original article

The prevalence of celiac disease in Saudi patients with type 1 diabetes mellitus

Mohammed Zaid Aljulifi,[abc] Moeber Mahzari,[bcd] Lujain Alkhalifa,[bcd] Esra Hassan,[bcd] Abdullah Mohammed Alshahrani,[e] Abdulwahed Abdulaziz Alotay[bcf]

From the [a]Department of Family Medicine, College of Medicine, Majmaah University, Riyadh, Saudi Arabia; [b]Department of Medicine, Division of Endocrinology, King Abdulaziz Medical City, Ministry of National Guard Health Affairs, Riyadh, Saudi Arabia; [c]King Abdullah International Medical Research Center, Riyadh, Saudi Arabia; [d]College of of Medicine, King Saud bin Abdulaziz University for Health Sciences, Riyadh, Saudi Arabia; [e]Department of Family Medicine, College of Medicine, University of Bisha, Asir, Saudi Arabia; [f]Department of Medicine, College of Medicine, Imam Muhammad bin Saud Islamic University, Riyadh, Saudi Arabia

BACKGROUND: Celiac disease (CD) is an autoimmune disease that is highly associated with type 1 diabetes mellitus (T1DM). The reported prevalence of CD in patients with T1DM in Saudi Arabia varies and the number of studies is limited.

OBJECTIVES: Determine the prevalence of CD diagnosed with anti-tissue transglutaminase (anti-tTG) antibodies or by endoscopic biopsy in adolescents and adults with T1DM.

DESIGN: Cross-sectional, retrospective medical record review.

SETTING: Tertiary care center.

PATIENTS AND METHODS: The study population included adolescents and adults with T1DM who were screened for CD between 2010 and 2019. The study variables included age, sex, age at diagnosis of T1DM, age of positive celiac screening, glycated hemoglobin (HbA1c), total daily insulin dose, frequency of diabetic ketoacidosis (DKA) and other autoimmune diseases.

MAIN OUTCOME MEASURES: The prevalence of celiac disease in adolescents and adults with T1DM.

SAMPLE SIZE: 539 patients.

RESULTS: The prevalence of positive celiac test results was 11.5% (n=62). A small proportion (n=5, 8%) of the positive CD group was diagnosed with T1DM after they tested positive with the celiac screening test. Ten (16%) were diagnosed with T1DM and CD in the same year. The rest of the sample had a positive screening test after being diagnosed with T1DM. There was no statistically significant difference between the CD positive and negative groups for HbA1C, DKA frequency, microvascular complications of diabetes or thyroid disorder. For histopathological confirmation of CD, only 37% (n=23) of the group with a positive screening test underwent endoscopy. In this group, 43% (n=10) had normal endoscopic biopsy findings, 21.7% (n=5) had partial villous atrophy and 34.7% (n=8) had total villous atrophy.

CONCLUSIONS: This study highlights the importance of screening for CD in T1DM patients. CD prevalence is high in patients with T1DM, despite the high likelihood of underdiagnosis. Additional studies of different age groups and the use of different study methods are required. In addition, a unified national strategy to diagnose CD in T1DM patients is highly advisable.

LIMITATIONS: Retrospective, single-center, few confirmations of CD by intestinal biopsy.

CONFLICT OF INTEREST: None.

original article

Celiac disease (CD) is an autoimmune disease that affects the mucosal surface of the small intestine. CD is exacerbated by exposure to dietary gluten in genetically predisposed individuals.[1] Type 1 diabetes mellitus (T1DM), also an autoimmune disease, is highly associated with CD.[2]

Saudi Arabia has one of the highest T1DM prevalence rates globally; the country is currently ranked eighth in the world. Approximately 35 000 children and adolescents are diagnosed with T1DM. In addition, Saudi Arabia is rated fourth globally in terms of the incidence rate of T1DM, with 33.5 new cases annually per 100 000 individuals.[3] The reported prevalence of CD in at-risk individuals in Saudi Arabia varies and the number of studies are limited. **Table 1** summarizes the available literature related to CD prevalence in T1DM patients.[4-12] This study aimed to determine the prevalence of CD in adolescents and adults with T1DM. The clinical characteristics and differences between T1DM patients with or without a positive CD screening test were also investigated.

