ISSN: 0975-833X

Available online at http://www.journalcra.com

International Journal of Current Research
Vol. 11, Issue, 03, pp.2041-2046, March, 2019

DOI: https://doi.org/10.24941/ijcr.34606.03.2019

INTERNATIONAL JOURNAL OF CURRENT RESEARCH

RESEARCH ARTICLE

CELIAC DISEASE IN PATIENTS WITH DOWN SYNDROME IN SAUDI ARABIA: A META-ANALYSIS

***Mohammad-Ayman A. Safi**

Department of Medical Microbiology and Parasitology, Faculty of Medicine, King Abdulaziz University, Jeddah, Saudi Arabia

ARTICLE INFO

Article History:
Received 17th December, 2018
Received in revised form
26th January, 2019
Accepted 17th February, 2019
Published online 31st March. 2019

Key Words:
Saudi Arabia, CD prevalence in DS, Celiac Disease meta analysis, Heterogeneity.

ABSTRACT

Objectives: Although only three studies are available in Saudi Arabia concerning celiac disease (CD) in Down Syndrome (DS), they showed considerable variation in the serological prevalence (4-15.5 %) and in the prevalence of biopsy-proven CD (2-10.7%). Thus, we aim to use meta-analysis to examine the prevalence of celiac disease (CD) in patients with down syndrome (DS) in Saudi Arabia (SA) using meta-analysis for these three studies. **Methods:** We used the comprehensive systematic search through database and journals followed by selection processes. For data analysis we used two programs: 1-The statistical package for social science (IBM SPSS Inc). 2- The Comprehensive Meta-analysis program (CMA). **Results:** The three related articles involved 226 (51-91) DS patients with age range (0.5-18 years) covering children and adolescents. The CD positive patients showed considerable variation (4-15.5%) for the serological prevalence and (2-10.7%) for the prevalence of biopsy-proven CD. By Meta analysis the seroprevalence of CD (one serology at least) was 13.4% with moderate heterogeneity (I^2=46.519), while the prevalence of biopsy-proven CD 9.4% with moderate heterogeneity (I^2=29.229). Anti-tTG was used in all studies; as single in one study; with EMA and AGA in one studies; with EMA and AGA and ARA in one study. **Conclusion:** People who have DS in SA tend to develop CD at rates (9.4%) higher than the global prevalence (5.8%) and far above those in the Saudi general population (1.4%). The prevalence is high enough to motivate screening CD in DS children. There is a significant difference between the reported serologically- proven rates and the reported biopsy- proven rates (p = 0.002).

**Corresponding author:*
Mohammad-Ayman A. Safi

***Citation*: *Mohammad-Ayman A. Safi*, 2019.** "Celiac disease in patients with down syndrome in Saudi Arabia: A meta-analysis", *International Journal of Current Research*, 11, (03), 2041-2046.

INTRODUCTION

Down syndrome (DS), is a trisomy disorder, in which the patient possesses part or all of an extra chromosome 21 (Patterson, 2009 and Hickey *et al*., 2012). The parents of the affected individual are genetically normal (Hammer, 2010). DS is one of the most common chromosome abnormalities in humans (Dahl *et al*., 2013) with a rate of about one per 1,000 annual newborns (Weijerman and de Winter, 2010). The association of DS with celiac disease (CD) and other immune-related disorders is well-recognized (Goldacre *et al*., 2004). Although the international prevalence of CD in DS varies substantially among studies, a systematic review with meta-analysis showed that 5.8 % of patients with DS have biopsy-confirmed celiac disease (Du *et al*., 2017), a rate which is considerably above the global rate (0.7%) of CD among normal populations (Singh *et al.,* 2018). Moreover, a study performed in Tunisia, showed that more than 10% of the DS patients have biopsy-proven CD (Zitouni *et al*., 2003). In the Kingdom of Saudi Arabia, although only three studies (Saadah *et al*., 2012; Mehaidib *et al*., 2011and Al Ruwaily *et al*., 2017) discussed the prevalence of CD in DS (until week 3 of March 2018) (Safi, 2019; Safi and Safi, 2018), the reported CD prevalence showed considerable variation from 4 to 15.5% for the serological prevalence and from 2 to 10.7% for the prevalence of biopsy proven CD. The aim of this study was to examine the prevalence of CD in patients with DS in KSA using meta-analysis for these three studies.

MATERIALS AND METHODS

Systematic search and study selection: We commenced this study at King Abdulaziz University, Jeddah, Kingdom of Saudi Arabia (KSA) in week 3 of March, 2018 as a retrospective systematic review (Safi and Safi, 2018). We conducted database and journal search using the following key words: "celiac disease in Saudi Arabia", "celiac disease in Saudi children" and "prevalence of celiac disease in Saudi Arabia". Articles were obtained via PubMed (US National Library of Medicine, with no specific period), Ovid, EBSCO and scholar Google. Some other related articles were obtained through the library of king Fahd research centre of King Abdulaziz University, and directly from the editorial department of the two local journals (Saudi Journal of Internal Medicine and Journal of King Abdulaziz University Medical Science). Duplication between articles was checked via their titles, author(s) and year of publication. Study selection was performed by two steps of selection. The first selection was for

the inclusion of articles that are concerned with "celiac disease in Saudi Arabia", and their data were recorded using statistical package for social science [IBM SPSS Inc], Version 20. Chicago. The second selection was for the articles concerning the Down syndrome (DS), the data of which were kept as a separate SPSS file and were used in this study.

