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Seroprevalence of Celiac disease and Selective IgA deficiency in Birjand, Iran

Alireza Rahmani Motlaq

alirezarahmanimotlagh@gmail.com

Birjand University of Medical Sciences

Mahmoud Zardast

Birjand University of Medical Sciences

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Abstract

Celiac disease (CD) is an autoimmune GI disease characterized by gluten intolerance. We performed a cross-sectional study of CD and Selective IgA deficiency (SIgAD) among 4004 individuals aged one day to 97 years in Birjand, Iran. Methods included a cross-sectional survey of CD, SIgAD, and participants' symptoms, sampled at two leading laboratories of the city. The findings revealed a 3.36% seroprevalence of positive IgA Anti-tTG test for CD and a 4.86% seroprevalence of negative Total IgA test for SIgAD. Furthermore, we corroborated an increase in serum Total IgA levels and a decrease in serum Anti-tTG IgA levels with advancing age. The most frequent symptoms among CD suspects were abdominal pain and weight loss (30%). We also reported associations between sex, age, and serum levels or test results of total IgA and Anti-tTG IgA. Increased awareness of CD among some medical subspecialties and the availability of exact and sensitive serological tests have contributed to a rise in confirmed CD cases. We suggest that CD prevalence in Birjand might be among the highest. Further evaluations are required to describe CD and SIgAD status in the Middle East.

Introduction

Celiac disease (CD) is a chronic autoimmune enteropathy generated by dietary gluten consumption in a genetically predisposed population of all ages (1). The immunology mechanism of CD involves several key players, including T cells, B cells, and antibodies. When gluten is ingested, it is broken down into smaller peptides that can be recognized by T cells. In individuals with CD, certain T cells called CD4 + cells recognize gluten peptides as foreign and activate an immune response (2). The diagnostic approach to CD diagnosis depends on serologic tests, small intestine biopsies, and response to a gluten-free regimen (3–7). The predicted prevalence of CD is about 0.6% to 1.4% of the global population based on studies (8, 9). A total IgA level is recommended to assess Selective IgA deficiency (SIgAD), which is 5–15 times more common in CD individuals (6, 7, 10–12). The most prevalent primary immunodeficiency is SIgAD (12). SIgAD is a serum Total IgA level < 0.07 mg/dl among individuals aged four or more with the normal range of IgM and IgG (13–15). Most SIgAD patients have no clinical symptoms (16), and generally, serologic testing alone is insufficient for confirming CD. (17). Furthermore, the frequency of SIgAD in CD patients is 2%-3%, according to studies (18). The first serologic tests developed for CD were Anti-gliadin antibodies (AGAs) (19). IgA AGA has an equal to slightly greater sensitivity but substantially superior specificity against IgG AGA, increasing the IgA AGA test's accuracy (5, 20, 21). The specificity and sensitivity for both IgG and IgA AGA are estimated to be between 90% and 80%, with adults typically having lower specificities than children (20, 21). The gold standard for CD diagnosis is histological evidence of atrophy in the intestinal villi (22). Concerning specificity, the endomysial antibody (EMA) testing marked a significant advancement above AGA testing (6). After introducing anti-tissue transglutaminase (anti-tTG) testing, studies revealed increased accuracy, greater sensitivity, and equal specificity to EMA (20, 21). Deamidated gliadin peptide (DGP) testing has recently been accessible for clinical testing (6). Regarding sensitivity and specificity, IgA anti-DGP may be similar to IgA anti-tTG, based on the populations examined (11, 23). In addition, IgA anti-tTG testing outperforms IgA anti-DGP testing and is also considerably less expensive (6, 24). With this perspective, IgA anti-tTG is currently considered the preferred serologic test for CD confirmation (6). Due to cost and accuracy concerns, IgA anti-tTG testing combined with total IgA levels should be firstly conducted, followed by IgG anti-DGP testing in IgA deficient patients (6, 25, 26). Nevertheless, Celiac disease-associated costs such as the total IgA test indicate a considerable economic burden of the diagnostic technique, particularly in developing countries (27). Here, we conducted a cross-sectional survey of CD suspects to determine the seroprevalence of CD and SIgAD individuals. We also intended to perform primary data analysis to help individualize our region's healthcare program and pave the way for further investigations.

Materials and Methods

Ethical considerations

This study was approved by the Ethics Committee of Birjand University of Medical Sciences (reference code: 5669; 6 March 2021) and was conducted in accordance with the principles of the Declaration of Helsinki. Informed consent was obtained from participants. For participants younger than 18 years, including minors as young as one day old, both written and oral informed consent were obtained from their parent and/or legal guardian prior to the use of their clinical and laboratory information in the study.

Research design and population

This descriptive/analytical cross-sectional study was conducted on 4004 participants to assess the coincidence between CD demographics and laboratory results in the suspected population. We reviewed continual Anti-tTG IgA and Total IgA test results in Birjand, Iran, from March 2018 to October 2019. Demographic information of patients and laboratory data was obtained from patient records. CD suspects were individuals who had been recommended for CD assessment due to suspected clinical manifestations. Some variables were collected in a checklist, including demographic data, such as sex and age, the personal and familial medical history of CD or any immune insufficiencies, and physical examination and clinical characteristics such as chronic diarrhea, steatorrhea, unusual weight loss, anorexia, growth disorders, nausea or vomiting, abdominal cramps, oral lesions, constipation, hair loss, and fatigue.

Population sampling

Of a total of 4004 patients referred to both Imam Reza and Shafa laboratories between March 2018 and October 2019, 85 patients had low levels of serum Total IgA and were highly suspicious for SIgAD. Access by phone or interview to 35 individuals in person was impossible, or they refused to cooperate. Therefore they were excluded, and further analysis was conducted on 50 other participants.

