ADITUM

Journal of Clinical Case Reports and Clinical Study

Open Access Research Article

Celiac Disease Among Gastrointestinal Patients Attending A Gastro-Intestinal Endoscopy Unit: Prevalence, Symptoms, Signs, And Association with Age and Gender

Muhamed Ahmed Al-Haimi [1], Samah Mohsen Askar Al-Harthi[2], Hassan Abdulwahab Al-Shamahy[3]*

[1]Department of Medicine-Gastroenterology Division, Faculty of Medicine and Health Sciences, Sana'a University, Republic of Yemen.

[2]Department of Medicine, Faculty of Medicine, Dahmar University, Republic of Yemen.

[3]Medical Microbiology department, Faculty of Medicine, Genius University for Sciences & Technology, Dhamar city, Republic of Yemen.

Article Info

Received: July 12, 2022
Accepted: July 18, 2022
Published: July 20, 2022

***Corresponding author:** Hassan Abdulwahab Al-Shamahy, Medical Microbiology department, Faculty of Medicine, Genius University for Sciences & Technology, Dhamar city, Republic of Yemen.

Citation: Muhamed Ahmed Al-Haimi, Samah Mohsen Askar Al-Harthi, Hassan Abdulwahab Al-Shamahy (2022) "Celiac Disease Among Gastrointestinal Patients Attending A Gastro-Intestinal Endoscopy Unit: Prevalence, Symptoms, Signs, And Association with Age and Gender", Clinical Case Reports and Clinical Study, 4(7); DOI: http;//doi.org/07.2022/1.143.

.

Abstarct

Background and objectives: Celiac disease is a multisystem autoimmune disease that is triggered in genetically susceptible individuals by eating products containing gluten. It affects approximately 1% of the population worldwide, although a significant proportion of patients remain undiagnosed. The prevalence of celiac disease has not been well established in Yemen, either in the general population or in symptomatic patients. Therefore, the current study aimed to assess the prevalence of disease in asymptomatic patients undergoing upper GI endoscopy to investigate associated symptoms and signs; and whether CD prevalence differs significantly between different ages and genders in a tertiary hospital in Sana'a.

Methods: A cross-sectional study based on the results of esophagogastroduodenoscopy (EGD) and serological markers; total IgA anti-tissue transglutaminase (tTG), and total anti-endomysial IgA (EMA), for 111 patients with gastrointestinal symptoms who were all patients who attended endoscopy units in the research period in the Police Hospital. Data were collected by means of a pre-designed questionnaire then the results were analyzed.

Results: The patients were 49 males and 62 females, with a mean age equal to 27.6 ± 12.5 years (range, 4–64 years). The prevalence of CD among gastrointestinal patients was 16.2%. There was an association of CD with females (rate 19.4%, OR = 1.7, p = 0.31) but not statistically significant, and its prevalence among age groups was approximately equal except for 0% prevalence in >60 years of age. Looking at clinical signs and symptoms comparing the positive and negative CD group, there was a significant association between celiac disease and steatorrhea, weight loss, aphthous stomatitis, anemia, hair loss, dry skin, pruritus, depression, peripheral neuropathy, and amenorrhea , sterility, sterility, menopause, angular chilosis and dermatitis.

Conclusion: A high rate of CD was identified among gastrointestinal symptoms patients undergoing upper gastrointestinal endoscopy, arriving at the tertiary hospital in Sana'a, Yemen, and this demonstrates the importance of general practitioners in identifying patients with CD, especially in the absence of a medical facility for CD, and this was facilitated through the serological markers test. Our findings also indicate that celiac disease is more common in females, children and younger people, and there was an association between CD and the non-gastrointestinal classic symptoms of this disease as hair loss, dry skin, itching, depression, and peripheral neuropathy which can be used for clinical diagnosis.