PATIENTS AND METHODS

This study was a retrospective chart review of all adolescents and adults with T1DM who were screened for CD at King Abdulaziz Medical City, Riyadh, from 2010 to 2019. The sample was randomly selected from all patients diagnosed with T1DM who underwent a CD screening test at the institution using enzyme-linked immunosorbent assay. CD was diagnosed in adolescents and adults with T1DM using anti-tissue transglutaminase (anti-tTG) antibodies or by endoscopic findings. All biopsies were collected using esophagogastroduodenoscopy from the duodenum. Study variables included age, sex, age at diagnosis of T1DM, age of positive celiac screening, HbA1c, total daily dose, diabetes ketoacidosis (DKA) frequency and other autoimmune diseases.

Statistical analysis was performed by a biostatistician. Descriptive statistics, such as frequency, mean and median were calculated. A chi-square test was used to determine the association between CD in T1DM patients and other variables. If continuous data was not uniformly distributed, a nonparametric test used for comparisons. Data analysis was performed using Statistical Analysis Software (SAS) version 9.4. and IBM SPSS version 22. Ethical approval was obtained from the Institutional Review Board of King Abdullah International Medical Research Center with study number: RC19/295/R.

RESULTS

All 539 adolescents and adults diagnosed with T1DM were screened for CD using anti-tTG. More than half of the sample (55.3%) were adults (age > 19 years), and 56.6% were female (**Table 2**). A small proportion (11.5%, n=62)) of the sample was seropositive for CD, and CD was confirmed with endoscopy in only 2.4%. The prevalence of seropositive CD was higher in females (7.4%) than in males (4.1%). There was a statistically significant difference in the total daily insulin dose between the seropositive CD group and the seronegative CD group (*P*=.0001) (**Table 3**). The seropositive CD group required an average of 0.93 (0.35) units/kg insulin compared to 1.01 (0.38) units/kg in the seronegative CD group. The association between CD seropositivity and age at T1DM diagnosis, T1DM autoantibody positivity, thyroid diseases, and frequency of DKA or microvascular complications was not statistically significant. A third (n=23, 37%) of the 62 patients with seropositive CD underwent endoscopy to confirm the diagnosis. Almost half (43%, 10/23) had normal biopsy results (**Table 4**). **Figure 1** shows the distribution of antitissue transglutaminase levels. Differences in HbA1c levels between patients with and without CD were not statistically significant (*P*=.447 Mann-Whitney U test) (**Figure 2**).

DISCUSSION

The co-existence of T1DM and CD is well established as both diseases share a similar genetic predisposition, in particular the HLA genotype DR3-DQ2, and to a lesser extent, DR4-DQ8 are associated with both diseases.[5-8] The prevalence of a seropositive CD screening test in the T1DM patients in this study was 11.5%. However, only 2.4% of the cases were confirmed by biopsy. The CD prevalence in the current study was lower than that reported in the literature. Two studies that estimated the prevalence of CD in T1DM patients serologically and through biopsy reported the prevalence as 14.4% and 10.8%,[4] but CD prevalence in T1DM patients is consistently higher than in the general population. CD is estimated to be 5-7 times more frequent in diabetic patients compared to the general population.[9] In the general population of Saudi Arabia, the prevalence of CD is 2.7% through serology and 1.4% by biopsy, which is significantly lower than the prevalence in T1DM.[10] In Arab countries, the prevalence of CD in children with T1DM range from 5.5% to 20%.[11] Internationally, the prevalence ranges from 3%–12%.[12-14] There are multiple possible reasons for the low prevalence of confirmed CD in this study, including early screening of asymptomatic T1DM patients, the low referral rate for endoscopy by the treating physician, patient or family refusal to undergo an endoscopy, and loss of patient follow-up at the gastroenterology service.

original article

The 2018 American Gastroenterology Association's clinical practice guideline states that if the tissue trans-glutaminase–immunoglobulin level is high (>10 times the upper normal limit), it should be considered as a reliable and accurate test for diagnosing active CD. In addition, if the patient has a strongly positive TG2-IgA, combined with a positive endomysial antibody in a second blood sample, the positive predictive value for CD is virtually 100%.[15] Another option is the HLA test to confirm the diagnosis without sending for endoscopy.[13] These approaches are less cumbersome for patients and their families who choose to avoid an endoscopy.