Celiac disease and SIgAD concept

The CD diagnosis was based on positive CD serology and the duodenal biopsy, According to guidelines (28–30). The duodenal biopsy was unavailable for most participants; therefore, CD-suspected patients were investigated. In this study CD, suspected patients were defined with an Anti-tTG IgA of higher than 18 U/ml or patients with an Anti-tTG IgA of lower than 12 U/ml and under the expected level of Total IgA. Serum IgA concentration lower than 7 mg/dl in those older than four years defines SIgAD (31). Since the normal range of IgA varies in age groups, with a focused approach on SIgAD effect on patients with celiac disease, in this study, we divided all participants into seven equal groups, one day to 13 years, 14–27, 28–41, 42–55, 56–69, 70–83 and 84–97 years of age.

Serology and histology

All the CD suspects referred to the Emam Reza and Shafa laboratory in Birjand were included in this study to assess serum Anti-tTG IgA further or Total IgA. The serum Total IgA levels were determined using Immune nephelometry principles and Nephstar IgA laboratory kit (Nephstar, Goldsite Diagnostics, Inc., China) in 1746 individuals to identify SIgAD cases. Likewise, IgA antibody titers against tissue transglutaminase were also measured using a commercial ELISA kit called Seramun Diagnostica GmbH's Serazym anti-tTG IgA (Heidesee, Germany) or by chemiluminescent (CL) from blood samples (LIAISON, Germany) for CD screening. Having at least one positive serologic test (Anti-tTG IgA) is considered seropositive, and seronegativity is defined as a negative serologic test for Total IgA levels.

Statistical analysis

Analyses were conducted for the entire research group, IgA deficient patients, and CD-suspected patients, with correlation assessment between these variables. Descriptive statistics for continuous variables were presented as means ± standard deviations (SDs). Categorical variables were provided as frequency rates and percentages. The normal distribution of parameters was examined using Kolmogorov–Smirnov test. As data distribution was not normal, nonparametric tests were preferred to exploit. Pearson correlation coefficient analysis was performed to examine the correlations between metric variables, and the Mann-Whitney U test was used to compare two groups with not normally distributed parameters. For qualitative data comparison, the chi-square test was applied. Kruskal–Wallis was applied to compare means between three independent groups. All statistical analysis was done with SPSS® version 21.0 software (SPSS Inc., Chicago, IL, USA), and P-values lower than 0.05 were considered statistically significant.

Results

Study population attributes

From a total of 4004 participants registered at Emam Reza and Shafa laboratory; 1656 individuals were men (41.35%), and 2348 individuals were women (58.65%) with a male to female ratio of 0.7, aged from 1 day to 97 years with a median age of 27 years (mean and SD 27.84 ± 20.05). Two peak groups of age were seen among participants; 0–13 and 28–41 year-olds (Fig. 1). The mean ± SD for women aged 28.99 ± 19.50 was significantly higher ($P < 0.05$, = 0.000) compared to men, 26.22 ± 20.70 (Fig. 2). The demographic characteristics of all participants are presented in table-1.

Table 1
) Demographic data of participants.

Variables	**N (%)**
Age (Mean ± SD, years)	27.84 ± 20.05
Age (Median, years)	27
Age (Min-Max, years)	0–97
Male/Female	1656 (41.35%) / 2348 (58.65%)
SIgAD suspects	85 (4.86%)
Celiac suspects	123 (3.36%)

Serological data

During the study, 1746 Total IgA tests and 3656 Anti-tTG IgA tests were performed for patients clinically suspected of CD. The seroprevalence of negative Total IgA test results was 4.86% (85 blood samples) in 1746 and 2.12% in all subjects that propose possible SIgAD disease. Eighty-five seronegative patients were 37 men and 48 women, and thus the seroprevalence of SIgAD was 1:21 (85/1746) for all participants with Total IgA test: 1:36 (48/1746) for women and 1:47 (37/1746) for men. Also, the Positive seroprevalence for Anti-tTG IgA tests was 3.36% (123 blood samples) among 3656 test results and 3.07% among all individuals who suspected CD. Among the 123 seropositive patients, 37 were men and 86 were women, and thus the seroprevalence of CD was 1:30 (123/3656) for all participants with the Anti-tTG IgA test: 1:43 (86/3656) for women and 1:99 (37/3656) for men. The most prevalent age group among these 3656 patients was the first age group comprised of 1182 patients (0–13 years); also, the peak age of CD seropositivity was seen in this group (table-2). In addition, a trough (42–55 years) was seen in the fourth age group serum Total IgA amounts in both males and females (Fig. 3).

Table 2
) Determination of Total IgA and Anti-tTG IgA seroprevalence according to gender and age of individuals.

Variables/ Serum Total IgA and Anti-tTG IgA levels	Anti-tTG IgA					Total IgA				
	Positive N (%)	Negative N (%)	Borderline N (%)	Total N (%)	P value	Positive N (%)	Negative N (%)	Normal N (%)	Total N (%)	P value
Gender	37	1461	7	1505	0.015	42	37	677	756	0.746
Male	86	2047	18	2151		47	48	895	990	
Female										
Age	38	1135	9	1182	0.772	32	48	545	625	≤ 0.05
0 to 13 years	29	681	6	716		11	9	285	305	(0.000)
14–27 years	25	865	7	897		14	12	365	391	
28–41 years	21	519	1	541		15	12	228	255	
42–55 years	5	215	2	222		9	2	104	115	
56–69 years	5	85	0	90		8	2	39	49	
70–83 years	0	8	1	8		0	0	6	6	
84–97 years										

CD and SIgAD serology association

The results of analytic statistics (table-2) demonstrated that although there was no significant correlation between Total IgA results and genders (P value > 0.05, = 0.746), and Anti-tTG IgA results and Age groups (P value > 0.05, = 0.772); an association was seen between Anti-tTG IgA results and genders (P value < 0.05, = 0.015) and also between Total IgA results and Age groups (P value < 0.05, = 0.000). A strong positive correlation between age and serum Total IgA levels (P value < 0.05, = 0.000 – r = 0.269); and also a weaker negative correlation between age and serum Anti-tTG IgA levels (P value < 0.05, = 0.027 – r = -0.042) was seen (Figs. 4 and 5, respectively). There was no evidence of a connection between gender and serum Anti-tTG IgA and Total IgA levels (P value > 0.05, = 0.493 and 0.762, respectively). However, a correlation between age groups and serum levels of Anti-tTG IgA and Total IgA was seen during data analysis (P value < 0.05, = 0.030, and = 0.000, respectively). For the Total IgA test, the mean serum level was reported in patients between 0 to 13 years and 70 to 83 years as the lowest and the highest, respectively. These numbers are 84 to 97 years and 70 to 83, respectively.