Keywords: Celiac disease (CD), prevalence, signs, symptoms, upper gastrointestinal endoscopy, Yemen

Introduction

Internationally, celiac disease (CD) have an effect on between 1 in 100 and 1 in 170 people [1,2]. However, rates vary between different regions of the world from 1 in 300 to 1 in 40 [2]. It was also found that 1 out of every 105 blood donors carries IgA TG

in their blood. Because of the variable signs and symptoms, it is believed that about 85% of sufferers go undiagnosed [4]. It was also found that the percentage of people with a clinically diagnosed disease (symptoms trigger a diagnostic test) is 0.05-0.27% in most studies [1-4]. CD consequences from a reaction with gluten, which is a group of different proteins found in wheat and other grains such as barley and rye. Moderate amounts of oats, free from pollution with further gluten-containing grains, are regularly tolerated. The incidence of harms may depend on the type of oats. CD appears in people with a genetic predisposition. When exposed to gluten, the abnormal immune response may result in the production of many different auto-antibodies that can involve a number of distinct organs. In the small intestine, this causes an inflammatory reaction and may lead to villous atrophy. This affects the absorption of nutrients, often leading to anemia [1-4].

In the diagnosis of CD by histopathology; upper endoscopy is performed with a biopsy of the duodenum (beyond the duodenal bulb) or the jejunum to obtain multiple (four to eight) samples of the duodenum. It is known that not all areas may be affected equally; for example, if biopsies are taken from healthy intestinal tissue, the result will be a false negative [5]. Even in the same bioptic fragment, the presence of different degrees of damage may appear [6]. Most people with celiac disease emerge from a normal-looking small intestine on endoscopy before biopsies are examined in the lab. However, five findings at endoscopy have been associated with high specificity for celiac disease: 1-scalloping of small bowel folds (*pictured*), 2- paucity of folds, 3-mosaic pattern of the mucosa, 4- Submucosal vascular protrusion, 5- and nodular pattern of mucosa [7]. The gold standards in diagnosing CD are bowel biopsy and positive serological markers as tTG IgA and EMA IgA. European guidelines recommend that in adolescents and children with symptoms compatible with celiac disease, the diagnosis can be made without the need for an intestinal biopsy if tTG antibody titers are 10 times the upper limit of normal [8].

CD is a persistent autoimmune disease that primarily affects the small intestine, so classic symptoms include digestive problems such as chronic diarrhea, flatulence, loss of appetite, mala-absorption and failure of children to grow normally. This begins regularly between six months and two years of age. Non-classical symptoms are more common, especially in people older than 2 years. There may be moderate or absent gastrointestinal symptoms, a large number of symptoms related to any part of the body, or no visible symptoms. It is also associated with autoimmune diseases, such as type 1 diabetes, Hashimoto's, and thyroiditis [1,11]. There are limited studies in CD in Yemen [12,13] as well as studies in gastroenterology and/or autoimmune diseases are still limited in Yemen and only a few studies have been conducted on autoimmune diseases, and gastrointestinal diseases among adults and children [14-26]. Therefore, the current study aimed to assess the prevalence of disease in symptomatic patients undergoing upper gastrointestinal endoscopy to investigate associated symptoms and signs; and whether prevalence of CD varies greatly between different ages and genders in a tertiary hospital in Sana'a.

Materials and Methods

Study design and setting: This cross sectional study was conducted at the unit of endoscopy in the Police Hospital (PH) in Sana'a, Yemen.

Study population: The population of this study were all patients whom referred to endoscopy unit.

Inclusion criteria: All patients referred to the endoscopy unit at the time of the study with gastrointestinal symptoms with different ages and genders, willing to participate, not previously diagnosed as CD.

Inclusion criteria: Patients with chronic liver diseases, irritable bowel disease, and acute viral gastroenteritis.

