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RESEARCH ARTICLE

CELIAC DISEASE AMONG SHORT STATURE PATIENTS IN SAUDI ARABIA, META-ANALYSIS

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ABSTRACT

Objectives: Previously, we retrieved sixteen studied concerning celiac disease (CD) among at-risk individuals in Saudi Arabia (SA) involving five studies concerning CD among short stature (SS) individuals. We present a characterization and meta-analysis for these five studies. **Methods:** Data from the relevant studies were analyzed using the Statistical Package for Social Sciences (IBM SPSS Inc) and the Comprehensive Meta-analysis (CMA) program. This study was conducted at King Abdulaziz University, Jeddah, SA from March to July 2018. **Results:** All studies involved seroscreening, while endoscopies were used in three studies. The prevalence of seropositive-CD was 16.1% (95% confidence interval [CI]=11.7–21.7)with high heterogeneity (I^2=83.576), while the prevalence of biopsy-proven CD was 6.7% (95% CI=4.6–9.5) with lower heterogeneity (I^2=50.944). Anti-transglutaminase (Anti-tTG) antibodies were used in two studies (with anti-gliadin [AGA] in one and anti-endomysial [EMA] and AGA in the other). EMA alone was used in two studies, and one study was without details**.** Four studies occurred in the Riyadh region, and one study was in the Western region. Females with CD were 1.5 times more prevalent than males. Study subjects' ages were 1.37–21 years. **Conclusion:** The prevalence of biopsy-proven CD (6.7%) was within the global range of 2.9% to 8.3% while the seroprevalence (16.1%) was high. No significant difference between the reported (by the studies) serologically-proven rates and biopsy-proven rates was noted (p = 0.205).

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INTRODUCTION

Short stature (SS) is a common endocrine problem (Wilton, 1991 and Colaco, 1991), presenting with multiple difficulties (psycological, emotional, obstetric with high maternal mortality) (Jiang, 1999 and Sokal *et al*., 1991). SS in children is considered among the at-risk group of celiac disease (CD), representing the most frequent extra-intestinal symptoms of CD following iron-deficiency anemia (Bottaro *et al*., 1999). In SS of CD, growth recovery can be prompt after gluten withdrawal (Troncone *et al*., 2016). In SS patients, the prevalence of CD was estimated to be more common than growth hormone deficiency (GHD) or any other organic disorders (Meazza, 2009). Globally, CD in SS ranges from 0.05% to 59.1% depending on the region of the study (Bonamico, 1992 and Rossi, 1993); a narrower range was also reported to be from 2.9% to 8.3% (Meazza, 2009). Additionally, it is possible to find growth retardation in an asymptomatic CD even with normal CD serological markers. This type of case requires checking for the presence of risk alleles (HLA genotyping) after excluding other malabsorption-related conditions followed by continuous monitoring for the development of CD serological markers (Bozzola, 2014). In Saudi Arabia (Week 3 of March) (Safi, 2019), five articles were found to be specifically concerned with CD among SS individuals (Saadah, 2004; Assiri, 2010; Al-Ruhaily and Malabu, 2009; Al-Jurayyan, 2012; Al-Jurayyan, 2013), for which the current study represents a meta-analysis for the pool of these five studies.

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Data and Methods

This study was conducted at King Abdulaziz University, Jeddah, Saudi Arabia (SA) on Week 3 of March, 2018.The involved data (of the related five studies) were part of a previous retrospective Analytical Review (Safi, 2019). Datawere stored in a separate SPSS (statistical package for social sciences) file and used in this study.

Strategy for systematic search and study selection

Three steps were used in the systematic search.

- A comprehensive 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". This step was described in tails in our previous analytical review (Safi and Safi, 2018) in which 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 Abdul-Aziz University Medical Science. Duplication between articles was checked via their titles, author(s) and year of publication.

- A process of first selection (inclusion/exclusion for articles concerning "celiac disease in Saudi Arabia", and their data were recorded using statistical package for social science [IBM SPSS Inc], Version 20, Chicago, that was also detailed in our previous systematic review (Safi and Safi, 2018).
- A process of second selection was for the articles that are concerned with the short stature (SS)] and kept as a separate SPSS file that was used in this study.