Before labeling the screening as negative, normal IgA levels and ingestion of a normal diet including gluten have to be confirmed as IGA deficiency and a strict gluten-free diet could lead to falsely negative CD serological testing. In case of absence or low anti-tTG with suspected symptoms or equivocal biopsy sample results, the HLA test is an option in such patients.[13] In

our study, normal IgA level was confirmed in all patients. However, HLA testing for high-risk loci for CD is not an essential diagnostic test and has no additional diagnostic benefit in case of high anti-tTG levels.[15] The exact role of HLA testing in the diagnosis of CD and T1DM is not clear yet in clinical practice.[13,15] One possible use of HLA testing is as a screening tool for asymptomatic children with T1DM to help in the decision of whether to proceed to endoscopy based on the results. This is based on the fact that most patients with high-risk HLA loci for CD and T1DM usually demonstrate islet cell autoimmunity first followed by enterocyte autoimmunity later in life.[7] The TEDDY study showed that development of islet cell autoimmunity is significantly associated with subsequent development of tTG antibodies, whereas the opposite was not true.[7] In this study, only 5 patients (0.92%) were diagnosed with CD before T1DM. One of the five patients was diagnosed with CD at 9 years of age and was later di-

Table 1. Summary of local Saudi studies on celiac disease prevalence in T1DM patients.

First author and journal	Sample size/type of study	Mean age group (years)[a]	Sitting	Screening method	Prevalence
Alashwal et al. Saudi Med J 2003; 24: 1113-1115[5]	123 T1DM/ Cross sectional	10 (4)	King Faisal Specialist Hospital and Research Centre, Riyadh	Gliadin and reticulin antibodies and biopsy	Antibodies alone ~8.1% Antibodies + biopsy ~4.9%
Saadah, OI et al. Journal of Pediatric Gastroenterology and Nutrition 2004; 39: S211[6]	110 T1DM/ Cohort	11 (4.3)	King Abdulaziz University Hospital, Jeddah	IgA Antigliadin (AGA-A) and or anti tTG antibody	Antibodies alone ~21% Antibodies + biopsy ~10%
Alhussaini A et al. BMC Gastroenterol. 2012 Dec 23;12:180[7]	106 T1DM/ Prospective	8.5 (2.8)	King Saud Medical City, Riyadh	anti-tTG and endomyseal antibody (EMA)	Antibodies alone ~24.5% Antibodies + biopsy ~11.3%
Saadah, OI et al. Saudi Med J 2012; Vol. 33 (5): 541-546[8]	430 T1DM/ retrospective hospital record-based study	10.7	King Abdulaziz University Hospital, Jeddah	anti-tTG antibody	Antibodies alone ~21.2% Antibodies + biopsy ~11.2%
Al-Agha et al. Saudi Med J 2015; 36: 26-31[9]	228 T1DM/ Cross sectional	10.9	King Abdulaziz University Hospital, Jeddah	IgA anti-tTG	Antibodies alone ~19.7%
Alshareef et al. Int J Diabetes Metab Disord 2016; 1: 1-4[10]	218 T1DM/ Cross sectional	21.3 (7.2)	King Fahad Armed Forces Hospital. Jeddah	Anti-tTG antibodies	Antibodies alone ~7.3% Antibodies + biopsy ~4.6%
Alhakami Saudi Med J 2016; 37: 386-391[11]	202 T1DM/ Cross sectional	11.3	Aseer Central Hospital, Abha	Anti -tTG-IgA and EMA	Antibodies alone ~10.4%
Alghamdi RA. IOSR Journal of Pharmacy and Biological Sciences (IOSR-JPBS) 2018; 13: 22-26[12]	268 T1DM/ retrospective record-based study	12.14 (4.33)	Albaha, southwestern region, King Fahad Hospital	Anti-tTG	Antibodies alone ~7.1%

[a]Standard deviation when available.

