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

Mohammad-Ayman A Safi1* and Hadia M-A Safi2

1Associate Professor, Department of Medical Microbiology and Parasitology, King Abdulaziz University, Jeddah, Saudi Arabia
2Medical intern, Ibn Sina National College for Medical Studies, Jeddah, Saudi Arabia

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 early1980s 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) immunofluorescece 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 tow 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].

*Correspondence to: Mohammad-Ayman A Safi, Associate Professor of Immunology, Department of Medical Microbiology and Parasitology, Faculty of Medicine, King Abdul-Aziz University, PO Box 80205, Jeddah 21589, Kingdom of Saudi Arabia, , Tel: +966 (12) 6400000., Ext 21116, Fax: +966 (12) 6403749, E-mail: aymansafi3@hotmail.com

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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 iTGA 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). 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)", 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 included as children [95,96] are considered 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**

1. **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, week 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*                  | 42                                                       | 27                                  | 2                                | 74           |
|                         | 21-52 [78-87]                                            | 53-75                               | 88-91                            | 76-77        |
|                         | 92-94                                                   | 78-94 non-PubMed                    | 21-77                            |
|                         | 78-94 non-PubMed                                         |                                     |                                  |
| Not celiac**            | 36                                                       |                                     |                                  |              |
|                         | References                                               |                                     |                                  |
|                         | excluded                                                 |                                     |                                  |
| Total                   | 110                                                      |                                     |                                  |
| non-Saudi**             | 46                                                       |                                     |                                  |              |
|                         | Total                                                   | 110                                 |                                  |
|                         | 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

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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 |
|------------------|----------|--------|----------------|------------|-------------------|-------------------|---------------------|--------|-------------------------|
| 35               | 34       | 4      | Al-Hussaini A, et al/2013 | Not applicable | 1/0 (11) | one patient case study | 12(2) | case study | TTG-IgA, and biopsy |
| 49               | 46       | 4      | Al Hemidan, A, et al/2006 | Not applicable | 1/0 (3) | one patient case study | 13(3) | case study | TTG-IgA, EMA-IgA, and biopsy |
| 50               | 43       | 4      | Al Faraikh S, et al/2005 | Not applicable | 2/1 (25,30,42) | 3 patients case study | 16(1) | case study | TTG-IgA, and biopsy |
| 55               | 20       | 4      | Tahouni S, A/Khairallah 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 patient case study | 2(1) | case study | CD patient on GFD |
| 62               | 25       | 4      | Al-Judabi B, et al/2015 | Not applicable | 1/0 (68) | one case study | 2(2) | case study | TTG and biopsy |
| 65               | 38       | 4      | Masoodi I, et al/2012 | Not applicable | 0/1 (27) | one patient case study | 12(1) | case study | TTG-IgA, and biopsy |
| 68               | 2        | 4      | Azzam NA, et al/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 | emeil to author |
| 70               | 4        | 4      | Yasawy MI, et al/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      | Ablowalia M, et al/1996 | Not applicable | 1/0 (25) | one patient case study | 21(2) | case study | AGA,ARA and biopsy |
| 75               | 15       | 4      | Nazer HM, et al/1991 | Not applicable | 2/1 (11,15,4) | 3 lymphangiseredectasia manq | 13(1) | case study | biopsy and GFD no improvement |
| 88               | 50       | 4      | Alahdal AM/2015 | Not applicable | 0/1 (44) | one case | 1(1) | case study | TTG-IgA, and biopsy |
| 89               | 53       | 4      | Ahmed M-E K, et al/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, AGA, and biopsy |