Statistical Analysis

Data analysis was performed using the statistical package for social sciences (IBM SPSS Inc), Version 20, Chicago and withthe Comprehensive Meta-analysis program (CMA), Version 3 software program (Biostat, USA). I squared (I^2) was used to evaluate heterogeneity. Interpretation of I^2 values follows the following pattern: (1) 0% (no heterogeneity);(2) <25% (low heterogeneity); (3) 25% to 49% (moderate heterogeneity); and (4) >50% (high heterogeneity) (Singh 2018). The results were illustrated in tabulated form, diagrams, and figures. Results were considered significant if the p-value was <0.05.

Accordingly, study individuals were divided into three groups based on age: (1) pediatric (<12 years in male, <10 years in female); (2) adults and adolescents (>12 years); and (3) pediatrics with adults (and/or adolescents) (>1 year [or 1–18 years]).

RESULTS

*Selection and characterization of the pertinent studies (Figure 1 and Table 1).*Following the first selection, seventy-four articles were retrieved that were concerned with CD in KSA, from which 5 articles (second selection) were retrieved concerning CD in SS individuals (Figure 1), The data from these studies were recorded using the SPSS Version 20. Characterization of these studies is shown in Figure 1 and Table 1.These studies were arranged chronologically according to the year of publication, covered a wide range of ages (1.37–21 years) and three age groups (Table 1): (1) children (4.5–12 years) (one article); (2) children and adolescents (1.37–17.6 years) (three articles); and (3) children and adolescents and adults (12–21 years) (1 article). These studies covered two regions in SA (Table 1): (1) Riyadh (four articles) and the Western region (one article). Table 1 also illustrates the different cohorts and prevalence for both seropositivity and biopsy-proven conditions. Pattern of the reported (by the studies) positivity is shown in Table 1 and Figure 2. Seropositivity was reported by three studies (Saadah, 2004; Assiri, 2010 and Al-Ruhaily and Malabu, 2009) as 24%, 4% and 16.5%). While biopsy-proven positivity was reported by the five studies (Saadah *et al.,* 2004; Assiri, 2010; Al-Ruhaily and Malabu, 2009; Al-Jurayyan, 2012; Al-Jurayyan *et al*., 2013) as 9.5%, 4%, 10.9%, 2.5% and 4.5%. Table 2 illustrates the total cohorts, total number of positivity values, and both seropositivity and biopsy-proven positivity rates. The total cohort of seropositivity was 258 (range was 63–104) with a total positivity of 34 and positivity rate of 13.17% (Table 2),

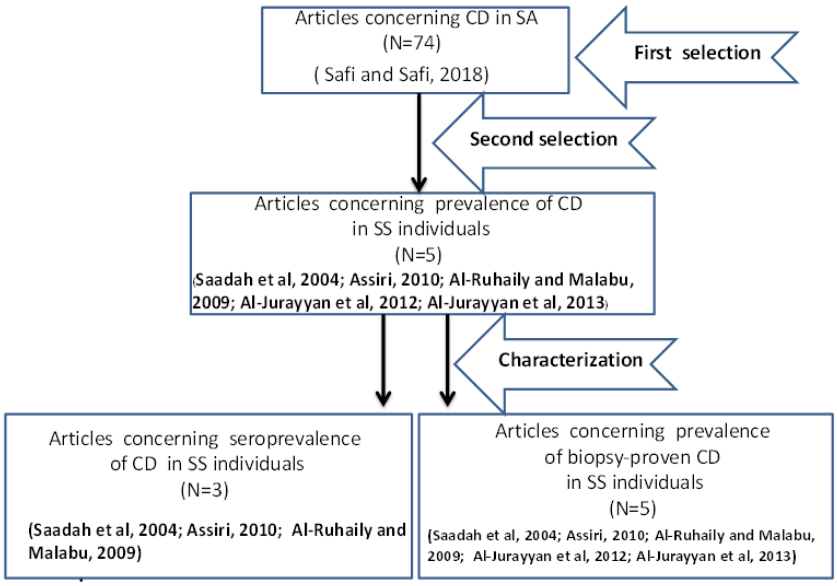


Figure 1. PRISMA flow-diagram showing the selection process of the pertinent studies CD- celiac diseases, KSA - Kingdom of Saudi Arabia, SS - short stature