CD serology and symptom-related variables

Of 85 seronegative individuals for the Total IgA test, 35 could not continue or refused to cooperate. Of the other 50 patients, we took a questionnaire that included patients' demographics and symptoms. The prevalence of symptoms is discussed in table-3. Abdominal pain (n = 15; 30%) and Weight loss (n = 15; 30%) were the most frequent symptoms. Two diagnoses of the eligible SIgAD patients (n = 50) were confirmed as CD, and three were highly suggestive for further CD investigation but did not continue the diagnostic course. Likewise, some of the other confirmed diagnoses were Hypothyroidism (n = 3), IBS (n = 3), Malignancies (n = 3), Diabetes (n = 2), and Anemia (n = 1).

Discussion

Our study provides a valuable evaluation of CD and SIgAD among a large study population in Birjand, one of the CD-prevalent cities in Iran and maybe one of the most prevalent worldwide. The present data suggest a clear statement of CD and SIgAD in the Middle East. The test of choice for serologic confirmation of CD is IgA anti-tTG due to its reasonable price and acceptable sensitivity and specificity (90–98% and 95–97%, respectively), especially in developing countries (6, 24, 27, 32). Previous pieces of the literature suggest that IgA anti-tTG test is a false negative in SIgAD patients; therefore, a total IgA level is recommended to assess SIgAD (6, 12, 17). Unfortunately, the total IgA test cost indicates a considerable economic burden on the diagnostic technique (27). Our study was designed to ascertain the prevalence of CD-positive sera and SIgAD individuals. Considering an authentic relationship between serum IgA Anti-tTG levels and the villous atrophy degree (33) and a study by Nejad et al. that assessed CD epidemiology in Iran; the need for performing initial serological diagnostic tests in the high-risk population of developing countries was discussed (34). Because there have been found that the CD prevalence in the Middle East is as common as in Europe, especially in Iran, a high CD prevalence has been reported (35). The mean IgA Anti-tTG serum concentration was 12.97 U/ml, while the cutoff point was 18 U/ml. The outcomes of our investigation propose a positive IgA Anti-tTG test of about 3%, which is far above recent worldwide reports. Similarly, research by Saberi-Firouzi and colleagues on healthy participants revealed a 0.56% seroprevalence for CD in Shiraz, much lower than reports from other cities in Iran (36). Two studies administered in Russia and studies in two cities and a province of Iran suggested a seroprevalence of 1.4%, 0.9%, 1.2%, and 1.1%, respectively (34, 37, 38). A recent systematic review and meta-analysis showed a CD global seroprevalence of 1.4% (39). Also, Ashtari et al., in a recent study, reported a seroprevalence of 1.6% in the Middle East region (40). To the best of our knowledge, the CD seroprevalence in Birjand city is among the highest. Likewise, according to recent studies, Spain is a SIgAD prevalent country with a ratio of > 1:500 (31). This ratio was reported as 1:651 in Iran by Aghamohammadi et al. with a cutoff of 5 mg/dl for the total IgA test (41). Also, other studies suggest similar numbers, 1:700 in the Fars province of Iran with a cutoff of 10 mg/dl (42), 1:300 to 1:800 in European countries (13), 1:875 in England (43), 1:965 in Brazil (44), 1:18500 in Japan (45), 1:143 in the Arabian Peninsula (46), and 1:223 to 1:1000 in the USA (47). Because SIgAD may result in false negative results of the Anti-tTG IgA test, the prevalence of SIgAD among CD patients is important. It is 10 to 15 times above the general population (47–50). This ratio varies among different studies, 1:39 to 1:57 (48, 49, 51, 52). Furthermore, the prevalence of CD among SIgAD patients ranges from 10% to 30%, depending on approached population (53–56). In the current research, we discovered two patients with CD among 50 SIgAD patients (4%). One of the important results in the present study was a two or three times higher frequency of disease in women than men (70% vs. 30%), which was reported in the majority of international epidemiological investigations on CD, especially in Iran. A similar distribution of CD was discovered in research by Ale Taha et al. Several investigations suggest a female to male ratio of 2:1 to 3:1 (57). Although this ratio was 11:10 in Sari and, in contrast, 9:10 in the Kerman city of Iran (38), in a study by Masjedizadeh et al., a 1.08 female to male ratio was seen that showed a female predominance in keeping with other studies (58–60). The CD diagnosis peak age was in the first age group (0–13 years); in another study carried out by HB cook et al., this peak was reported in the second decade of life (58). Likewise, CD may develop at all ages and is frequent in childhood, adolescents, and adulthood. In the present study, individuals aged between 1 day to 97 years and 0–13 years were the most prevalent age range. According to other research, about 20% of patients were beyond 60 at the time of diagnosis (61–63). The earlier study by Ahmadi et al. found that the average range of age in CD patients was 34.57 y ± 1.24 (64), Shahbazkhani et al., in a study, reported a mean age of 39.79 y ± 16.77 among CD patients (65). In two other studies carried out in three cities in Iran, the mean age of participants was reported as 45.3 (range 29–83), 35.5 ± 10.8 years (range 18–66), and 31.9 ± 10.4 years (range 18–59) (36, 38). Also, in a study by Khoshnia et al., this measurement was reported as 50 years (66). While the present study reports a mean age of 26.8 y ± 19.5. According to the clinical symptoms of CD, gastrointestinal symptoms constitute the majority of symptoms (67). In addition, the most frequent symptoms among CD suspect SIgAD patients were abdominal pain (30%) and weight loss (30%). Other symptoms were growth problems (22%), loss of appetite (22%), constipation (14%), chronic diarrhea or steatorrhea (8%), and nausea and vomiting (8%). Abdominal bloating and diarrhea were mentioned as the most frequent clinical manifestations in the article written by Khoshnia et al. (66). Based on studies in some Middle East countries, the CD

was responsible for nearly 20% of chronic diarrhea cases in both adults and children (68–70). In research on the Middle Eastern population by Barada et al., the prevalence of abdominal pain, weight loss, and diarrhea was about 30%, 70%, and 60%, respectively (71). We also found some evidence suggesting a significant increase in serum Total IgA levels with age that is in agreement with research performed by Weber-Mzell et al. (72) and a mild decrease of serum Anti-tTG IgA levels similar to another investigation by Vivas et al. (73). According to this data, it could be possible to individualize the Total IgA test in CD suspects to resolve the cost-benefit dilemma, particularly in developing countries.