Statistical Analysis: Data analysis was performed by the statistical package for social science (IBM SPSS Inc), Version 20, Chicago; and by the Comprehensive Meta-analysis program (CMA), Version 3. Software program (Biostat, USA). I squared (I^2) was used to evaluate heterogeneity. I^2 values of 0%, <25%, 25% to 49% and >50% denoted no, low, moderate and high heterogeneity, respectively (Singh *et al*., 2018). The results were illustrated in tabulated form, diagrams and figures. $P < 0.05$ was considered statistical significant in this study.

RESULTS

Selection and characterization of the pertinent studies (Figure 1 and Table 1): The first selection revealed seventy-four articles concerned with CD in KSA (Safi and Safi, 2018), from which three articles (second selection) were obtained concerning CD in DS individuals (Figure 1), These studies were arranged chronologically according to the year of publication; and their characterization is shown in Table 1 and Figure 1.

Regions: The three studies which were arranges according to the region of the study, covered two regions of KSA (Table 1): the western region (Saadah *et al.,* 2012) and Riyadh (AL Mehaidib *et al.,* 2011 and Al Ruwaily *et al.,* 2017). The two articles from Riyadh region were from the same center (King Faisal Specialist Hospital and Research Center).

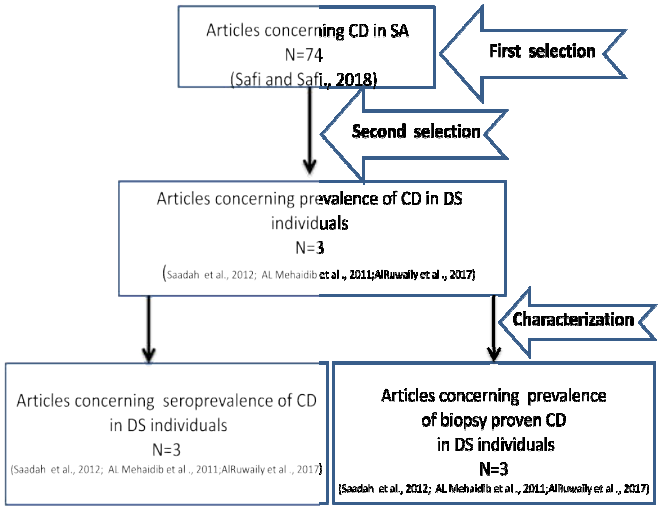
Age ranges and age groups*:* One study (poster) only provided an abstract with no details of age ranges and age groups (Mehaidib *et al.,* 2011). The other two studies (AL Mehaidib *et al.,* 2011 and Al Ruwaily *et al.,* 2017) covered a wide an age-range from 0.5 to 18 years, and age groups of children and adolescents.

Different cohorts and prevalence (rate %) for both seropositivity and biopsy-proven conditions: The different reported serologically-proven rates that were reported by the three studies (Saadah *et al*., 2012; AL Mehaidib *et al*., 2011; AlRuwaily *et al.,* 2017) and the reported biopsy-proven rates are shown in Table 1 and Figure 1. Seropositivity and the biopsy-proven positivity were both reported by the three studies. The reported serologically-proven rates were 4%, (Saadah *et al* ., 2012), 14.28% (AL Mehaidib *et al.,* 2011) and 15.5 % (Al Ruwaily *et al.,* 2017). The reported biopsy-proven rates were 2%, (Saadah *et al* ., 2012), 10.7% (AL Mehaidib *et al.,* 2011) and 12.38% (Al Ruwaily *et al.,* 2017). There was a significant difference between the reported serologically-proven rates and the reported biopsy- proven rates ($p = 0.002$). The pooled serologically-proven rates and the pooled biopsy-proven rates were 9.8% and 8.4% respectively. Table 2 illustrates the cohorts' ranges and rates for both seropositivity and biopsy-proven positivity. The cohort-ranges were 51- 91 patients for both the seropositive and the biopsy-proven conditions. While the seropositivity were 2-13 and the biopsy-proven positivity were 1-9. Table 2 also illustrates a comparison between Meta analysis and traditional statistical analysis for rates of CD in DS population.

Female to male ratio: The ratio of the total females (47) over the total males (16) was 3/1 (Table 1). Region wise (Table 1), the western region showed the highest F/M ratio (12/4=3/1) followed by Riyadh region (35/16 =2.2/1).