Table 2. Patient characteristics (n=539).

Variable	Celiac screening (positive) (n=62, 11.5%)	Celiac screening (negative) (n=477, 88.5%)	Total (n=539, 100%)	P value
Age group (years)				
>10-19	31 (5.8)	210 (39.0)	241 (44.7)	.4506
>19 - <65	31 (5.8)	267 (49.5)	298 (55.3)	
Gender				
Males	22 (4.1)	212 (39.3)	234 (43.4)	.229
Females	40 (7.4)	265 (49.2)	305 (56.4)	
Marital status				
Single	52 (9.7)	422 (78.3)	474 (87.9)	
Married	9 (1.7)	53 (9.8)	62 (11.5)	.3518
Other	1 (0.2)	2 (0.4)	3 (0.6)	

Data are number (%) by column total.

Table 3. History of type 1 diabetes and related comorbidities and complications (n=539).

Variable	Celiac screening (positive)	Celiac screening (negative)	P value
Age at T1DM diagnosis (years)[a]	10.6 (5.2)	11.6 (5.7)	.1583
Duration of T1DM (years)[b]	9 (8)	10.5 (9)	.637
Type 1 diabetes autoantibodies (positivity)			
Positive	23 (6.9)	204 (61.26%)	
Negative	3.30 (11)	95 (28.53%)	.9451
Total daily insulin (units)[b]	48.5 (25.5)	58 (33)	<.001
Insulin dose (units/kg/body weight)[b]	0.86 (0.455)	0.962 (0.463)	.136
Thyroid disease	13 (2.4)	73 (13.5)	.2519
Frequency of diabetic ketoacidosis			.9967
Never	32 (5.9)	243 (45.1)	
More than one/year on average	25 (4.6)	197 (36.6)	
One/year on average	4 (0.7)	29 (5.4)	
More than one/year on average	1 (0.2)	8 (1.5)	
Microvascular complications			
Retinopathy alone	2 (0.4)	24 (4.5)	
Nephropathy alone	5 (0.9)	47 (8.7)	.7034
Neuropathy alone	1 (0.2)	-	
Nephropathy + retinopathy	4 (0.7)	14 (2.6)	

Data are number (%) by column total or [a]mean (standard deviation) or [b]median (interquartile range) unless noted otherwise.

agnosed with T1DM when he was 12 years old. In addition, only 10 patients (1.85%) were positively screened for CD in the same year of T1DM diagnosis. The HLA test was not part of the study variables, as this study was retrospective. Overall, HLA predisposition alone does not seem to explain the association between CD and T1DM. It seems that an environmental trigger common between T1DM and CD could be the cause to elicit the autoimmunity for both diseases; this is supported by the fact that early gluten introduction is a risk factor for T1DM development and as it is known that gluten ingestion is the trigger for CD.[8,16]

In the current study, 24% of CD-positive patients were diagnosed with CD before or in the same year as the T1DM diagnosis. These patients had CD symptoms earlier, leading to CD diagnosis, followed by T1DM diagnosis later. This finding is consistent with reports that 10%-25% of patients diagnosed with T1DM are diagnosed with CD first.[12] The majority of the patients are generally diagnosed with CD after the T1DM diagnosis. One cohort study on 5891 children found that CD autoimmunity is usually present later after T1DM autoimmunity.[7] A possible explanation for the sequential association between T1DM then CD is the commonality of tTG as an antigen expressed in both islet cells and enterocytes. Therefore, with islet cell destruction in T1DM pathogenesis, tTG antibodies have been developed,

Table 4. Characteristics of T1DM patients who were CD positive (n=62).