Data collection and laboratory diagnosis: 111 symptomatic patients undergoing endoscopy were enrolled in this study. Among them, 49 (44.1%) males and 62 (55.9%) females attended pediatric clinics, internal medicine clinics, and gastroenterology units and referred to endoscopy unit in KUH from April 2020 to January 2021. Data were collected by predesigned questionnaire including demographic data, history and physical examination results, (symptoms and signs). CD cases diagnosis were based on the results of esophagogastroduodenoscopy (EGD), serological markers; total IgA anti-tissue transglutaminase (tTG), and total IgA anti-endomysial (EMA) IgA. By enzyme-linked immunosorbent assay (ELISA), positive ATtg IgA and EMA IgA criteria greater than 10 times the upper limit of normal (ULN) in children or less than 10 times the ULN but confirmed by small bowel biopsy, were the criteria used to measure the prevalence of celiac disease. Hemoglobin levels (to define anemia based on a hemoglobin concentration less than 11 g/dL) were also included. The subjects were divided into categories based on gender and age. Clinical signs, symptoms and other diseases associated with celiac disease were also collected and analyzed.

Data analysis: The whole data were analyzed by IBM SPSS Statistics 22.Ink (International Business Machines Corporation, New York, USA). The outcomes for variables were given in the form of rates (%). Chi Square was used for categorical variables that measured association among categorical variables. *P*-values less than 0.05 were considered significant. Odds of celiac disease (odds ratio, OR) were also analyzed by sex, age groups, symptoms and signs, with 95% *CI*, X^2 and *p* to test for significance of association with the above factors.

Results

The study included 49 males (44.1%) and 62 females (55.9%). Considering ages, mean ± SD = 27.6 ± 12.5 years and range = 4–64 years; Most of the patients were in the age group 20-40 years (58.6%), followed by 4-19 years (20.7%), then 41-60 years (18%), while only 3 (2.7%) were over 60 years old (Table 1). Looking at the signs of serology; AtTG was positive in 18 (16.2%) patients, and EMA was positive in 23 (20.7%) patients. With histological findings, IEI was positive in 78 (70.3%), while only 18 (16.2%) were positive for villous atrophy. When sensitivity and specificity of the methods used for diagnosis were considered by comparing villous atrophy as a standard test for CD diagnosis, the AtTG test was 100% sensitive and specific to diagnostic CD, for EMA sensitivity was 94.4% and specificity 93.5%, while less sensitivity occurred for IEI (88.8%) and very low specificity (34.1%) for IEI occurred (Table 2).

Table 1: Age and gender distribution of patients referred for upper gastrointestinal endoscopy with intestinal symptoms in the police hospital endoscopy unit, Sana'a, Yemen

Characters	Number	%	P
Gender			
Male	49	44.1	<0.05
Female	62	55.9	
Age groups			
4-19 years	23	20.7	<0.05
20-40 years	65	58.6	
41-60 years	20	18	
>60 years	3	2.7	
Total	111	100	Mean ±SD =27.6±12.5 years
			Range= 4-64years

*significance level less than 0.05 (P).

Table 2: The positive rate of Celiac disease markers among patients referred for upper gastrointestinal endoscopy with intestinal symptoms

Results	Serology		Histology		Prevalence of CD
	AtTG No (%)	EMA No (%)	IEI No (%)	Villus atrophy No (%)	
Positive	18 (16.2)	23 (20.7)	78 (70.3)	18 (16.2)	18 (16.2)
Negative	93 (83.7)	88 (79.2)	33 (29.7)	93 (83.7)	93 (83.7)
sensitivity	100	94.4	88.8	Reference	
Specificity	100	93.5	34.1		

Table 3 shows the association of positive celiac disease with different sex and age groups for patients who completed UG endoscopy. There was a slightly higher rate of CD among females (19.4%) with an OR equal to 1.7 while in males it was 12.2%; and the differences were not statistically significant. The highest incidence of CD was in the 41-60 year group (20% with OR = 1.4), followed by the 2-19 year group (17.7%) and the 20-40 year group (15.4%), while all cases in the >60 year group were negative for CD, while the differences were not statistically significant for all ages results.

