associated with celiac disease were reported [115,116]. In Italy, prevalence of CD in RA was nil [117]. In UK, the overall prevalence of celiac disease in RA is 0.63% [118], while an arthritis is present in 26% of CD patients, with difference between patients on a regular diet (41%) and patients on a gluten-free diet (21.6%) [119].

Two studies of questionnaire survey to the families of CD patients. One showed a significant negative socio-economic impact of Gluten-

Free Diet (GFD) on children with CD & their families [25]. And one questionnaire about the adherence to GFD [32] showed that 60% of the involved children were reported to be strictly adherent to GFD; the younger age at diagnosis and the shorter duration since the diagnosis the better adherence rate.

Adherence to Gluten-Free Diet can be evaluated by different methods: serology [tTG-Ab (TG2) test], rebiopsy and dietitian interviews or/and questionnaire; however, antibodies take 1.5-3 months to normalize, but the finally, complete histological resolution may not occur until 2 years of GFD [120]. "Celiac Dietary Adherence Test" (CDAT), a 7-question survey that allows a standardized evaluation of adherence and is superior to the tTG-Ab test [121]. Patient interview for monitoring dietary compliance has been proven to be more sensitive than serology [122].

Globally, the degree of strict adherence to a GFD is strongly variable with a range of 42% to 91% [123]. Less adherence is among adolescents, and adults diagnosed in childhood; due to lack of knowledge, poor availability and/or labeling of gluten free products, and difficulties in obtaining and/or identifying gluten-free food when dining out [124].

The information, within the articles, indicate for the usage of four serological tests (AGA, ARA, EMA and tTG-Abs), in addition to the biopsy test. Globally, these investigations were described in the fall of the second half of the last century [7-16] (see the introduction). However, with the start of this century (in 2004) a new test (DGPAs) was introduced for the detection of deamidated gliadin peptide Abs, which is promising according to its sensitivity and specificity [125] and appears to be possibly more useful than tTG in children below the age of 7 years and/or in IgA-immunocompromised patients [126,127]. We found no mention (within the articles) to this new serological test. Recently (in 2013), the first electrochemical immunosensor for DGPAs was described, as a good alternative to the traditional ELISA kits [128].

Amongst the retrieved 74 articles, information of cooperation between biopsy and different serological markers in each article were found within 63 articles, the maximum usage (54%) was for tTG-Ab, followed by 16% for CD proven by biopsy, 20% for markers without tTG-Ab [EMA, ARA, AGA with different combinations, 6% for Biopsy and GFD and the minimum usage (4%) was for AGA-Ab without tTG-Ab. (more detailed description is found in the result section). This type of pattern can be attributed to two reasons: 1- AGA test has low (sensitivity) and {specificity} [IgA-AGA (85%), {90%}; IgG-AGA (85%), {80%}] while tTG-Ab possesses high sensitivity and specificity [IgA-tTG (98%), {98%}], as well as EMA (95%), {99%} and ARA (72%),{99%} [129,130]. 2- Tests for ARA and EMA are based on indirect immunofluorescence which requires an individual reading of each sample under a fluorescent microscope, is costly, time consuming and leads to inter-observer variability [131].

HLA typing is also missing in the retrieve articles. This test identifies whether a patient possesses the haplotypes DQ2 or DQ8, the absence of which excludes the possibility of CD [132]. HLA-DQ2 and/or HLA-DQ8 typing is useful in both and diagnosis and epidemiological

evaluation. Among the global population, HLA-DQ2 and/or HLA-DQ8 typing is present in 98.6% of patients with CD, and in 40% of the general population who do not have the diagnosis of CD [133].

Conclusion

Over the last decades, the availability of both specific and sensitive serological markers for CD, accompanied with technical advances have led to improvement in the frequency and accuracy of data on CD in SA. Since 1990, there have been multiple studies concerning the status of CD from many parts of SA, using many types of studies and covering a wide range of conditions, for both the general population and at-risk patients. Most results showed strongly variable rates of CD, among the general population and among at-risk patients, in different studies in SA. However, some conditions still need to be evaluated, such as the small intestinal bacterial overgrowth (SIBO) among patients with celiac disease unresponsive to gluten-free diet (GFD [134,135].

IgA- anti-tTG and AGA showed the highest and the lowest utilization rate respectively, due to their level of sensitivity and specificity which were high [sensitivity (98%) and specificity {98%}] in tTTG-Ab, in comparison with AGA [(85%), {90%}]. Although EMA and ARA possess high sensitivity and specificity, they have some drawbacks including low reproducibility and high inter-observer variability, as both based on indirect immunofluorescence which requires an individual reading of each sample under a fluorescent microscope. The literature from SA missed the new currently used test for deamidated gliadin antibodies (DGP-IgG and DGP-IgA), and the DQ2 or DQ8 typing which is employed for both epidemiology and diagnosis, only when negative, to rule out the possibility of CD diagnosis.

Recommendations

1. Meta-analysis for the different studies of CD prevalence in general population and in each of at-risk patients [Diabetes Mellitus (T1DM), down syndrome (DS) and short stature (SS)]
2. Evaluation of DGP-IgG and DGP-IgA in comparison with the other serological markers.
3. Evaluation of DQ2/ DQ8 typing for both diagnosis and epidemiology.
4. Evaluation of Small intestinal bacterial overgrowth (SIBO) among patients with celiac disease unresponsive to gluten-free diet (GFD).

These recommendations will be our plan for future separate publications.

Ethical approval

The collected data were part of a retrospective literature review; thus, a written ethical approval was not obtained before commencing the study.

Disclosures

Both authors have read and approved this manuscript. The current study was not funded or supported by any drug company. This paper is unique and is not under consideration by any other publication and has not been published elsewhere.

Conflicts of interest

The authors declare that they have no conflicts of interest.

Author contributions

Dr. Safi MA provided the framework of the study, wrote, reviewed and extensively edited the manuscript and gave it its final form. Both authors made the updated literature search, prepared the graphs and tables. Dr. Safi HMA also helped in the SPSS statistics.

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