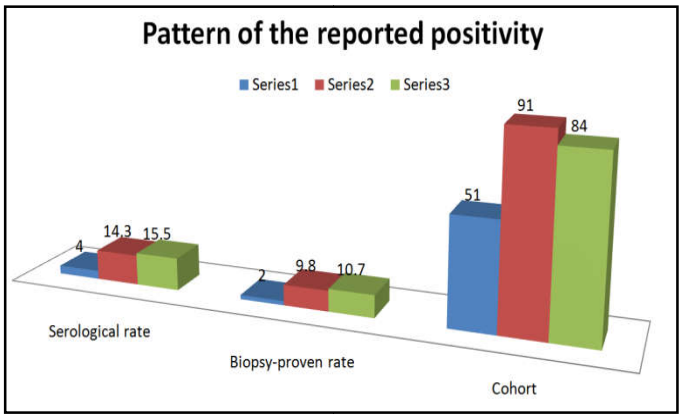
Duration span: Table 1 illustrates that the three included studies (Saadah *et al* ., 2012; AL Mehaidib *et al.,* 2011 and Al Ruwaily *et al.,* 2017) were published between 2011 and 2017, covering the durations of 1/2007-8/2011 (Saadah *et al* ., 2012), a retrospective period up to 2011 (AL Mehaidib *et al.,* 2011) and 2003-2013 (Al Ruwaily *et al.,* 2017).

Pattern of serology and biopsy: As shown in Table 1, anti-tTG was used in all studies; as single in one study (Saadah *et al* ., 2012) ; with EMA and AGA in two studies (AL Mehaidib *et al.,* 2011; AlRuwaily *et al.,* 2017) and with EMA and AGA And ARA in one study (AL Mehaidib *et al.,* 2011). Biopsy confirmation was used in the three studies (Saadah *et al*., 2012; AL Mehaidib *et al.,* 2011; AlRuwaily *et al.,* 2017).



KSA - Kingdom of Saudi Arabia, DS – Down syndrome.

Figure 1 - PRISMA flow-diagram showing the selection process of the pertinent studies. CD- celiac diseases,



Series 1. Saadah *et al.,* 2012; Series 2. AlMehaidib *et al.,* 2011; Series 3. Al Ruwaily *et al.,* 2017

Figure 2. Comparison between the retrieved studies. Cohort and CD prevalence (Seropositivity rate[%] and biopsy- proven rate[%]) of CD among Down Syndrome (DS) patients

Meta analysis: Meta analysis was performed using the Comprehensive Meta-analysis program (CMA). Meta analysis was performed for the three Studies

Table 1. Characterization of the identified studies concerning CD among DS individuals in Saudi Arabia

Study	Year	Region	Serology	tTG*	Biopsy**	Female/Male	Seropositive/ Cohort (Rate%)#	Biopsy-proven positivity/ Cohort (Rate%)#	Refused (without) endoscopy	Age ranges/years (age groups)	Period
Saadah Etalm, 2012	2012	(Western)	tTG-IgA	Yes	Yes	12/4	2/51 (4%)	1/51 (2%)	Non	0.5-16.6 (children and adolescents)	January 2007 – August 2011
AL Mehaidib *et al.,* 2011	2011	(Riyadh)	tTG, Ema, AGA, ARA	Yes	Yes	24/8	13/91 (14.28%)	9/91= (9.8%)	22	None (poster)	retrospectively
Al Ruwaily *et al.,* 2017	2017	(Riyadh)	tTG, EMA, AGA	Yes	Yes	11/8	13/84 (15.5 %)	9/84 (10.7%)	……	1-8(children and adolescents)	2003-2013
Pooled	2011-2017	1/(Western) 2/(Riyadh)		All	All	47/16^	28/226 (12.38)	19/226 (8.4)	22	.5-16.6 (children and adolescents)	2003-2013

A significant difference between the reported serologically- proven rates and the reported biopsy- proven rates ($p = 0.002$).
*Anti-tTG was used in all studies; as single in one study ; with EMA in two studies; with AGA in two studies; with ARA in one study.
** biopsy was used in all studies. ^ F/M =47/16=3/1. ^^ Two studies (AL Mehaidib et al ., 2011 and AlRuwaily et al ., 2017) in Riyadh region and one study (Saadah et al ., 2012) in the western region. tTG – tissue Transglutaminase, AGA - antigliadin antibodies, EmA - endomysial antibodies, IgA- immunoglobulin, ARA - antireticulin antibodies.

Table 2. Rate of CD in DS population; comparison between Meta analysis and traditional statistical analysis

	Serologically			Biopsy -proven		
	Cohort (Range)	Number of positive results (range)	Rate%	Cohort (range)	Number of positive results (range)	Rate%
Number of studies		3	3	3	3	3
Duration	2011-2017	2011-2017	2011-2017	2011-2017	2011-2017	2011-2017
Traditional statistical analysis	226 (51-91)	28 (2-13)	28/226 =12.38%	226 (51-91)	19 (1-9)	19/226 =8.4%
Meta analysis*	(51-91)	(2-13)	13.4%	(51-91)	(1-9)	9.4%

*Meta analysis as in Table 4 and Table 6.