Table 3: The association of positive celiac diseases with different sex and age groups of patients completed UG endoscopy

Characters		celiac disease n=18		***OR***	***CI 95%***	***X^2***	***p***
		No	%				
Gender							
Male	n=49	6	12.2	0.2	0.2-1.6	1.0	0.31
Female	n=62	12	19.4	1.7	0.59-4.9	1.0	0.31
Age groups							
2-19 years	n=23	4	17.4	1.1	0.3-37	0.02	0.86
20-40 years	n=65	10	15.4	0.8	0.3-2.3	0.07	0.77
41-60 years	n=20	4	20	1.4	0.4-4.7	0.25	0.61
>60 years	n=3	0	0.0	0.0	undefined	0.59	0.43
Total	n=111	18	16.2				

OR=Odds ratio, CI 95% = 95% confidence limits, X^2 = chi square, p= p value

Looking at clinical signs and symptoms comparing the positive and negative CD group, there was a significant association between celiac disease and steatorrhea with rate was100% (p<0.0001), weight loss rate of 94.4% (OR=20.6,CI=2.6-161, p<0.0001) , aphthous stomatitis 83.3% (OR=15.2, CI=4.1- 57.3, p<0.0001), anemia 77.8% (OR=6.3,CI=1.9 – 20.9, p<0.0001), hair loss rate 77.8% (OR=15.6, CI=4.5 - 55, p<0.0001), dry skin 72.2% (OR=10.1, CI=3.2 -31.9, p<0.0001), pruritus 17.8% (OR=17.8, CI=4.5 - 69.8, p<0.0001), depression 44.4% (OR=2.9, CI=1.1- 8.3, p<0.0001), peripheral neuropathy 22.2% (OR=5.1, CI=1.2 -21, p=0.01), amenorrhea with 22.2% (OR=6.3,CI=1.4-28, p=0.007), infertility 16.7% (OR=18.4, CI=11.7- 188, p<0.0001), angular chilosis 22.2% (OR=13, CI=2.2 - 77.7, p<0.0001), and dermatitis with rate equal to 38.9% (OR=19.1, CI=4.3 – 84.7, p<0.0001) (Table 4).

.

Table 4: The association of positive celiac diseases with Clinical signs and symptoms comparing with that negative celiac disease of patients completed UG endoscopy

Symptoms and signs	Patients with intestinal symptoms **n=111**		**celiac disease n=18**		**OR**	***CI* 95%**	X^2	***p***
	No	%	%	No				
Abdominal pain	108	97.3	18	100	undefined		0.59	0.43
Anorexia	84	75.7	18	100	undefined		6.9	0.008
Flatulence	104	93.7	18	100	undefined		1.4	0.029
Chronic diarrhea	105	94.6	18	100	undefined		1.2	0.26
Steatorrhoea	47	42.3	18	100	undefined		29.2	<0.0001
Abdominal distention	101	91	17	94.4	1.8	0.2-15	0.31	0.57
Weight loss	59	53.2	17	94.4	20.6	2.6-161	14.7	<0.0001
Nausea –vomiting	80	72.1	17	94.4	8.1	1.1-63.7	5.3	0.02
Heart burn	92	82.9	16	88.9	1.7	0.3-8.5	0.54	0.45
Aphthus stomatitis	38	34.2	15	83.3	15.2	4.1-57.3	23	<0.0001
Anemia	47	42.3	14	77.8	6.3	1.9-20.9	11.1	<0.0001
Hair loss	31	27.9	14	77.8	15.6	4.5-53	26.5	<0.0001
Dry skin	32	28.8	13	72.2	10.1	3.2-31.9	19.7	<0.0001
Arthralgia	33	29.7	9	50	2.8	1.1-8.1	4.2	0.03
Itching	12	10.8	8	44.4	17.8	4.5-69.8	25.2	<0.0001
Depression	28	25.2	8	44.4	2.9	1.1-8.3	4.2	0.04
Dermatitis	10	9	7	38.9	19.1	4.3-84.7	23.3	<0.0001
Angular chilosis	6	5.4	4	22.2	13	2.2-77.7	11.1	<0.0001
Headache	12	10.8	4	22.2	3	0.8-11.4	2.9	0.08
Backache	14	12.6	4	22.2	2.3	0.65-8.6	1.8	0.17
Peripheral neuropathy	9	8.1	4	22.2	5.1	1.2-21	5.7	0.01
Amenorrhea	8	7.2	4	22.2	6.3	1.4-28	7.2	0.007
Infertility	4	3.6	3	16.7	18.4	11.7-188	10.5	0.001
Dermatitis herpetiformis	1	0.9	1	5.6	undefined		5.2	0.02
Anxiety	2	1.8	1	5.6	5.4	0.3-90.7	1.7	0.19
Convulsion	2	1.8	1	5.6	5.4	0.3-90.7	1.7	0.19
Total	111	100	18	16.2				