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### Association with diabetes mellitus – 8 articles

| Article | Year | Authors | Methodology | Serology Test | Biopsy | Sample Size | Diagnosis | Follow-up Period | Conclusion |
|---------|------|---------|-------------|---------------|--------|-------------|-----------|------------------|------------|
| 27      | 2016 | Al-Hakami et al. | By serology (21/202=10.4%) | 202 T1DM patients | 2013 to 2014 | EMA and TTG |          |                  |            |
| 33      | 2015 | Al-Agha AE et al. | By serology and biopsy (27/258=10.7%) | 228 children | 2013 to 2014 | TTG-IgA and biopsy |          |                  |            |
| 37      | 2012 | Al-Hassaini A. et al. | By serology (19/106=17.9%) | 106 children | 2012-2014 | TTG-IgA, EMA-IgA, and biopsy |          |                  |            |
| 39      | 2012 | Al-Agha AE et al. | By serology (21/202=10.4%) | 33 (27/228=19.7%) | 2013-2014 | EMA and biopsy |          |                  |            |
| 51      | 2018 | Al-Ashwal AA et al. | By serology (10/123=8.1%) | 11/123=4.9% | 1995-1996 | AGA, ARA IgA, and biopsy |          |                  |            |
| 78      | 2015 | Al-Hakami AM/2016 | By serology (58/315=18.4%) | 40/18=6.9% | 2009 to 2012 | TTG-IgA, EMA-IgA, and biopsy |          |                  |            |
| 83      | 2016 | Al-Agha AE et al. | By serology (16/218=7.3%) | 218 (16 with CD) | 2009 | TTG and biopsy |          |                  |            |
| 87      | 2004 | Saadah O.I et al. | By serology (23/110=21%) | 110 diabetic children and adolescents (1-18-Y) | 1995-1996 | AGA,TTG,biopsy |          |                  |            |

### Prevalence – 7 articles

| Article | Year | Authors | Methodology | Serology Test | Biopsy | Sample Size | Diagnosis | Follow-up Period | Conclusion |
|---------|------|---------|-------------|---------------|--------|-------------|-----------|------------------|------------|
| 23      | 2017 | Al-Hussaini A. et al. | By serology (221/7930=2.78%) | 7930 (6-15Y) | 2014 to 2016 | TTG-IgA, EMA-IgA, and biopsy |          |                  |            |
| 26      | 2016 | Al-Hakami AM/2016 | By serology (58/315=18.4%) | 315 at-risk subjects | 2016 | TTG-IgA, EMA-IgA, and biopsy |          |                  |            |
| 28      | 2016 | Al-Mendalawi MD/2016 | Not applicable | Not applicable | 2016 | None/comments |          |                  |            |
| 29      | 2016 | Almadi MA, Aljebreen AM | Not applicable | Not applicable | 2016 | None/comments |          |                  |            |
| 30      | 2015 | Al Hatlani MM/2015 | 3% by tTG | 1141 participants | 2015 | IGG-TTG |          |                  |            |
| 61      | 2013 | Aljebreen AM, et al/2013 | By serology(26/1167=2.2%) | 1167 students | 2013-2014 | EMA-IgA and EMA-IgG |          |                  |            |
| 64      | 2012 | Khayyat YM/2012 | By serology(3/204=1.5%) | 204 blood donors | 2012-2014 | TTG-IgA |          |                  |            |

### CD and skeletal conditions – 6 articles

| Article | Year | Authors | Methodology | Serology Test | Biopsy | Sample Size | Diagnosis | Follow-up Period | Conclusion |
|---------|------|---------|-------------|---------------|--------|-------------|-----------|------------------|------------|
| 36      | 2013 | Assiri A, et al/2013 | 10/26 (38.4%) | 204 (mean 35) | 2013 | TTG-IgA, EMA-IgA, and biopsy |          |                  |            |
| 38      | 2012 | Fouad MA, et al/2012 | Global literature review | Literature review | 2012 | None/review |          |                  |            |
| 42      | 2012 | AlJurayyan NA, et al/2012 | 6.17% Rickets du to CD | EMA,AGa,ARA an biopsy | 2012 | N/A |          |                  |            |
| 61      | 2015 | Assiri AM, et al/2015 | Physicians’ survey | 109 physicians completed the survey | 2015 | None/survey |          |                  |            |
| 84      | 2010 | Jouhari O/2010 | 43% of IBD had Low BMD | NS | 2010 | None |          |                  |            |
| 90      | 2012 | Othman H and Ouda SA/2012 | 70% of CD had low BMD | NS | 2012 | None |          |                  |            |