Table 3. Data for Meta analysis for seroprevalence of CD among SS in SA

Study name	Event rate	Sample size	Event rate	Logit event rate	Standard Error
Saadah OI *et al.* 2012	0.040	51	0.040	-3.178	0.715
Al Mehaidib *et al.* 2011	0.142	91	0.142	-1.799	0.300
Al Ruwaily F *et al.* 2017	0.155	84	0.155	-1.696	0.301

Table 4. Prevalence (by fixed and random models) with the heterogeneity of seropositive CD among SS in SA (by fixed and random models)

Model	**Number of studies**	Effect size and 95% internal			Test of null (2-Tail)		Hetrogeneity				Tau – squared			
		Point estimate	Lower limit	Upper limit	Z-value	P-value	Q-value	Df (Q)	P-value	I- Squared	Tau Squared	Standard Error	Variance	Tau
Fixed	3	0.134	0.094	0.188	-9. 141	0.000	3.740	2	0.154	46.519	0.127	0.283	0.080	0.356
Random	3	0.124	0.072	0.204	-6. 421	0.000								

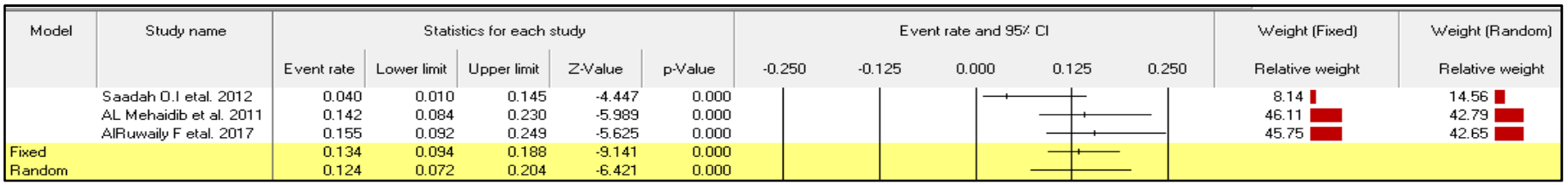


Figure 3. Prevalence of seropositive CD among SS in SA (by fixed and random models) with statistics and relative weight for each study

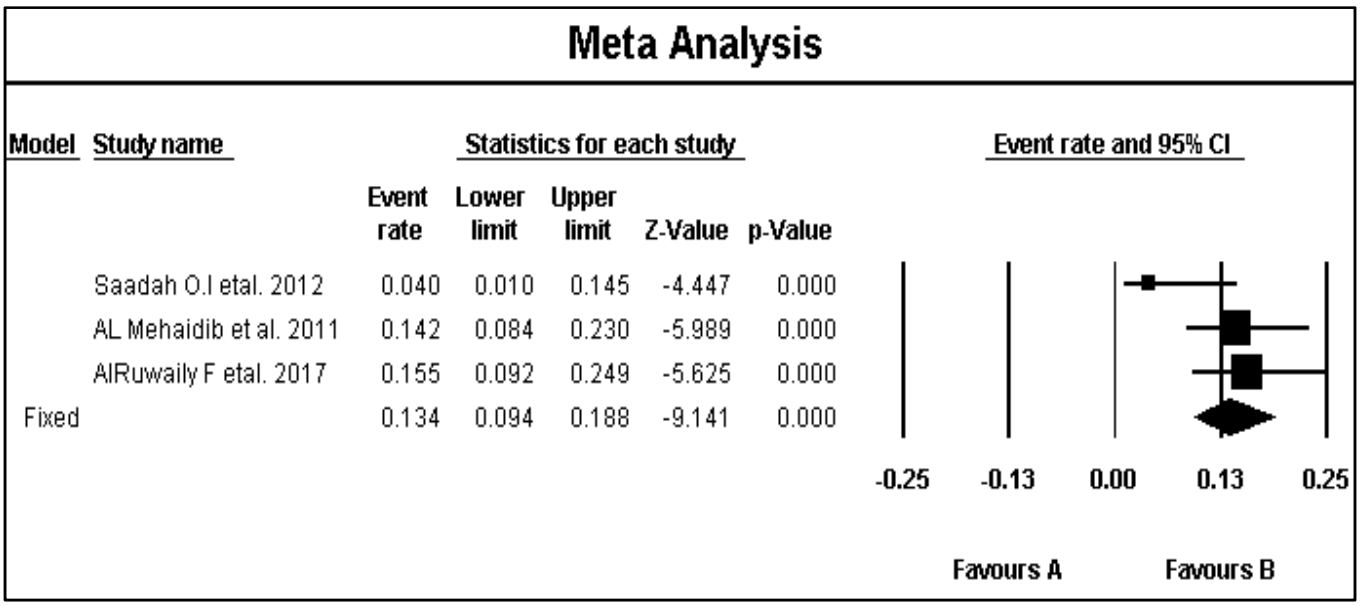


Figure 4. Forest plot for Prevalence of seropositive CD among SS in SA

Table 5. Data for Meta analysis for prevalence of seropositive CD in DS

Study name	Event rate	Sample size	Event rate	Logit event rate	Standard Error
Saadah et al.2012	0.020	51	0.020	-3.892	1.000
Al Mehaidib et al.20111	0.098	91	0.098	-2.220	0.353
Al Ruwaily et al. 20172	0.107	84	0.107	-2.122	0.353