Variable	Finding
tTG-IgA level[a]	163.1 (53.2-261.4)
tTG-IgG level[b]	13.5 (5.0-34.8)
Number of patients with T1DM diagnosis and positive celiac screening	
Celiac before diabetes	5 (8.1%)
Celiac and diabetes together	10 (16.1%)
Celiac after diabetes	47 (75.8%)
Number of patients who underwent endoscopy	23 (37.1)
Endoscopy findings	
Normal	10 (43.5)
Partial villous atrophy	5 (21.7)
Total villous atrophy	8 (34.8)

Data are number (%) or median (interquartile range). [a]tTG-IgA>30 units is considered moderate to strong positive; 20-30 units is weak positive AND <20 units is negative. [b]tTG-IgG>30 units is considered moderate to strong positive; 20-30 units is weak positive AND <20 units is negative.
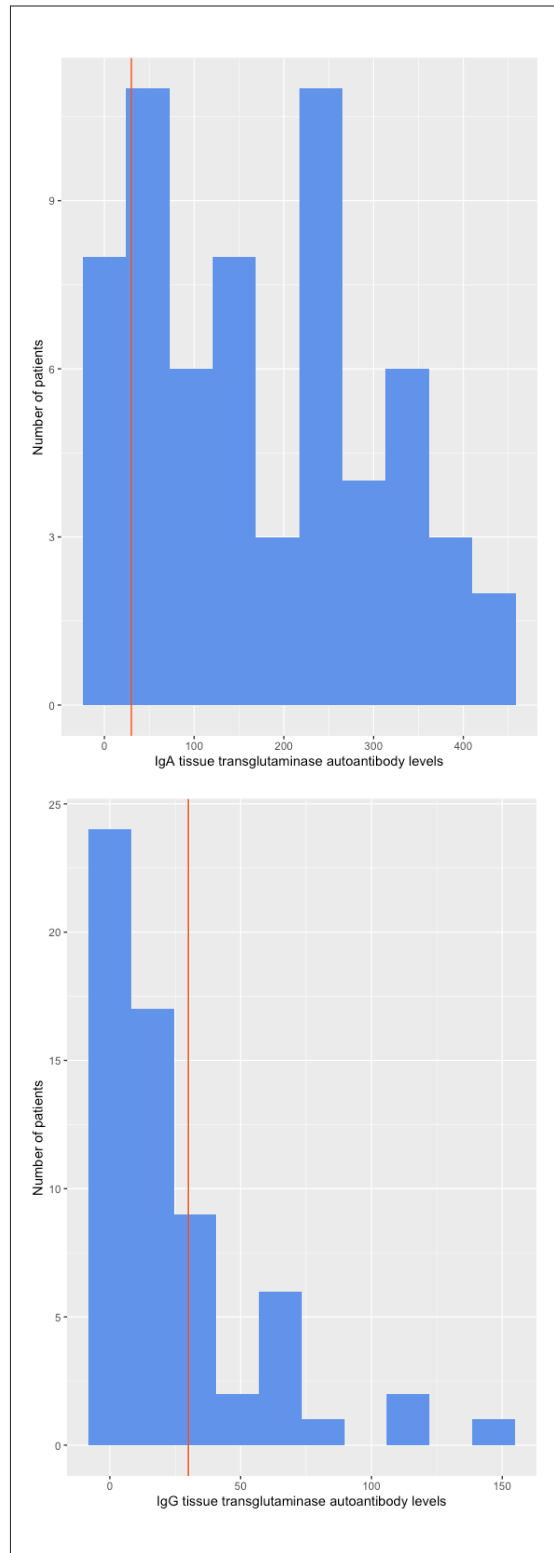
Figure 1. Distribution of tTG-IgA (top) and tTG-IgG (bottom) levels in 62 patients with celiac disease (>30 units [vertical line] is considered moderate to strong positive).
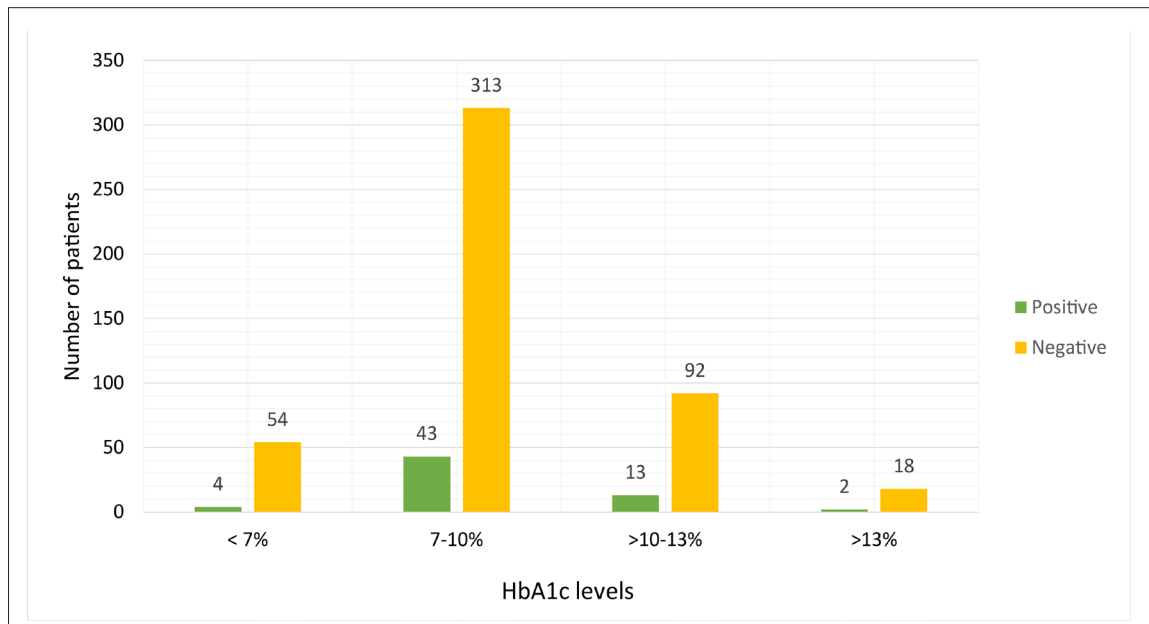
Figure 2. Distribution of the sample according to celiac screening and HbA1c level.