### Genetic – 5 articles

| Article | Year | Authors | Methodology | Serology Test | Biopsy | Sample Size | Diagnosis | Follow-up Period | Conclusion |
|---------|------|---------|-------------|---------------|--------|-------------|-----------|------------------|------------|
| 31      | 2015 | Saadah O.I et al/2015 | Not applicable | 97 unrelated patients and 123 controls | 2015 | AGA,TTG-IgA, EMA-IgA, and biopsy |          |                  |            |
Safi M-A and Safi H M-A (2018) Celiac disease and its serological pattern in Saudi Arabia: a systematic review

| Study Reference | Patients | Controls | Methodology | Results | Association Comment |
|-----------------|----------|----------|-------------|---------|---------------------|
| Al-Aama JY, etal/2017 | 100 | 100 | TTG-IgA, EMA-IgA, biopsy | 56.45% (21-19) | Negative |
| Banaganapalli B, etal/2017 | 15 | 15 | CD proven | NS (P&A, Adolescents) | Meta-analysis, Polymorphism is associated with CD |
| Khan S, etal/2016 | Not applicable | | Meta-analysis | 5(3) | Not applicable |
| Al-Aama JY, etal/2017 | 100 patients and 100 controls | | | 1(1) | Negative |
| Banaganapalli B, etal/2017 | 15 patients after remission and 15 controls | | | 1(1) | Negative |
| Al-Ajlan AS/2016 | 482 controls and 498 IBD | | Biomarkers and biopsy | | January 2012 to January 2013 |

**Association with short stature (5 articles)**

| Study Reference | Patients | Controls | Methodology | Results | Association Comment |
|-----------------|----------|----------|-------------|---------|---------------------|
| Al-Aama JY, etal/2017 | 9.6% of IBD | 56/45 | Biomarkers and biopsy | | Negative |
| Banaganapalli B, etal/2017 | 21-19 | | Biomarkers and biopsy | | Negative |
| Al-Ajlan AS/2016 | 2012-2013 | | Biomarkers and biopsy | | NS for CD |
| Assiri AM/2010 | 2012-2013 | | Biomarkers and biopsy | | Negative |
| Al-Ajlan AS/2016 | 2012-2013 | | Biomarkers and biopsy | | Negative |

**Clinical and/or lab characterization (presentation) (5 articles)**

| Study Reference | Patients | Controls | Methodology | Results | Association Comment |
|-----------------|----------|----------|-------------|---------|---------------------|
| Fouda MA/2017 | 86.9% | 149/69 (1-75) | Biomarkers and biopsy | | Positive |
| Saeed A, etal/2017 | 20.1% of biopsies | 64/318 (20.1%) | Biomarkers and biopsy | | Negative |
| Al Attas RA/2002 | 4.0% in CD; By EMA: 7.6% in CD. | 64/81 (0.9-36) | Biomarkers and biopsy | | Negative |
| Abdullah AMA /1990 | 27.14% (32/84) | 9/84= 10.9% | Biomarkers and biopsy | | Negative |
| Al-Mayouf SM/2011 | 42.8% (18/42) | 10/8 (5-15) | Biomarkers and biopsy | | Negative |
| Vangone A/2014 | Not applicable | | Biomarkers and biopsy | | Negative |

**Association with autoimmune disease(s) (3 articles)**

| Study Reference | Patients | Controls | Methodology | Results | Association Comment |
|-----------------|----------|----------|-------------|---------|---------------------|
| Al-Mayouf SM/2011 | 2/51=4% | 0/1 (0.5-16.6) | Biomarkers and biopsy | | Negative |
| AlRuwaily F, etal/2017 | 27/84 (32.14 %) | 84 | Biomarkers and biopsy | | Negative |

**Association with Down syndrome (3 articles)**

| Study Reference | Patients | Controls | Methodology | Results | Association Comment |
|-----------------|----------|----------|-------------|---------|---------------------|
| Al-Ruwaily F, etal/2017 | 2/51=4% | 0/1 (0.5-16.6) | Biomarkers and biopsy | | Negative |
| AlRuwaily F, etal/2017 | 27/84 (32.14 %) | 84 | Biomarkers and biopsy | | Negative |