Conclusion

Our findings suggest that the CD prevalence in Birjand, eastern Iran, may be among the highest in the world. Further investigations are needed to ascertain the true prevalence.

Limitations

The main strength of our study is the large study population, which represents a considerable number of the Birjand population. Our research also had limitations; our study population was restricted to two leading laboratories in Birjand city, with total IgA or Anti tTG-IgA or both tests. We were also faced with a lack of appropriate gold standard testing for CD confirmation, such as endoscopic and pathology results in most patients, due to using large datasets. As a result, we could not provide precise figures for patients who tested negative for Anti tTG-IgA and had a duodenal biopsy.

Declarations

Ethics approval and consent to participate

Ethical approval for the study was obtained from the Ethics Committee of Birjand University of Medical Sciences (reference code: 5669; 6 March 2021), and the study was conducted in accordance with the principles of the Declaration of Helsinki. Informed consent was obtained from all participants. For participants younger than 18 years, including minors as young as one day old, both written and oral informed consent were obtained from their parent and/or legal guardian prior to the use of their clinical and laboratory information in the study.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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Author Contribution

Author Contributions Statement Dr. M.Z. conceived the study. Dr. A.R.M. designed the study and developed the study protocol. Dr. A.R.M. identified and collected the data, performed the laboratory data extraction, prepared and analyzed the

data, and interpreted the results. Dr. A.R.M. wrote and edited the manuscript and prepared all tables and figures. Dr. M.Z. reviewed the manuscript critically. Dr. A.R.M. and M.Z. reviewed and approved the final manuscript.

Data Availability

Availability of data and materials The datasets generated and/or analyzed during the current study are not publicly available due to ethical, confidentiality, and institutional restrictions. The de-identified data are held by the relevant university, hospital, and laboratory institutions. Requests for access to the data may be considered by the relevant Ethics Committee and institutional authorities, subject to applicable approvals and data-sharing policies. The authors cannot directly share the raw datasets without such authorization.

References

1. Rodrigo, L. et al. Cutaneous and mucosal manifestations associated with celiac disease. *Nutrients* **10** (7), 800 (2018).
2. Ludvigsson, J. F. et al. The Oslo definitions for coeliac disease and related terms. *Gut* **62** (1), 43–52 (2013).
3. Health NIo. NIH Consensus Development Conference on Celiac Disease,"National Institutes of Health Consensus Development Conference Statement,"NIH & Bethesda MD. June; (2004).
4. Kagnoff, M. F. AGA institute medical position statement on the diagnosis and management of celiac disease. *Gastroenterology* **131** (6), 1977–1980 (2006).
5. Rostom, A., Murray, J. A. & Kagnoff, M. F. American Gastroenterological Association (AGA) Institute technical review on the diagnosis and management of celiac disease. *Gastroenterology* **131** (6), 1981–2002 (2006).
6. Leffler, D. A. & Schuppan, D. Update on serologic testing in celiac disease. *Official J. Am. Coll. Gastroenterology| ACG*. **105** (12), 2520–2524 (2010).
7. Rubio-Tapia, A., Hill, I. D., Kelly, C. P., Calderwood, A. H. & Murray, J. A. American College of Gastroenterology clinical guideline: diagnosis and management of celiac disease. *Am. J. Gastroenterol.* **108** (5), 656 (2013).
8. Fasano, A. & Catassi, C. Celiac disease. *N. Engl. J. Med.* **367** (25), 2419–2426 (2012).
9. Rajput, M. S., Chauhan, A. & Makharia, G. K. Epidemiology of Celiac Disease. Advances in Celiac Disease: Improving Paediatric and Adult Care. :7. (2022).
10. Reddick, B. K. & Crowell, K. What blood tests help diagnose celiac disease? 2006.
11. Lewis, N. & Scott, B. Meta-analysis: deamidated gliadin peptide antibody and tissue transglutaminase antibody compared as screening tests for coeliac disease. *Aliment. Pharmacol. Ther.* **31** (1), 73–81 (2010).
12. Wang, N. et al. Selective IgA deficiency in autoimmune diseases. *Mol. Med.* **17** (11), 1383–1396 (2011).
13. Yel, L. Selective IgA deficiency. *J. Clin. Immunol.* **30** (1), 10–16 (2010).
14. Notarangelo, L. D. et al. Primary immunodeficiencies: 2009 update. *J. Allergy Clin. Immunol.* **124** (6), 1161–1178 (2009).
15. Wang, N. & Hammarström, L. IgA deficiency: what is new? Current opinion in allergy and clinical immunology. ;**12**(6):602–608. (2012).
16. Latiff, A. H. A. & Kerr, M. A. The clinical significance of immunoglobulin A deficiency. *Ann. Clin. Biochem.* **44** (2), 131–139 (2007).
17. Pelkowski, T. D. & Viera, A. J. Celiac disease: diagnosis and management. *Am. Family Phys.* **89** (2), 99–105 (2014).
18. Loayza DdLÁM, Spátola, M. A. A., de Campos, A. L. G., Pucci, C. M. & Gossweiler, C. O. Prevalence and characteristics of selective IgA deficiency in celiac patients. *Revista de Gastroenterol. del. Peru: organo oficial de la. Sociedad de Gastroenterol. del. Peru*. **41** (1), 11–15 (2021).