Strategy for age grouping

Puberty is defined with a cut-off level of 10 and 12 years for females and males, respectively (Al-Agha *et al*., 2015). The term children and adolescent denotes individuals who were 1–18 years (Al-Agha, 2015, Saadah, 2012 and Saadah, 2012).

while the total biopsy-proven cohort was 478 (range 63–110 with a total positivity of 28 and positivity rate of 5.85%). However, higher rates were obtained by meta-analysis for both seropositivity (16.1%) and biopsy-proven positivity (6.7%) (Table 2, 4, and 6).

Table 1. Characterization of the identified studies concerningthe prevalence of celiac disease (CD) in short Stature (SS) populationin Saudi Arabia

Studyreference number (region)	Year of publication	Region	Serology	TTG*	Biopsy**	Female /Male	Seropositivity/ Cohort (Rate%)#	Biopsy-proven positivity/ Cohort (Rate%)#	Refused (without) endoscopy	Age ranges/years (age groups)	Period
Saadah, etal	2004	(Western)	TTG,AGA	Yes	Yes	NS	15/63 (24%)	6/63 (9.5%)	3	1.37-17.6 (children & adolescents)	retrospectively
Al-Ruhaily, Malabu	2009	(Riyadh)	EMA	No	Yes	NS	4/104 (4%)	4/104 (4%)	……	12-21 (children & adolescents & adults)	January 1997 - December 2006.
Assiri	2010	(Riyadh)	TTG-IgA, EMA-IgA,	Yes	Yes	11/1	15/91 (16.5%)	10/91 (10.9%)	……	4.5-12 (children)	August 2002 - December 2008
Al-Jurayyanetal	2012	(Riyadh)	celiac screening	?	Yes	2/88	……	3/110 (2.5%)	……	2.5-14 (children & adolescents)	January 1990 - December 2009
Al-Jurayyan *et al*	2013	(Riyadh)	EMA	No	Yes	NS	……	5/110 (4.5%)	……	2.5-14 (children & adolescents)	January 1990 - December 2009
						13/9^	34/258 (13.17%)	28/478 (5.5%)	3		

No significant difference between the reported serologically- proven rates and the reported biopsy- proven rates (p = 0.3).*tTG was used in two studies; with AGA in 1; with EMA and AGA in 1. EMA alone in 2 studies, and one study without details.** biopsy was used in all studies.^ F/M =13/9=1.5/1. ^^ Four studies (Assiri, 2010; Al-Ruhaily and Malabu, 2009; Al-Jurayyan *et al*., 2012; Al-Jurayyan *et al*., 2013) in Riyadh region and one study in the western region (Saadah *et al*., 2004). tTG–tissue Transglutaminase, AGA - antigliadin antibodies, EmA - endomysial antibodies, IgA- immunoglobulin, ARA - antireticulin antibodies.

Table 2. Rate of CD in short stature (SS) population in Saudi Arabia; comparison between Meta analysis and traditional statistical analysis

Number of studies(Duration)		**Cohort(Range)**		**Positivity(Range)**		**Reported prevalence ranges**	**Prevalence By Meta-analysis* (Heterogeneity=I^2)***		**Prevalence By traditional analysis=positivity/cohort**	
Serologically	Biopsy-proven	Serologically	Biopsy-proven	Serologically	Biopsy-proven		Serologically	Biopsy-proven	Serologically	Biopsy-proven
3 (2004-2010)	5 (2004-2013)	258 (63-104)	478 (63-110)	34% (4-15)	28% (3-10)	4%-19%	16. 1% (83.576)	6.7% (50.944)	13. 17%	5.85%