**Association with Down syndrome (3 articles)**

| Study Reference | Patients | Controls | Methodology | Results | Association Comment |
|-----------------|----------|----------|-------------|---------|---------------------|
| AlRuwaily F, etal/2017 | 27/84 (32.14 %) | 84 | Biomarkers and biopsy | | Negative |
| AlRuwaily F, etal/2017 | 2/51=4% | 0/1 (0.5-16.6) | Biomarkers and biopsy | | Negative |

**Association with Down syndrome (3 articles)**

| Study Reference | Patients | Controls | Methodology | Results | Association Comment |
|-----------------|----------|----------|-------------|---------|---------------------|
| AlRuwaily F, etal/2017 | 27/84 (32.14 %) | 84 | Biomarkers and biopsy | | Negative |

Safi M-A and Safi H M-A (2018) Celiac disease and its serological pattern in Saudi Arabia: a systematic review

**Pattern of celiac disease in adolescent and/or children=3 articles**

53 7 1 Fouda MA, et al/2017 1.5% Not applicable (correction) Not applicable (correction) 7(1) Not applicable (correction to reference 38) None/correction

**Association with cardiac conditions=1 article**

24 4 8 Fathy A, et al/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 (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, et al/2010 Not applicable 32/18 (10-18) 50 CD and 50 controls 1(1) prospective CD proven by biopsy

**Psychiatric=1 article**

81 54 1 Alharbi KL, et al/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 ő, et al/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, et al/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 Pediat Gastroenterol Nutr,10=Sci Rep,12=Sadun J Paediatri,15=Osteoporos Int,16=Ann Trop Paediatri,19= Can J Gastroenterol Hepatol, 20=PLoS One, 21=J Mov Disord, 23=J Cell Biochem, 24=Case Rep Gastroenterol, 25=Pediatr Gastroenterol Hepatol Nutr, 28=Arab J Gastroenterol, 33=Dis Markers, 34=JAMA Pediat, 35=Ann Hepatol, 36=BMC Gastroenterol, 39=Clin Paediatri, 40=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=KAU; Med. Sci, 52=Pediatr Gastroenterol Hepatol Nutr, 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-jeddah; 2= King Saud University, Riyadh; 3=not Saudi; 4=29= King Fahad 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 Abdulilah 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 Alabullah 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;26/Umm 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**
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.

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               |
| Male              | 53            | 0             | 167 | 884  | 17.31          | 29.50               |

1=Thirty one journals with one publication each: J Pediatr Gastroenterol Nutr, Sci Rep,Osteoporos Int, Ann Trop Paediat, 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 Prac, 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 bualiz University, American Journal of Medicine and Medical Sciences, Annals of Medical and Health Sciences Research, Int J Diabetes Metab Disord, KJISR Journal of Pharmacy and Biological Sciences (KJISR-PBS), 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
Table 4. Type of study versus Field of study

| Field                                    | Type of study | Total (%) |
|------------------------------------------|---------------|-----------|
| Prevalence                               | Cross sectional | 2(28.56) [11.11] |
|                                          | Prospective   | 3(35.38) [16.66] |
|                                          | Case report   | 1(14.28) [25] |
|                                          | Letter to the editor | 1(14.28) [25] |
|                                          | Genetic       | 2(28.56) [100] |
|                                          | Case-control  | 1(14.28) [100] |
|                                          | Meta-analysis | 2(28.56) [100] |
|                                          | Review        | 1(14.28) [100] |
|                                          | Pilot prospective | 1(14.28) [100] |
|                                          | Animal experiment | 1(14.28) [100] |
|                                          | Corrigendum to previous publication | 1(14.28) [100] |
|                                          | Total (%)     | 7(100.00) [9.45] |
|                                          | Diet          | 6(8.1) [1.35] |
|                                          | Diet          | 5(6.94) [15.65] |
|                                          | CD and skeletal | 3(33.33) [5.55] |
|                                          | General       | 2(2.7) [15.65] |
|                                          | Breast fed and CD and autistic | 1(100.00) [16.66] |
|                                          | Pattern of Down syndrome | 1(100.00) [16.66] |
|                                          | Effect of thyroidism | 1(100.00) [25] |
|                                          | CD and pregnancy | 1(100.00) [25] |
|                                          | Psychiatric disease | 1(100.00) [16.66] |
|                                          | Extra-abdominal condition pattern | 1(100.00) [16.66] |
|                                          | Quality of life questionnaire | 1(100.00) [16.66] |

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.