which in genetically susceptible individuals leads to CD development later.[7]

Patients with CD frequently present with few or no symptoms and it is important to adhere to the recommendation to screen for CD early after the T1DM diagnosis in children and adolescents. It is advisable to consider celiac screening at the time of diagnosis of T1DM and 2 to 5 years after diagnosis. Screening is indicated in any T1DM patient with symptoms suggestive of CD.[17-20]

In the current study, although not statistically significant, the seropositive CD patients had been diagnosed with T1DM for a longer period and were diagnosed at a younger age, compared to seronegative CD patients. This finding is similar to that of Saadah et al, who reported that T1DM patients with CD had T1DM for a longer period.[21] Additional support was provided by a study from Germany with 1326 T1DM patients, reporting that the CD-affected patients were diagnosed at a significantly younger age with diabetes.[12]

The current study found a significant difference in the daily insulin dose between seropositive and seronegative CD patients. In contrast, Saadah et al reported no difference in the insulin requirement between CD-positive and CD-negative patients with T1DM.[21] There was no significant difference in the HbA1C levels between the seropositive and non-celiac groups in this study, and there were more seropositive CD female T1DM patients. These findings are similar to previous local reports.[21-24] In contrast, Kaspers et al reported in a study done in Germany that T1DM patients with CD had lower levels of HbA1C, compared to patients with T1DM and no CD.[12] In our study, there was no statistical difference between seropositive and seronegative CD patients in terms of admissions with DKA. This finding is similar to the findings reported in a Swedish national study.[25] There was also no statistical association between thyroid disease and CD. The association of CD with thyroid diseases in T1DM patients has not been consistently reported in the local literature.[21,24] A Swedish population-based cohort study reported that CD in T1DM patients was a risk factor for both hypothyroidism (HR 1.66 [95% CI 1.30–2.12]) and hyperthyroidism (HR 1.72 [95% CI 0.953.11). This excess risk was highest in patients who had CD for 10 years or more (HR, 2.22; 95% CI 1.49, 3.23).[26] The reasons for the differences reported in the Saudi studies are possibly related to the methodology; most were retrospective with a relatively small sample sizes, relatively short follow-up duration, type of screening test used for CD and the target age groups. Our study highlights the importance of screening for CD in T1DM patients. The study's limitations include being retrospective and the rate of CD confirmation with an intestinal biopsy was low in the sample. Additional prospective Saudi studies are required to assess the CD risk in patients with T1DM and its influence on other concomitant health problems in this patient population. In addition, a unified national guideline for the diagnosis of CD in patients with T1DM is highly advisable.