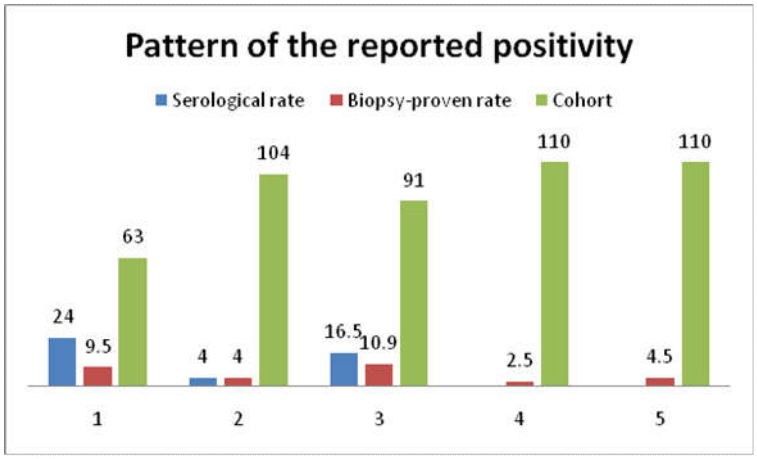
*Meta analysis and Heterogeneity=I^2as in Table 4 and Table 5.

Table 3. Data for Meta analysis of seropositivity prevalence for CD among Short SS in SA

	Study name	Event rate	Sample size	Event rate	Logit event rate	Standard Error
1	Al-RuhailyD,Malabu 2009	0.040	104	0.040	-3.178	0.500
2	Assiri AM 2010	0.165	91	0.165	-1.621	0.282
3	Saadah OI etal.2004	0.240	63	0.240	-1.153	0.295

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

.Model		. Effect size and 95% internal .			Test of null (2-Tail) .	.	Heterogeniety		. .		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	0.161	0.117	0.217	-8. 740	0.000	12.177	2	0.002	83.576	0.594	0.750	0.562	0.771
Random	3	0.130	0.054	0.282	-3. 866	0.000								



1-Saadah *et al* ;2004
2-Al-Ruhaily & Malabu; 2009
3-Assiri (2010)
4-Al-Jurayyan *et al*; 2012
5-Al-Jurayyan *et al*; 2013

Figure 2. Cohort and CD prevalence (Seropositivityrate[%] and biopsy- proven rate[%]) of CD among Short Status (SS) patients in the retrieved studies

Model	Study name	Statistics for each study					Event rate and 95% CI	Weight (Fixed)	Weight (Random)
		Event rate	Lower limit	Upper limit	Z-Value	p-Value	-0.40 -0.20 0.00 0.20 0.40	Relative weight	Relative weight
	Al-Ruhaily AD1, Malabu UH. 2009	0.040	0.015	0.100	-6.351	0.000		14.25	28.63
	Assiri AM 2010	0.165	0.102	0.256	-5.741	0.000		44.74	35.88
	Saadah, O. I etal 2004	0.240	0.150	0.360	-3.907	0.000		41.01	35.49
Fixed		0.161	0.117	0.217	-8.740	0.000			
Random		0.130	0.054	0.282	-3.866	0.000			

Figure 3. Prevalence (by fixed and random models) with statistics and relative weight for each study