OR=Odds ratio, CI 95% = 95% confidence limits, X^2 = chi square, p= p value

Discussion

AtTG was positive in 18 (16.2%) of our patients, and the production of AtTG could be explained by the sedation being the reaction by which glutamate residues are formed by cleavage of the epsilon-amino group of a glutamine side chain. The transamide process, occurring three times more often than deamidation is the cross-linking of the glutamine residues of the gliadin peptide to the lysine residues of tTG in a reaction catalyzed by transglutaminase. Cross-linking may occur either inside or outside the active site of the enzyme. The latter case produces a permanently covalently bound complex between gliadin and tTg. This results in the formation of new epitopes that are believed to stimulate the primary immune response by which auto-antibodies against tTg are developed [27,28], this interaction confirms the specificity of AtTG in CD diagnosis.

In the current study, when the sensitivity and specificity of the methods used for diagnosis were considered by comparing villous atrophy as a standard diagnostic test for CD, the AtTG test was 100% sensitive and specific; and intended for diagnostic CD so that this test could be used as an alternative to an endoscopic procedure. Due to the invasive nature of the endoscopic procedure, patients' reluctance to undergo scope examination and biopsy sampling, as well as the many pitfalls related to histology, a growing interest has emerged in the past decades in non-biopsy diagnosis of CD. This has already been validated in pediatric CD