Table 6. Prevalence (by fixed and random models) with the heterogeneity

Model		Effect size and 95% internal			Test of null (2-Tail)		Hetrogeneity				Tau – squared			
	Number of studies	Point estimate	Lower limit	Upper limit	Z-value	P-value	Q-value	Df (Q)	P-value	I- Squared	Tau Squared	Standard Error	Variance	Tau
Fixed	3	0.094	0.960	0.142	-9. 395	0.000	2.826	2	0.243	29.229	0.067	0.305	0.063	0.296
Random	3	0.089	0.051	0.153	-7. 478	0.000								

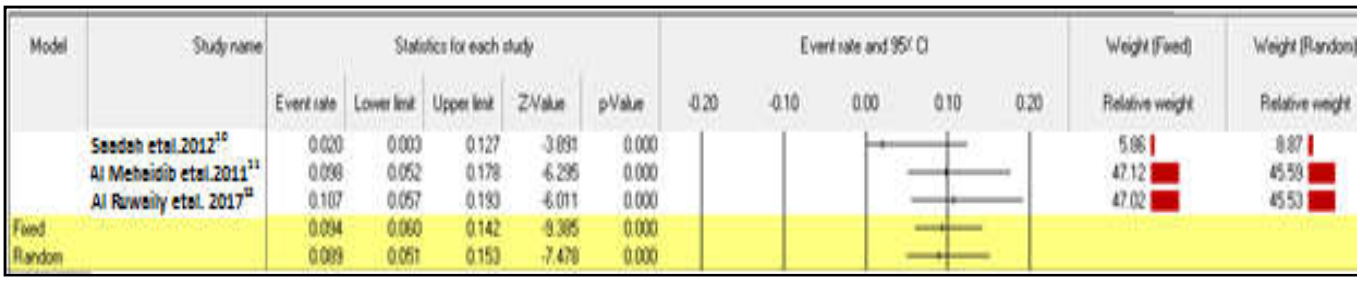


Figure 5. Prevalence of biopsy-proven CD (by fixed and random models) with statistics and relative weight for each study