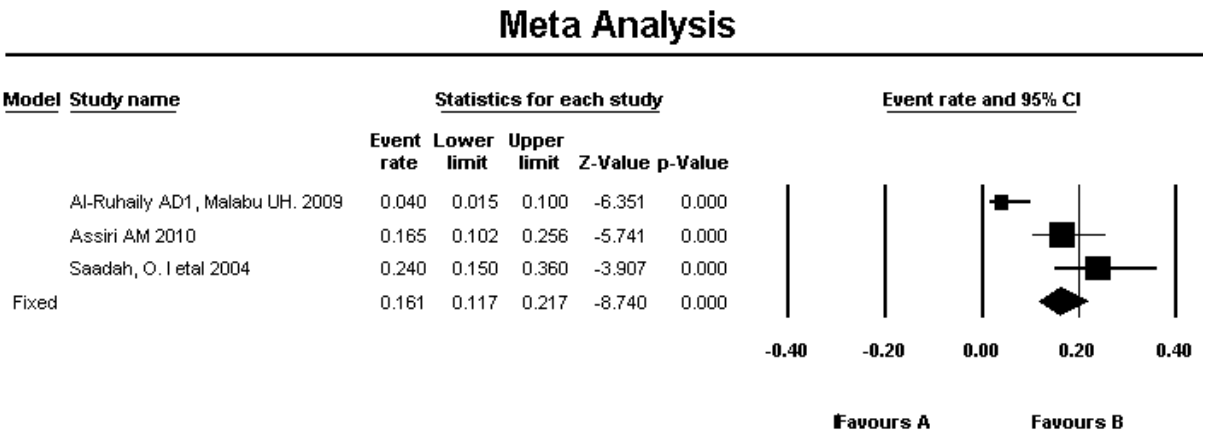


Figure 4. Forest plot for Prevalence of seropositive CD among SS in SA

Table 5. Data for Meta analysis of prevalence of biopsy-proven CD among SS in SA

	Study name	Event rate	Sample size	Event rate	Logit event rate	Standard Error
1	Al-Jurayyan N NA.etal2016	0.025	110	0.025	-3.664	0.611
2	Al-Ruhaily AD1, Malabu UH. 2009	0.040	104	0.040	-2.178	0.500
3	Assiri AM 2010	0.109	91	0.109	-2.101	0.336
4	Saadah, O. I etal 2004	0.095	63	0.095	-3.254	0.430
5	Al-JurayyanNAM.etal2013	0.045	110	0.045	--3.055	0.460

Meta-analysis

A meta-analysis was performed using the Comprehensive Meta-analysis (CMA) program. A meta-analysis was used for the three studies concerning CD seroprevalence in SS individuals (Saadah *et al*., 2004; Assiri, 2010; Al-Ruhaily and Malabu, 2009) and for the five studies concerning the prevalence of biopsy-proven CD in SS individuals (Saadah *et al*., 2004; Assiri, 2010; Al-Ruhaily and Malabu , 2009; Al-Jurayyan *et al*., 2012; Al-Jurayyan *et al*., 2013). The meta-analysis of seropositivity prevalence (Tables 3 and 4 and Figures 3 and 4) showed that CD prevalence (by fixed model) for the serologically proven CD (one serology at least) was 16.1% (95% CI=11.7–21.7) with high heterogeneity

(I^2=83.576) while the meta-analysis for the prevalence of biopsy-proven positivity (for five articles by fixed model) (Tables 5 and 6 and Figures 5 and 6) was 6.7% (95% CI=4.6–9.5) with a lower heterogeneity (I^2=50.944).

Female to male ratio: Gender information was found in two studies (Table 2).The ratio of total females (13) over total males (9) was 1.5/1 (Tables 2). Both studies were from the Riyadh region.

Duration span (Table 1)

The five included studies were published between 2004 and 2013 and covered a long period from 1990 until 2009 with one retrospective study without year limitation (Saadah, 2004).

most frequent after iron-deficiency anemia (Bottaro, 1999) in which growth recovery can be stimulated by gluten withdrawal (Troncone, 2010). CD in SS patients is more common than GHD or any other organic disorders (Meazza, 2009). Globally, CD in SS ranges from 0.05% to 59.1% depending on the region of the study (Bonamico, 1992 and Rossi, 1993); however, narrower rangeswere also reported to be from 2.9% to 8.3% (Meazza, 2009)[7]. The prevalence (according to the present meta-analysis) of biopsy-proven CD in SS in SA (6.7%) fits within this range, while the prevalence of the serologically-proven CD in SS was much higher (16.1%). Rates of CD in SS that were reported by the different retrieved studies for both the serologically-proven CD in SS (range = 4%–24%) and for the biopsy-proven CD in SS (range = 2.5% – 19.9%) demonstrate high heterogeneity (I^2=83.576 and

Table 6. Prevalence (by fixed and random models) with the heterogeneity by Meta analysis of biopsy-proven CD among SS in SA