19. O'Farrelly, C. et al. Alpha gliadin antibody levels: a serological test for coeliac disease. *Br. Med. J. (Clin Res. Ed)*. **286** (6383), 2007–2010 (1983).
20. Rostom, A. et al. The diagnostic accuracy of serologic tests for celiac disease: a systematic review. *Gastroenterology* **128** (4), S38–S46 (2005).
21. Hill, I. D. What are the sensitivity and specificity of serologic tests for celiac disease? Do sensitivity and specificity vary in different populations? *Gastroenterology* **128** (4), S25–S32 (2005).
22. Shalom, G. et al. Atopic dermatitis and celiac disease: a cross-sectional study of 116,816 patients. *Am. J. Clin. Dermatol.* **21** (1), 133–138 (2020).
23. Sugai, E. et al. Accuracy of testing for antibodies to synthetic gliadin–related peptides in celiac disease. *Clin. Gastroenterol. Hepatol.* **4** (9), 1112–1117 (2006).
24. Volta, U. et al. Deamidated gliadin peptide antibodies as a routine test for celiac disease: a prospective analysis. *J. Clin. Gastroenterol.* **44** (3), 186–190 (2010).
25. Villalta, D. et al. Testing for IgG class antibodies in celiac disease patients with selective IgA deficiency.: A comparison of the diagnostic accuracy of 9 IgG anti-tissue transglutaminase, 1 IgG anti-gliadin and 1 IgG anti-deaminated gliadin peptide antibody assays. *Clin. Chim. Acta*. **382** (1–2), 95–99 (2007).
26. Villalta, D. et al. IgG antibodies against deamidated gliadin peptides for diagnosis of celiac disease in patients with IgA deficiency. *Clin. Chem.* **56** (3), 464–468 (2010).
27. Long, K. et al. The economics of coeliac disease: a population-based study. *Aliment. Pharmacol. Ther.* **32** (2), 261–269 (2010).
28. Di Sabatino, A. & Corazza, G. R. Coeliac disease. *Lancet* **373** (9673), 1480–1493 (2009).
29. Caio, G. et al. Celiac disease: a comprehensive current review. *BMC Med.* **17** (1), 1–20 (2019).
30. Al-Bawardy, B. et al. Celiac disease: a clinical review. *Abdom. Radiol.* **42** (2), 351–360 (2017).
31. Yazdani, R., Azizi, G., Abolhassani, H. & Aghamohammadi, A. Selective IgA deficiency: epidemiology, pathogenesis, clinical phenotype, diagnosis, prognosis and management. *Scand. J. Immunol.* **85** (1), 3–12 (2017).
32. Hopper, A. D. et al. What is the role of serologic testing in celiac disease? A prospective, biopsy-confirmed study with economic analysis. *Clin. Gastroenterol. Hepatol.* **6** (3), 314–320 (2008).
33. Tursi, A., Brandimarte, G. & Giorgetti, G. M. Prevalence of antitissue transglutaminase antibodies in different degrees of intestinal damage in celiac disease. *J. Clin. Gastroenterol.* **36** (3), 219–221 (2003).
34. Nejad, M. R., Rostami, K., Emami, M. H., Zali, M. R. & Malekzadeh, R. Epidemiology of celiac disease in Iran: a review. *Middle East. J. Dig. Dis.* **3** (1), 5 (2011).
35. Rostami, K., Malekzadeh, R., Shahbazkhani, B., Akbari, M. & Catassi, C. Coeliac disease in Middle Eastern countries: a challenge for the evolutionary history of this complex disorder? Digestive and liver disease. ;**36**(10):694–697. (2004).
36. Saberi-Firouzi, M., Omrani, G. R., Nejabat, M., Mehrabani, D. & Khademolhosseini, F. Prevalence of celiac disease in Shiraz, southern Iran. *Saudi J. Gastroenterology: Official J. Saudi Gastroenterol. Association*. **14** (3), 135 (2008).
37. Savvateeva, L. V., Erdes, S. I., Antishin, A. S. & Zamyatnin, A. A. Overview of celiac disease in Russia: regional data and estimated prevalence. Journal of immunology research. ;2017. (2017).
38. Akbari, M. R. et al. Screening of the adult population in Iran for coeliac disease: comparison of the tissue-transglutaminase antibody and anti-endomysial antibody tests. *Eur. J. Gastroenterol. Hepatol.* **18** (11), 1181–1186 (2006).
39. Singh, P. et al. Global prevalence of celiac disease: systematic review and meta-analysis. *Clin. Gastroenterol. Hepatol.* **16** (6), 823–836 (2018). e2.
40. Ashtari, S. et al. prevalence of celiac disease in low and high risk population in Asia–Pacific region: A systematic review and meta-analysis. *Sci. Rep.* **11** (1), 1–13 (2021).