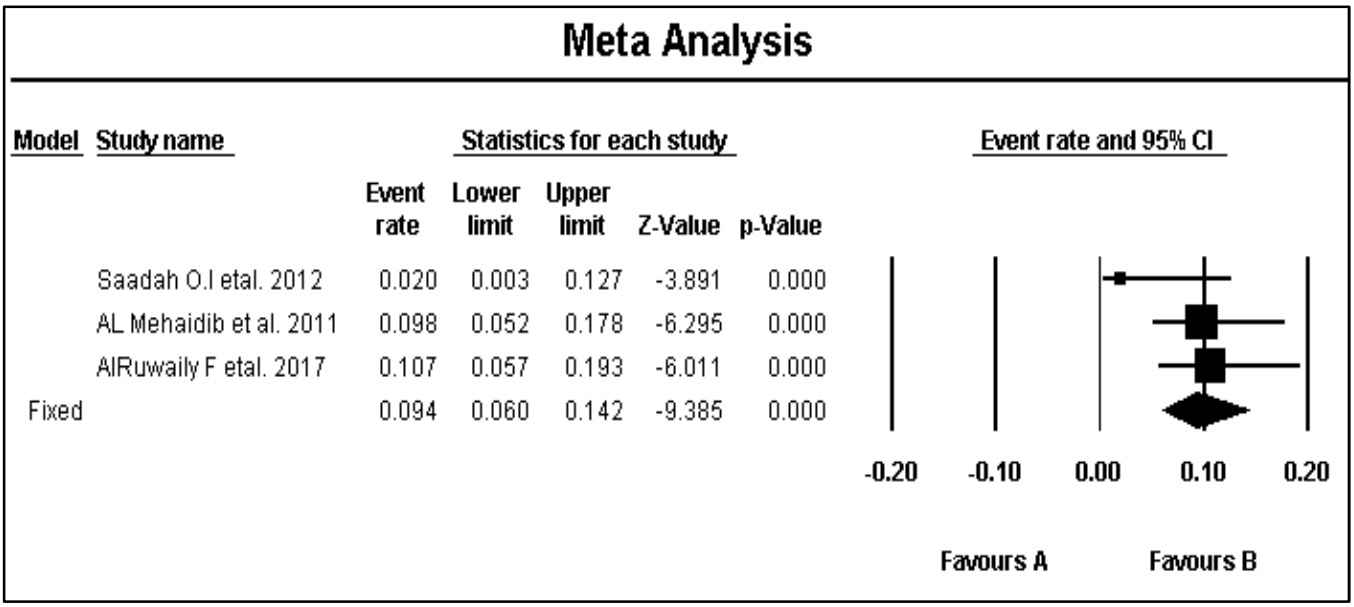


Figure 6. Forest plot for Prevalence of biopsy-proven CD among SS in SA

(Saadah *et al*., 2012; AL Mehaidib *et al.,* 2011; AlRuwaily *et al.,* 2017) concerning the prevalence of serologically-proven CD in DS and the prevalence of biopsy-proven CD in DS. The Meta analysis (by fixed model) of seropositivity (one serology at least) showed a prevalence of 13.4% (95% CI = 9.4–18.8) with moderate heterogeneity (I^2=46.519) (Tables 3 &4 and Figures 3 and 4). While the prevalence of Biopsy-Proven CD 9.4% (95% CI = 9.6–14.2) with moderate heterogeneity (I^2=29.229) (Tables 5 and 6 and Figures 5 & 6).

DISCUSSION

The current study represents the first and only Meta-analysis concerning prevalence of CD among DS in KSA. Following a systematic search, only three articles were found in this respect (Saadah *et al*., 2012; AL Mehaidib *et al*., 2011 and AlRuwaily *et al.,* 2017), that involved 226 (51,91 and 91) DS patients. The studies included one study from the western region (Saadah *et al*., 2012) and two studies from Riyadh region (AL Mehaidib *et al*., 2011; Al Ruwaily *et al*., 2017). The studies were published during the period 2011-2017 and covered different durations [1/2007-8/2011 (Saadah *et al*., 2012), a retrospective period up to 2011 (AL Mehaidib *et al*., 2011) and 2003-2013 (Al Ruwaily *et al.,* 2017)]. Saadah *et al*., 2012 from the western region described 51 children and adolescents (0.5-16.5 Years) between January 2007 and August 2011. Only two patients (2/51=4%) were tTG+ve. Both of them underwent biopsy-examination and only one had positive result (2% Biopsy-confirmed CD). AL Mehaidib *et al.* 2011 from Riyadh (King Faisal Specialist Hospital and Research Center), described in his poster the retrospective seropositivity of 91 Saudi DS children according to the following pattern {45/91(49.45%) AGAG, 27/91(29.67%) AGAA, 6/91(6.59%) ARA, 13/91(14.28 %) tTG, 6/91(6.59%) EMA}. Twenty three patients (9.5%) had biopsies with 9.8% (9/91) biopsy-confirmed CD. Al Ruwaily *et al*., 2017 from the same center in Riyadh, between 2003 and 2013, described the seropositivity (84 children and adolescents (1-18 Years) as 44/84 (52.38%) AGAG, 27/84 (32.14%) AGAA, 13/84(15.5%) tTG, 12/84(14.28%) EMA. Twenty two (of the positive tTg or EMA) had biopsies with a rate of 10.7% (9/84) for the biopsy-confirmed CD.

The seropositivity of the three studies showed a considerable variation between the western region (4%) (Saadah *et al*., 2012) and Riyadh region [14.28% (AL Mehaidib *et al.,* 2011) and 15.5% (AlRuwaily *et al*., 2017). In one study (Saadah *et al*., 2012), all of the seropositive patients had endoscopies with biopsies. In another study (AL Mehaidib *et al*., 2011) only 23 among 45 patients (who had positive serological marker(s)) had endoscopies with biopsies and 22 patients refused (without) the endoscopy. In the third study (AlRuwaily *et al*., 2017), biopsy was performed for 22 patients who tested positive for EMA or tTG antibodies while 3 patients (without biopsies) refused the endoscopy. The three studies were recent (2011, 2012 and 2017) if compared with international studies that go back to 1990 (Storm, 1990). In Al-Ruwailiy *et al*. 2017, biopsy was performed in 22 patients who tensed positive for EMA or tTG (13+12=25), indicating that 3 seropositive patients refused/without endoscopy. On the other hand, AlMehaidib *et al*. 2011 mentioned that biopsy was done in 23 patients who had positive serological marker, without any specification; while in the study of Saadah *et al*., 2012, all of the seroppositive patients had endoscopies with biopsies. This type of absence of uniformly performing biopsies in seropositive DS patients, can be considered as one limitation of the identified study, and consequently of the current Meta-analysis. The second limitation is the limited number of the involved studies (only 3) with limited number of the involved DS patients (only 226). In the current Meta- analysis the seroprevalence of CD (one serology at least) was 13.4% (95% CI = 9.4–18.8) with moderate (I^2=46.519), while the prevalence of Biopsy-Proven CD 9.4% (95% CI = 6.0–14.2) with moderate heterogeneity (I^2=29.2). The latter result (9.4%) is higher than the global Meta- analysis which revealed a prevalence of 5.8 % (95 % CI = 4.7-7.2 %) for the biopsy-confirmed CD in patients with DS (Du *et al*., 2017). Vice versa, international studies found an increased incidence of DS in CD compared to the general population (Marild *et al*., 2013 and Dias and Walker-Smith, 1990). In KSA, no literature was observed concerning DS in CD. One article was published in 2002 (Qari, 2002) describing the clinical presentation of sixteen adult CD (in the western region of KSA) with osteomalacia, iron deficiency anemia, diarrhea, malabsorption associated with growth failure and other autoimmune diseases (Insulin-dependent diabetes mellitus, Hashimoto's hypothyroidism and dermatitis herpetiformis), with no mention of DS. Some pro-inflammatory cytokine (including alpha tumor necrosis factor [αTNF], beta interleukin-1 [IL-1β] and interferon-gamma [IFN]) are present in increase levels in DS patients (Broers *et al.,* 2012; Carta *et al*.,2002 and Zaki *et al.,* 2017) and may contribute to the occurrence of CD in DS patients (Du *et al*., 2017). In addition to the distribution similarity of HLA genotypes (HLA-DQ2 and HLA-DQ8 haplotypes) in CD and DS patients compared to the general population (Sollid and Lie, 2005).