original article

REFERENCES

1. Fasano A, Catassi C. Celiac disease. New England Journal of Medicine. 2012;367(25):2419-26.

2. Rubio-Tapia A, Hill ID, Kelly CP, Calderwood AH, Murray JA, American College of G. ACG clinical guidelines: diagnosis and management of celiac disease. Am J Gastroenterol. 2013;108(5):656-76; quiz 77. Epub 2013/04/24. doi: 10.1038/ajg.2013.79. PubMed PMID: 23609613; PubMed Central PMCID: PMCPMC3706994.

3. International Diabetes Federation. 2017. Available from: http://fmdiabetes.org/wp-content/uploads/2018/03/IDF-2017.pdf

4. Safi M-AA. Celiac disease among at-risk individuals in Saudi Arabia. Saudi Medical Journal. 2019;40(1):9.

5. Tjon JM, van Bergen J, Koning F. Celiac disease: how complicated can it get? Immunogenetics. 2010;62(10):641-51. Epub 2010/07/28. doi: 10.1007/s00251-010-0465-9. PubMed PMID: 20661732; PubMed Central PMCID: PMCPMC2944025.

6. Alshiekh S, Maziarz M, Geraghty DE, Larsson HE, Agardh D. High-resolution genotyping indicates that children with type 1 diabetes and celiac disease share three HLA class II loci in DRB3, DRB4 and DRB5 genes. HLA. 2020.[[AUTHOR: the citation is incomplete]]

7. Hagopian W, Lee HS, Liu E, Rewers M, She JX, Ziegler AG, et al. Co-occurrence of Type 1 Diabetes and Celiac Disease Autoimmunity. Pediatrics. 2017;140(5):e20171305. Epub 2017/10/12. doi: 10.1542/peds.2017-1305. PubMed PMID: 29018046; PubMed Central PMCID: PMCPMC5654393.

8. Kurppa K, Laitinen A, Agardh D. Coeliac disease in children with type 1 diabetes. The Lancet Child & Adolescent Health. 2018;2(2):133-43.

9. Szaflarska-Popławska A. Coexistence of coeliac disease and type 1 diabetes. Prz Gastroenterol. 2014;9(1):11-7. Epub 2014/03/01. doi: 10.5114/pg.2014.40844. PubMed PMID: 24868293.

10. Safi M-AA. Prevalence of Celiac disease in Saudi Arabia: Meta-analysis. Global Vaccines and Immunology. 2018;3:1-6.

11. El-Metwally A, Toivola P, AlAhmary K, Bahkali S, AlKhathaami A, AlSaqabi MK, et al. The Epidemiology of Celiac Disease in the General Population and High-Risk Groups in Arab Countries: A Systematic Review. BioMed research international. 2020;2020:6865917. Epub 2020/07/01. doi: 10.1155/2020/6865917. PubMed PMID: 32596351; PubMed Central PMCID: PMCPMC7292982.

12. Kaspers S, Kordonouri O, Schober E, Grabert M, Hauffa BP, Holl RW, et al. Anthropometry, metabolic control, and thyroid autoimmunity in type 1 diabetes with celiac disease: A multicenter survey. J Pediatr. 2004;145(6):790-5. Epub 2004/12/08. doi: 10.1016/j.jpeds.2004.07.031. PubMed PMID: 15580203.

13. Husby S, Koletzko S, Korponay-Szabó IR, Mearin ML, Phillips A, Shamir R, et al. European Society for Pediatric Gastroenterology, Hepatology, and Nutrition Guidelines for the Diagnosis of Coeliac Disease. Journal of Pediatric Gastroenterology and Nutrition. 2012;54(1):136-60. doi: 10.1097/MPG.0b013e31821a23d0. PubMed PMID: 00005176-201201000-00028.