41. Aghamohammadi, A. et al. Primary immunodeficiency disorders in Iran: update and new insights from the third report of the national registry. *J. Clin. Immunol.* **34** (4), 478–490 (2014).
42. Nabavizadeh, S. H., Karimi, M. H., Esmaeilzadeh, H., Attarhoseini, M. & Askarisarvestani, A. The prevalence and clinical manifestations of IgA deficiency among blood donors at transfusion centers in Shiraz, Southern Iran. *Am. J. Clin. Experimental Immunol.* **10** (4), 112 (2021).
43. Holt, P. & Tandy Na, Anstee, D. Screening of blood donors for IgA deficiency: a study of the donor population of south-west England. *J. Clin. Pathol.* **30** (11), 1007–1010 (1977).
44. Carneiro-Sampaio, M. et al. Frequency of selective IgA deficiency among Brazilian blood donors and healthy pregnant women. *Allergol. Immunopathol.* **17** (4), 213–216 (1989).
45. Yazdani, R. et al. Clinical phenotype classification for selective immunoglobulin A deficiency. *Expert Rev. Clin. Immunol.* **11** (11), 1245–1254 (2015).
46. Al-Attas, R. A. & Rahi, A. H. Primary antibody deficiency in Arabs: first report from eastern Saudi Arabia. *J. Clin. Immunol.* **18** (5), 368–371 (1998).
47. Chow, M. A., Lebwohl, B., Reilly, N. R. & Green, P. H. Immunoglobulin A deficiency in celiac disease. *J. Clin. Gastroenterol.* **46** (10), 850–854 (2012).
48. Heneghan, M. A., Stevens, F. M., Cryan, E. M., Warner, R. H. & McCarthy, C. F. Celiac sprue and immunodeficiency states: a 25-year review. *J. Clin. Gastroenterol.* **25** (2), 421–425 (1997).
49. Cataldo, F., Marino, V., Ventura, A., Bottaro, G. & Corazza, G. Prevalence and clinical features of selective immunoglobulin A deficiency in coeliac disease: an Italian multicentre study. *Gut* **42** (3), 362–365 (1998).
50. McGowan, K. E., Lyon, M. E. & Butzner, J. D. Celiac disease and IgA deficiency: complications of serological testing approaches encountered in the clinic. *Clin. Chem.* **54** (7), 1203–1209 (2008).
51. Cataldo, F., Marino, V., Bottaro, G., Greco, P. & Ventura, A. Celiac disease and selective immunoglobulin A deficiency. *J. Pediatr.* **131** (2), 306–308 (1997).
52. Pallav, K., Xu, H., Leffler, D. A., Kabbani, T. & Kelly, C. P. Immunoglobulin A deficiency in celiac disease in the United States. *J. Gastroenterol. Hepatol.* **31** (1), 133–137 (2016).
53. Korponay-Szabó, I. R. et al. Elevation of IgG antibodies against tissue transglutaminase as a diagnostic tool for coeliac disease in selective IgA deficiency. *Gut* **52** (11), 1567–1571 (2003).
54. Savilahti, E., Pelkonen, P. & Visakorpi, J. IgA deficiency in children: A clinical study with special reference to intestinal findings. *Arch. Dis. Child.* **46** (249), 665–670 (1971).
55. Klemola, T. Immunohistochemical findings in the intestine of IgA-deficient persons: number of intraepithelial T lymphocytes is increased. *J. Pediatr. Gastroenterol. Nutr.* **7** (4), 537–543 (1988).
56. Meini, A. et al. Prevalence and diagnosis of celiac disease in IgA-deficient children. *Ann. Allergy Asthma Immunol.* **77** (4), 333–336 (1996).
57. Aletaha, N., POURSHAMS, A. & Shahbazkhani, B. Celiac Disease. (2007).
58. Cook, H. B. et al. Adult coeliac disease: prevalence and clinical significance. *J. Gastroenterol. Hepatol.* **15** (9), 1032–1036 (2000).
59. Masjedizadeh, R. et al. Celiac disease in south-west of Iran. *World J. Gastroenterology: WJG*. **12** (27), 4416 (2006).
60. Ludvigsson, J. F. et al. Symptoms and signs have changed in Swedish children with coeliac disease. *J. Pediatr. Gastroenterol. Nutr.* **38** (2), 181–186 (2004).
61. Catassi, C. et al. Coeliac disease in the year 2000: exploring the iceberg. *Lancet* **343** (8891), 200–203 (1994).
62. James, M. W. & Scott, B. B. Coeliac disease: the cause of the various associated disorders? *Eur. J. Gastroenterol. Hepatol.* **13** (9), 1119–1121 (2001).
63. Green, P. H. & Jabri, B. Coeliac disease. *Lancet* **362** (9381), 383–391 (2003).

64. Ahmadi, B. & Zaherara, M. Prevalence of celiac disease in patients with irritable bowel syndrome in Kerman, Iran. *J. Kerman Univ. Med. Sci.* **22** (3), 319–327 (2015).
65. Shahbazkhani, B., Mehrabi, G., Nasiritosi, M., Forotan, H. & Asefirad, S. Celiac disease in cryptogenic hypertransaminasemia. *Tehran Univ. Med. J.* ;**68**(7). (2010).
66. Khoshnia, M. et al. Celiac disease in gonbad-kavoos. *Govaresh* **10** (3), 131–133 (2012).
67. Lo, W., Sano, K., Lebwohl, B., Diamond, B. & Green, P. H. Changing presentation of adult celiac disease. *Dig. Dis. Sci.* **48** (2), 395–398 (2003).
68. Qari, F. A. Clinical presentation of adult celiac disease in Western Saudi Arabia. *Saudi Med. J.* **23** (12), 1514–1517 (2002).
69. Rostami, K., Shahbazkhani, B. & Malekzadeh, R. Microenteropathy; the entity of the new millennium. Overview of the second asian symposium on coeliac disease, October 18–21, 2003, Tehran. Romanian journal of gastroenterology. ;13(1):29–31. (2004).
70. Sima, H., Hekmatdoost, A. & Ghaziani, T. Seroprevalence of coelic disease among autoimmune and HBV chronic hepatitis in Tehran Iran. *Govaresh* **7** (237), 34 (2003).
71. Barada, K., Bitar, A., Mokadem, M. A. R., Hashash, J. G. & Green, P. Celiac disease in Middle Eastern and North African countries: a new burden? *World J. gastroenterology: WJG*. **16** (12), 1449 (2010).
72. Weber-Mzell, D. et al. Gender, age and seasonal effects on IgA deficiency: a study of 7293 Caucasians. *Eur. J. Clin. Invest.* **34** (3), 224–228 (2004).
73. Vivas, S., Vaquero, L., Rodríguez-Martín, L. & Caminero, A. Age-related differences in celiac disease: Specific characteristics of adult presentation. *World J. Gastrointest. Pharmacol. Ther.* **6** (4), 207 (2015).