Conclusion

We conclude a high prevalence of CD in DS individuals in KSA; almost one CD in every ten DS patients, which is much higher than CD in normal population in KSA (Safi, 2018) and the global prevalence of CD in DS (Du *et al*., 2017); which is in favor of CD screening in asymptomatic DS children (Hill *et al*., 2005) in DS children with CD-related symptoms (Bull, 2011). There is a significant difference between the reported serologically- proven rates and the reported biopsy-proven rates (p = 0.002).

Recommendation

- Only three studies are present concerning CD among DS in KSA, with limited number of the involved DS patients (only 226). Which cover only two regions, Riyadh region and the western region, and representing only one center in each of these two regions. Thus, establishing studies in other regions of SA, and/or a notional study to cover most regions of SA is recommended.
- Study of influence of some cytokines, such as the pro-inflamatory cytokine including alpha tumor necrosis factor [αTNF], beta interleukin-1 [IL-1β] and interferon-gamma [IFN]) that are present in increase levels in DS patients (Carta *et al*., 2002; Zaki *et al*., 2017 and Sollid and Lie., 2005) and may contribute to the occurrence of CD in DS patients (Du *e et al*., 2017).
- Study of the distribution similarity of HLA genotypes (HLA-DQ2 and HLA-DQ8 haplotypes) in CD and DS patients compared to the general population (Sollid and Lie., 2005). Keeping in mind the existence of a recent

interesting study in SA (Al-Hussaini *et al*., 2018) which reported one of the highest frequencies of CD-predisposing HLA-DQ genotypes among healthy general populations (52.7%) worldwide.

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

Disclosure: 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 author declares that there is no conflict of interest.

Financialsupportandsponsorship: Nil.

REFERENCES

AL Mehaidib, A., Kattan, H., AL Rrowaily, F. and AL Dekhail, W. 2011. Prevalence of celiac disease in Saudi children with Down syndrome: a retrospective study. *J Gastroenterol Hepatol.,* 26 (Suppl. 5): 16–288. Poster Abstract 306. page 84.

Al-Hussaini, A., Alharthi, H., Osman, A., Eltayeb-Elsheikh, N. and Chentoufi, A. 2018. Genetic susceptibility for celiac disease is highly prevalent in the Saudi population. *Saudi J Gastroenterol.,* 24(5):268-273.

AlRuwaily, F., Kattan, HA., AlMehaidib, A M. and AlDekhail, W. 2017. Prevalence of celiac disease in Saudi children with Down syndrome: A retrospective study. *International Journal of Pediatrics and Adolescent Medicine,* 2017; 4(2): 51-53.

Broers, CJ., Gemke, RJ., Weijerman, ME., van der Sluijs, KF. and van Furth, AM. 2012. Increased pro-inflammatory cytokine production in Down Syndrome children upon stimulation with live influenza A virus. *J Clin Immunol*., 32:323-329.

Bull, MJ. 2011. Committee on Genetics. Health supervision for children with Down syndrome. *Pediatrics,* 128:393-406.

Carta, MG., Serra, P., Ghiani, A., Manca, E., Hardoy, MC., Del Giacco, GS., Diaz, G., Carpiniello, B. and Manconi, PE. 2002. Chemokines and pro-inflammatory cytokines in Down's syndrome: an early marker for Alzheimer-type dementia? *Psychother Psychosom,* 71:233-236.

Dias, JA. and Walker-Smith, J. 1990. Down's syndrome and celiac disease. *J Pediatr Gastroenterol Nutr.,* 10:41-43.

Du, Y., Shan, LF., Cao, ZZ., Feng, JC. and Cheng Y. 2017. Prevalence of celiac disease in patients with Down syndrome: a meta-analysis. *Oncotarget*, 9(4):5387-5396. PMID: 29435186.