14. Sahin Y, Cakir MD, Isakoca M, Aydin Sahin D. Prevalence of Celiac Disease in Children with Type 1 Diabetes Mellitus in the South of Turkey. Iran J Pediatr. 2019;30(1):e97306. Epub 2019-12-01. doi: 10.5812/ijp.97306.

15. Husby S, Murray JA, Katzka DA. AGA clinical practice update on diagnosis and monitoring of celiac disease—changing utility of serology and histologic measures: expert review. Gastroenterology. 2019;156(4):885-9.

16. Norris JM, Barriga K, Klingensmith G, Hoffman M, Eisenbarth GS, Erlich HA, et al. Timing of initial cereal exposure in infancy and risk of islet autoimmunity. Jama. 2003;290(13):1713-20.

17. Pham-Short A, Donaghue KC, Ambler G, Phelan H, Twigg S, Craig ME. Screening for Celiac Disease in Type 1 Diabetes: A Systematic Review. Pediatrics. 2015;136(1):e170-6. Epub 2015/06/17. doi: 10.1542/peds.2014-2883. PubMed PMID: 26077482.

18. Association AD. 4. Comprehensive Medical Evaluation and Assessment of Comorbidities: Standards of Medical Care in Diabetes-2020. Diabetes care. 2020;43(Suppl 1):S37.

19. Association AD. 13. Children and Adolescents: Standards of Medical Care in Diabetes– 2020. Diabetes Care. 2020;43(Supplement 1):S163-S82.

20. Mahmud FH, Elbarbary NS, Frohlich-Reiterer E, Holl RW, Kordonouri O, Knip M, et al. ISPAD Clinical Practice Consensus Guidelines 2018: Other complications and associated conditions in children and adolescents with type 1 diabetes. Pediatr Diabetes. 2018;19 Suppl 27(Suppl 27):275-86. Epub 2018/08/02. doi: 10.1111/pedi.12740. PubMed PMID: 30066458; PubMed Central PMCID: PMCPMC6748835.

21. Saadah OI, Al-Agha AE, Al Nahdi HM, Bokhary RY, Bin Talib YY, Al-Mughales JA, et al. Prevalence of celiac disease in children with type 1 diabetes mellitus screened by anti-tissue transglutaminase antibody from Western Saudi Arabia. Saudi Med J. 2012;33(5):541-6. Epub 2012/05/17. PubMed PMID: 22588816.

22. Alshareef M, Aljabri K, Bokhari S, Al Jiffri A, Abu Elsaoud H, Akl A. The prevalence of celiac disease in saudi patients with type 1 diabetes mellitus: cross sectional study. Int J Diabetes Metab Disord. 2016;1(1):1-4.

23. Al-Hussaini A, Sulaiman N, Al-Zahrani M, Alenizi A, El Haj I. High prevalence of celiac disease among Saudi children with type 1 diabetes: a prospective cross-sectional study. BMC gastroenterology. 2012;12(1):180.

24. Al-Hakami AM. Pattern of thyroid, celiac, and anti-cyclic citrullinated peptide autoantibodies coexistence with type 1 diabetes mellitus in patients from Southwestern Saudi Arabia. Saudi Med J. 2016;37(4):386-91. Epub 2016/04/08. doi: 10.15537/smj.2016.4.13571. PubMed PMID: 27052281; PubMed Central PMCID: PMCPMC4852016.

25. Kurien M, Mollazadegan K, Sanders DS, Ludvigsson JF. A nationwide population-based study on the risk of coma, ketoacidosis and hypoglycemia in patients with celiac disease and type 1 diabetes. Acta diabetologica. 2015;52(6):1167-74. Epub 2015/09/26. doi: 10.1007/s00592-015-0808-y. PubMed PMID: 26403595.

26. Kurien M, Mollazadegan K, Sanders DS, Ludvigsson JF. Celiac Disease Increases Risk of Thyroid Disease in Patients With Type 1 Diabetes: A Nationwide Cohort Study. Diabetes Care. 2016;39(3):371-5. Epub 2015/12/19. doi: 10.2337/dc15-2117. PubMed PMID: 26681723.