Figures

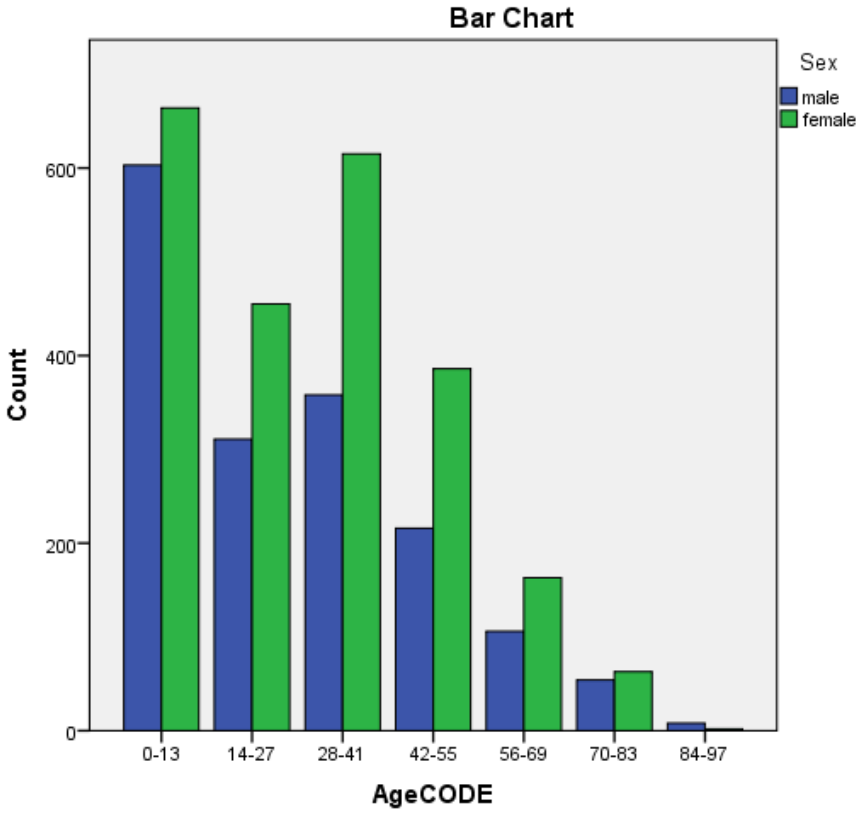

Figure 1

Source population age distribution.

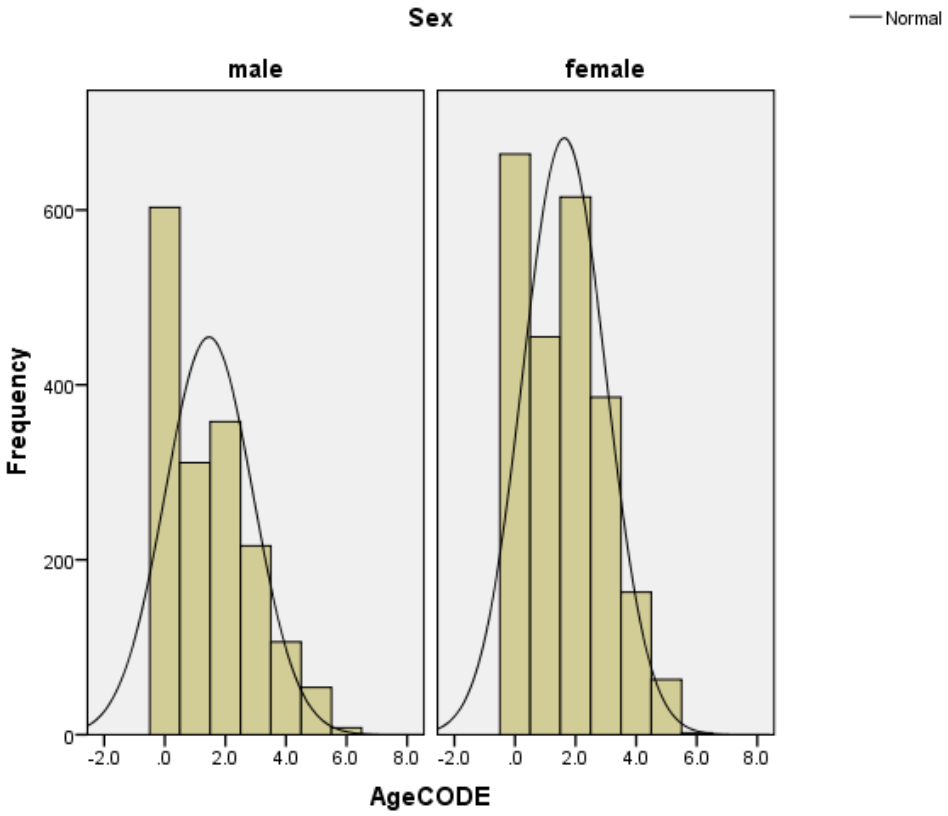

Figure 2

Age distribution by sex.