Goldacre, MJ., Wotton, CJ., Seagroatt, V. and Yeates, D. 2004. Cancers and immune related diseases associated with Down's syndrome: a record linkage study. *Arch Dis Child.,* 89: 1014-101.

Hammer, edited by Stephen J. McPhee, Gary D. 2010. "Pathophysiology of Selected Genetic Diseases". Pathophysiology of disease : an introduction to clinical medicine (6th ed.). New York: McGraw-Hill Medical. pp. Chapter 2.

Hickey, F., Hickey, E. and Summar, KL. 2012. "Medical update for children with Down syndrome for the pediatrician and family practitioner". *Advances in Pediatrics,* 59 (1): 137–57. PMID 22789577.

Hill, ID., Dirks, MH., Liptak, GS., Colletti, RB., Fasano, A., Guandalini, S., Hoffenberg, EJ., Horvath, K., Murray, JA., Pivor, M. and Seidman, EG. 2005. North American Society for Pediatric Gastroenterology, Hepatology and Nutrition. Guideline for the diagnosis and treatment of celiac disease in children: recommendations of the North American Society for Pediatric Gastroenterology, Hepatology and Nutrition. *J Pediatr Gastroenterol Nutr.,* 40:1-19

Malt, EA., Dahl, RC., Haugsand, TM., Ulvestad, IH., Emilsen, NM., Hansen, B.,Cardenas, YE., Skøld, RO., Thorsen, AT. and Davidsen, EM. Feb 5, 2013. "Health and disease in adults with Down syndrome". Tidsskrift for den Norske Laegeforening : Tidsskrift for Praktisk Medicin, NY Raekke. 133 (3): 290–4. PMID 23381164.

Marild, K., Stephansson, O., Grahnquist, L., Cnattingius, S., Soderman, G. and Ludvigsson, JF. 2013. Down syndrome is associated with elevated risk of celiac disease: a nationwide casecontrol study. *J Pediatr.,* 163:237-242.

Patterson, D. 2009. "Molecular genetic analysis of Down syndrome". *Human Genetics,* 126 (1): 195–214. PMID 19526251.

Qari, FA. 2002. Clinical presentation of adult celiac disease in Western Saudi Arabia. *Saudi Med J.,* 23: 1514-1517.

Saadah, OI., Al-Aama, JY., Alaifan, MA., Bin Talib, YY. and Al-Mughales, JA. 2012. Prevalence of celiac disease in children with Down syndrome screened by anti-tissue transglutaminase antibodies. *Saudi Med J.,* 33(2):208-10. PMID: 22327766.

Safi, M-A A. 2018. Prevalence of Celiac disease in Saudi Arabia: meta-analysis. GVI, 3(1). Accessed September 30, 2018 <https://www.oatext.com/pdf/GVI-3-134.pdf>

Safi, M-A. 2019. Celiac disease among at-risk individuals in Saudi Arabia. *Saudi Med J.,* 40(1):9-18. <https://www.smj.org.sa/index.php/smj/article/view/smj.2019.1.23892/11168>.

Safi, M-A A. and Safi, HM-A. 2018. Celiac disease and its serological pattern in Saudi Arabia; A systematic review. Global Vaccines and Immunology 3: 1-15. https://www.oatext.com/pdf/GVI-3-133.pdf.

Singh, P., Arora, A., Strand, TA., Leffler, DA., Catassi, C., Green, PH., Kelly, CP., Ahuja, V. and Makharia, GK. 2018. Global Prevalence of Celiac Disease: Systematic Review and Meta-analysis. *Clin Gastroenterol Hepatol.,* 16(6):823-836.PMID:29551598.

Sollid, LM. and Lie, BA. 2005. Celiac disease genetics: current concepts and practical applications. *Clin Gastroenterol Hepatol.,* 3:843-851.

Storm, W. 1990. Prevalence and diagnostic significance of gliadin antibodies in children with Down syndrome. *Eur J Pediatr.,* 149:833-834.

Weijerman, ME. and de Winter, JP. 2010. "Clinical practice . The care of children with Down syndrome" . *European Journal of Pediatrics,* 169 (12): 1445–52 PMID 20632187.

Zaki, ME., El-Bassyouni, HT., Tosson, AM., Youness, E. and Hussein, J. 2017. Coenzyme Q10 and pro-inflammatory markers in children with Down syndrome: clinical and biochemical aspects. *J Pediatr (Rio J).,* 93:100-104.

Zitouni, M., Gharbi Yermani, M., Laadhar Kharrat, L., Kallel Sellami, M., Gandoura, N. and Makni, S. 2003. Email Author. Prevalence of serological markers related to celiac disease in patients with trisomy 21 in Tunisia (Article). [Prévalence des marqueurs sérologiques de la maladie cœliaque au cours de la trisomie 21 en Tunisie]. Annales de *Biologie Clinique*, Volume 61, Issue 6, Pages 673-677.

****