Model		Effect size and 95% internal			Test of null (2-Tail)		Heterogeniety				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	5	0.067	0.046	0.095	-13. 372	0.000	8.154	4	0.096	50.944	0.211	0.297	0.088	0.459
Random	5	0.060	0.035	0.102	-9. 659	0.000								

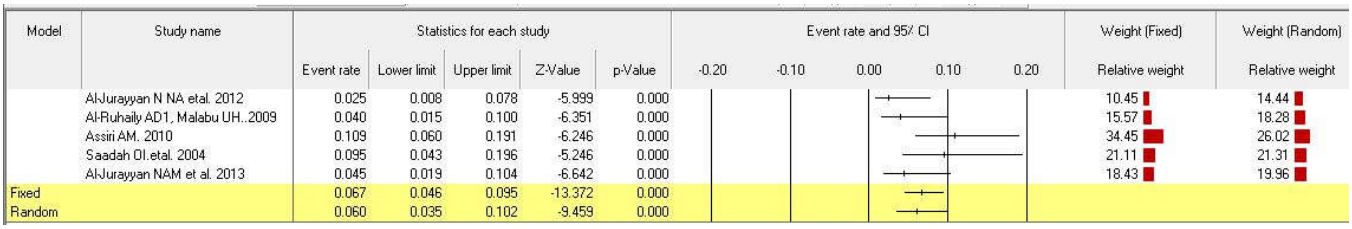


Figure 5. Prevalence of biopsy-proven CD (by fixed and random models) with statistics and relative weight for each study

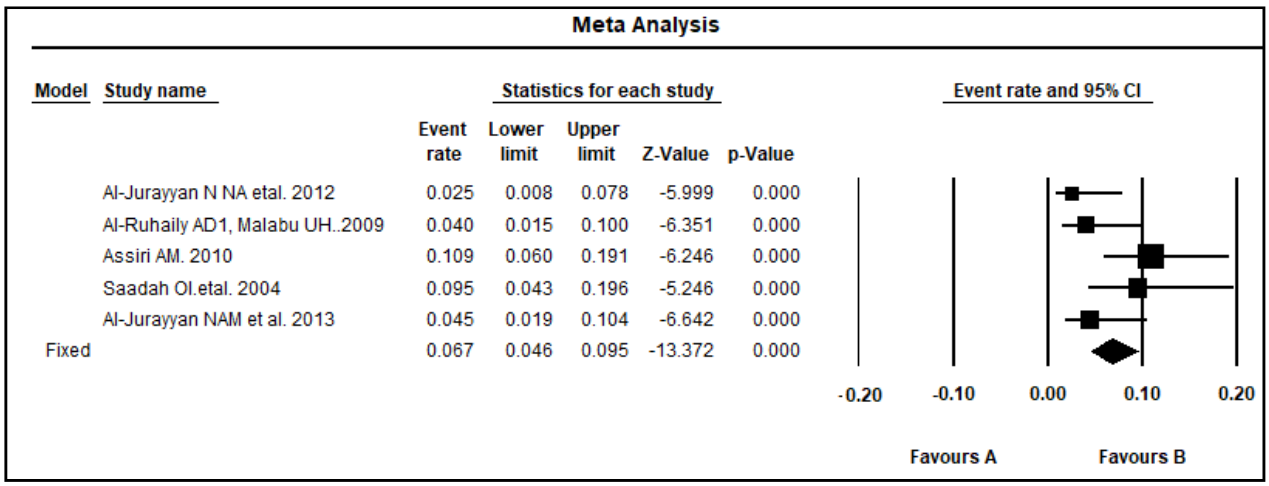


Figure 6. Forest plot for Prevalence of biopsy-proven CD among SS in SA

Pattern of serology and biopsy

Anti-tTG was used in two studies with AGA in one study and with EMA and AGA in the other one. EMA was used alone in two studies, and one study did not have details while biopsies were done in all of the studies (Table 2).