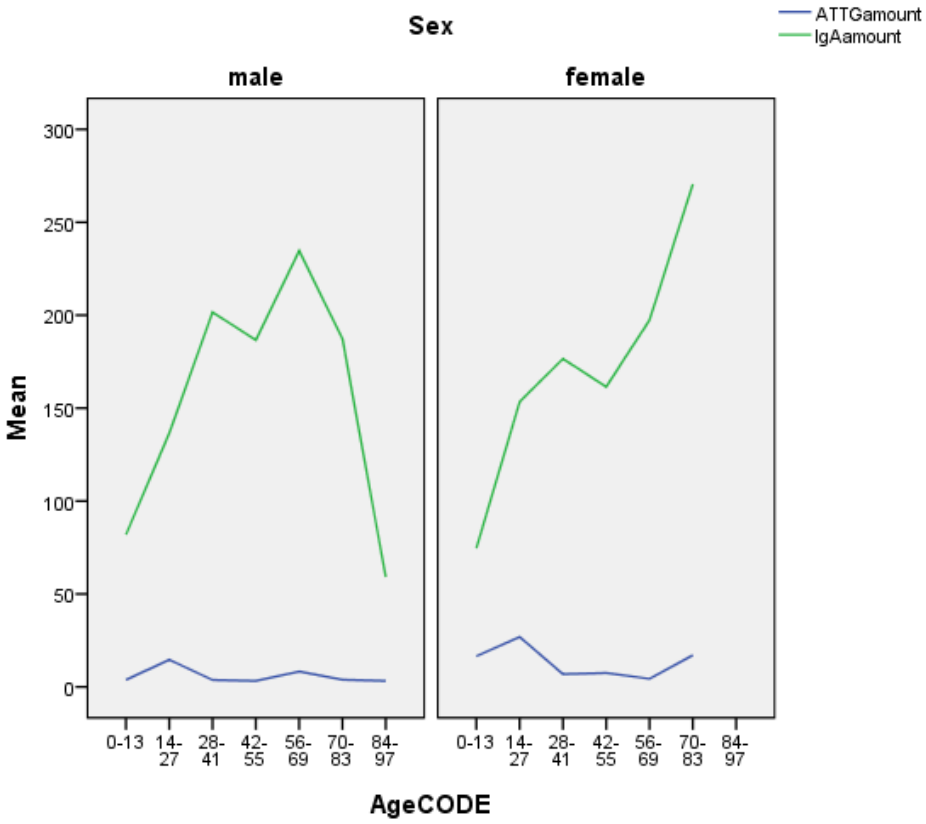

Figure 3

Serum levels of Total IgA and Anti tTG IgA in different ages according to sex.

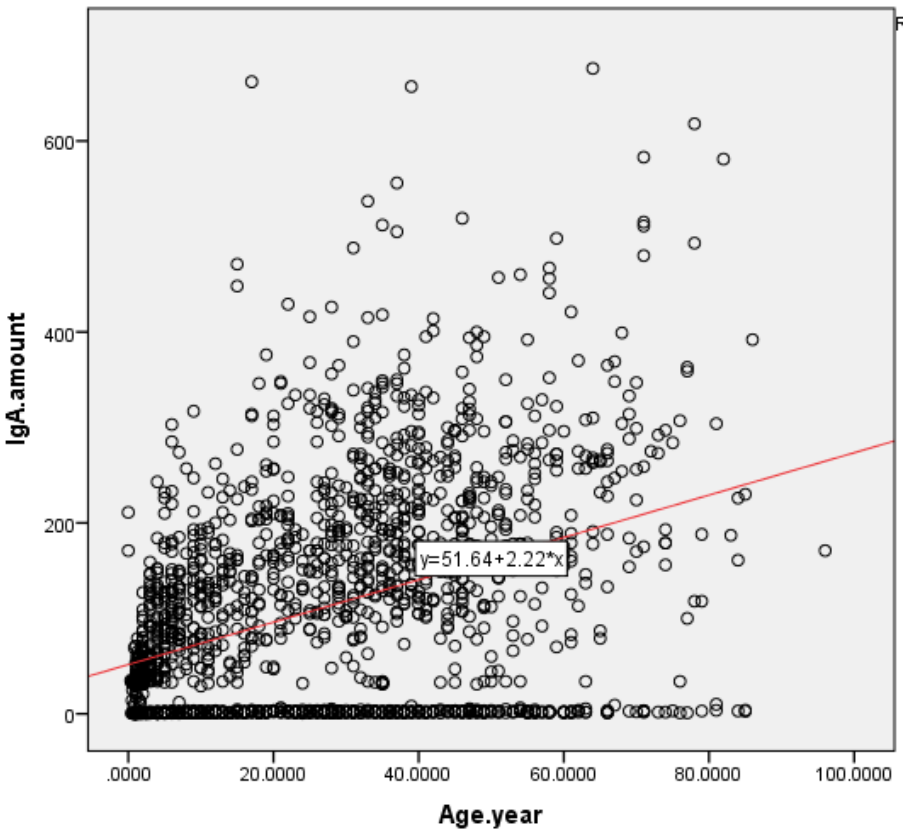

Figure 4

Age distribution of serum Total IgA levels.

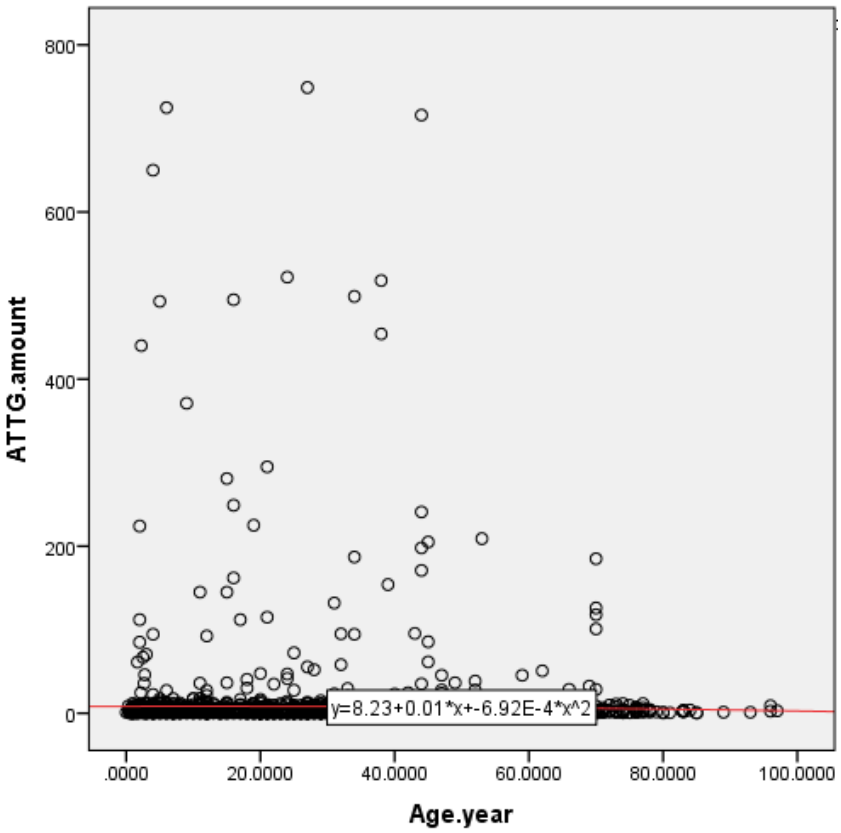

Figure 5

Age distribution of serum Anti tTG IgA levels.