IX. 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), ARA with EMA (12), ARA 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 [22,30,3,35,39,40,50,62,65,83,88] of tTG-IgA and biopsy; eleven articles [21,
Table 5. Commencing date of different serology and histology

| Test | AGA | ARA | EMA | TTG | Histology |
|------|-----|-----|-----|-----|-----------|
| Year | 1996 | 1996 | 1996 | 2004 | 1990 |

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

| Test       | iTG | EMA | AGA | ARA | Biopsy |
|------------|-----|-----|-----|-----|--------|
| Valid      | Yes | Yes | Yes | Yes | Yes    |
| No         | No  | No  | No  | No  | No     |
| CD proven  | Yes | Yes | Yes | Yes | Yes    |
| Biopsy and improvement by GFD | Yes | Yes | Yes | Yes | Yes |
| animal model | No  | No  | No  | No  | No     |
| Review and questionnaire | Yes | Yes | Yes | Yes | Yes |
| Total      | 74  | 74  | 74  | 74  | 74     |

Table 7. Cross-tabulation between different serological tests

| Test | AGA | ARA | EMA |
|------|-----|-----|-----|
| Yes  | Yes | Yes | Yes |
| No   | No  | No  | No  |
| Total| 18  | 35  | 53  |

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

| Serology with/without histology | Frequency | Article's (reference) No |
|---------------------------------|-----------|--------------------------|
| iTG-IgA, and biopsy             | 11        | 22,30,33,35,39,40,50,62,65 |
| iTG-IgA, EMA-IgA, and biopsy    | 11        | 21,23,24,26,36,37,45,49,59,66,68 |
| CD proven by biopsy             | 10        | 25,32,41,46,56,57,58,67,81,90 |
| AGA,ARA,EMA,biopsy             | 5         | 42,48,52,70,91 |
| EMA, iTG Ab,AGA, and biopsy     | 3         | 31,54,82 |
| AGA, ARA,biopsy                | 2         | 44,85 |
| AGA and biopsy                  | 2         | 69,73 |
| AGA, EMA-IgA, and biopsy        | 1         | 89 |
| AGA, ARA and biopsy             | 2         | 74,51 |
| Biopsy and no improvement by GFD | 1       | 75 |

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 serology of CD in SA.

The period 1988–1994, indicated that all serology except iTG-Ab (EMA, AGA and ARA) were used during that period (1989–1994). Also, there was no mention for iTG-Ab in the publications of 2001, 2002 and 2003 [73, 71 and 51 respectively]. The first mention of iTG-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 9. Chronological Pattern of Serology & Biopsy

| Year | Frequency |
|------|-----------|
| 1990 | 3         |
| 1991 | 4         |
| 1992 | 5         |
| 1993 | 6         |
| 1994 | 7         |
| 1995 | 8         |
| 1996 | 9         |
| 1997 | 10        |
| 1998 | 11        |
| 1999 | 12        |
| 2000 | 13        |
| 2001 | 14        |
| 2002 | 15        |
| 2003 | 16        |
| 2004 | 17        |
| 2005 | 18        |
| 2006 | 19        |
| 2007 | 20        |
| 2008 | 21        |
| 2009 | 22        |
| 2010 | 23        |
| 2011 | 24        |
| 2012 | 25        |
| 2013 | 26        |
| 2014 | 27        |
| 2015 | 28        |
| 2016 | 29        |
| 2017 | 30        |
| 2018 | 31        |

Figure 5. Chronological Pattern of Serology & Biopsy
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 DQ2/8 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 described, as a good alternative to the traditional ELISA kits [128]. Recently (in 2013), the first electrochemical immunosensor for 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. However, with the start of this century (in 2004) a new test (DGPAs) was introduced for monitoring dietary compliance has been proven to be more sensitive than serology [122].

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). 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 monitoring dietary compliance has been proven to be more sensitive than serology [122].

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 0.05-0.056% [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 T-TG-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 monitoring dietary compliance has been proven to be more sensitive than serology [122].

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). The 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 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 TTG-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 status (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

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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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