DISCUSSION

This study represents the first and only meta-analysis for the CD status among SS individuals in SA. Among the extra-intestinal symptoms in CD, SS in children appears to be the

I^2=50.944, respectively). On the other hand, it is not uncommon to have CD in a CD-asymptomatic child that has growth retardation even if the CD serological markers were normal; thus, in such case, after excluding other malabsorption conditions, the presence of risk alleles (HLA genotyping for DQ2/ DQ8 haplotypes) should be checked, and the patient should be strictly followed for the development of CD serological markers (Bozzola *et al*., 2014). Malnutrition such as zinc malabsorption was considered the reason behind the growth retardation in CD (Catassi, and Fasano, 2004), and autoimmune disorders of the pituitary gland may also be another pathogenetic mechanism for delayed growth in CD

children (Collin *et al*., 2001) which may be attributed to the existence of shared epitopes between AGA and self-antigens (Kamradt and Mitchison 2001). In this respect, an association has been reported between presence (positivity) of *anti-pituitary antibodies* (in newly diagnosed CD patients with height growth impairment) and a reduction of insulin-like growth factor-1 (IGF-I) levels (Delvecchio, 2010). *Anti-pituitary and anti- hypothalamus autoantibodies* (in CD) have also been detected in children with GHD without catch-up growth after starting a gluten-free diet (GFD), suggesting the onset of autoimmune hypophysitis involving somatotropic cells (Iughetti *et al*., 2006). Thus, it is advised to test for anti-pituitary and anti-hypothalamus antibodies in all patients with CD-associated growth impairment (Iughetti *et al*., 2006). Turner syndrome is another important cause of SS in girls and is frequently associated with CD (6%–18% of patients). Therefore, subjects with Turner syndrome should be periodically screened for CD in order to make a diagnosis as soon as possible (Bonamico *et al*., 2002).

The hunger hormone, ghrelin, is a newly discovered gastrointestinal hormone that is produced by ghrelinergic cells in the gastrointestinal tract (Sakata *et al*., 2010 and Inui *et al*., 2004). This hormone regulates appetite and plays a significant regulatory role in energy use (Burger and Berner, 2014). In children and adults with CD, mean serum ghrelin levels are higher than in controls, and they decrease after at least six months on a GFD (Selimoglu *et al*., 2006; Lanzini *et al*., 2006; Capristo *et al*., 2005 and Peracchi *et al*., 2003). Furthermore, ghrelin values were shown to negatively correlate with body mass index (BMI) (Lanzini *et al*., 2006). Therefore, it was suggested that ghrelin could serve as a reliable marker for monitoring adherence to the GFD in children and adults with CD (Meazza *et al*., 2014). However, growth is not always affected by CD since obese CD patients are taller than non-obese CD subjects (Nwosu *et al*., 2013), due to differential mechanisms that are still active during CD and prevail over malabsorption (Meazza *et al*., 2014 and Yu *et al*., 1997) and compensation of the malabsorption (due to atrophy of the duodenum and jejunum) by enhanced absorption in the distal intestinal segments in which morphological mucosal changes occur (Semeraro *et al*., 1986). This compensatory hypothesis could explain why some CD children present as overweight/obese and why some CD children do not show growth retardation (Meazza *et al*., 2014).

Conclusion

This study represents the first meta-analysis concerning the prevalence of CD in SS individuals in SA. Both the prevalence of biopsy-proven CD (6.7%) and seroprevalence (16.1%) were higher than those in the normal population that we previously reported (1.4% and 2.7%, respectively). Females with CD were 1.5 times as prevalent as males. No significant difference between the reported serologically- proven and biopsy-proven rates were noted ($p = 0.205$).

Recommendations

- Study DQ2/ DQ8 haplotypes in asymptomatic CD with growth retardation even if the CD serological markers were normal.
- Evaluation of the hunger hormone, ghrelin, which negatively correlates with the BMI (Lanzini *et al*., 2006) and with adherence to GFD in children and adults with CD (Meazza *et al*., 2014).
- Evaluation of anti-pituitary and anti-hypothalamus antibodies in patients with CD-associated growth impairment (Meazza *et al*., 2014).

Ethical approval

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

Disclosures: The current study was not funded or supported by any drug company. This paper is unique, is not under consideration by any other journal, and has not been published elsewhere.

Conflicts of Interest: The author declares that there is no conflict of interest.

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