and has been implemented since 2012 ESPHGAN Guidelines, which allowed the diagnosis of CD without biopsies in European symptomatic children who met the three diagnostic criteria: tissue transglutaminase antibodies greater than 10 times the upper limit of normal (ULN).), positive antibody (EMA) and positive HLA-DQ2/DQ8 haplotype [8]. This allowed a significant reduction in the number of endoscopy needed to diagnose CD and especially pediatric CD [29]. Furthermore, the updated 2020 ESPHGAN Guidelines define lighter rules for a non-vital strategy for CD diagnosis, not requiring HLA testing and the presence of symptoms in children with IgA transglutaminase 2 (TG-2) antibody values 10 times ULN and positive EMA in a second serum sample [30]. Though the pediatric practice has motivated researchers and clinicians to turn to adult CDs to support the non-biopsy strategy, some have suggested more caution as there can be misdiagnosis with such bases, especially in primary care, and others against the omission of endoscopy and biopsies in duodenum in adult CD as a baseline for histology, comparison with follow-up biopsy in non-responders is needed [31,32]. In addition, while there is a good correlation between serology and mucosal injury at diagnosis, CD-bound antibodies do not accurately detect persistent villous atrophy in CD patients treated with a gluten-free diet [33]. Recently developed investigative tools, such as the HLA-DQ-based tetra-gluten-based blood test, may modify the way that diagnose CD in the near future, imminent verification and scalability. This technology, joint with validation of serology-based diagnostic algorithms, may lead to a change in diagnostic criteria because a small bowel biopsy is no longer necessary while patients continue to follow a gluten-containing diet. These revolutionizes may transform the roles of gastroenterologists, from diagnosis to management and follow-up. If an evidence-based, biopsy-free strategy is developed for diagnosis, the incidence of celiac disease may grow further and motivate interventional studies to prevent celiac disease in at-risk individuals [34]. In Yemen, the prevalence of CD has not been well estimated so far, and only two previous studies discussed were found for CD in adult fertility and CD among gastrointestinal patients [12, 13], and the current work is an attempt to determine the rate of CD among suspected clinically patients. The prevalence of celiac disease among patients with gastrointestinal symptoms undergoing endoscopy in the current study was 16.2%. Compared with our observations, the prevalence of CD in the current study exceeds the rate of CD among suspects GI patients in Al-dossary *et al.* study (9.2%) [12]. Also, compared to our observations, the prevalence of CD in Yemen exceeds the rate of CD among suspected patients with gastrointestinal symptoms as in Saudi Arabia, South Yorkshire, Amsterdam, the Netherlands and North America among the symptoms representing the gastrointestinal tract; 7.6%, 4.7%, 3.0% and 2.0%, respectively [35-38]. In addition, our result is higher than that presented by Dickey *et al.* and Hopper *et al.* [39,40] where the incidence of CD among patients with undiagnosed gastrointestinal symptoms was about 9%. In contrast to our average (16.2%), the prevalence of CD among Iranian patients with irritable bowel syndrome was about 12% and among patients with gastrointestinal symptoms in Italy was about 13% as reported by Shahbazkhani *et al.* and Carroccio *et al.* respectively [41,42].

Considering gender, there was an association between CD and females at a rate of 19.4% versus 12.2% of males (OR = 1.7, p = 0.31) (Table 3). This result is similar to that previously reported where the incidence of CD was higher in females than males (17.0 vs. 7.8 per 100,000 person-years) in the cohort analysis [43], but this may be for the reason that a higher proportion of men may remain undiagnosed. . A systematic review and meta-analysis also found a slight increase in seropositivity among women participating in screening studies [44] although some studies in adults found that men and women had similar seroprevalence rates [45, 46]. Finally, men may be less likely to undergo duodenal biopsy during upper endoscopy for indications such as diarrhea and weight loss, which may play a role in under-diagnosis [47]. CD can appear at any age, including the elderly [48]. It is known that the CD appeared for the first time in childhood and it thought that it was a disease of children only; However, it may appear at all ages. Considering the age in the current study, there was a higher rate in the 41-60 year age group where the rate was 20% (Table 2). This differs from what was previously reported as the incidence of CD was higher in the younger age group. This rise in CD at an older age can be explained by the fact that such diagnoses point to the late discovery of CD despite the long-suffering. Also, recent prospective cohort studies have found that most patients develop CD before the age of 10 years [49,50].

Looking at clinical signs and symptoms in the current study comparing the positive and negative CD group, there was a significant association between celiac disease and steatorrhea (100%), weight loss (OR=20.6), aphthous stomatitis (15.2), anemia (OR=6.3), hair loss rate (OR=15.6), dry skin (OR=10.1), pruritus (OR=17.8), depression (OR=2.9), peripheral neuropathy (OR=5.1), amenorrhea (OR=6.3), infertility (OR=18.4), angular chilosis (OR=13), and dermatitis (OR=19.1) (Table 4). These findings are almost similar to those reported in the literature where symptoms of untreated celiac disease include pale, loose, or oily stools (steatorrhea) and weight loss or failure to gain weight. Other common symptoms may be subtle or occur primarily in organs other than the intestine itself [51]. It's also possible to have celiac disease without any classic symptoms at all. This has been shown to comprise at least 43% of presentations in children [52].

Furthermore, many adults with latent disease may only develop fatigue or anemia [53]. Many undiagnosed individuals who consider themselves asymptomatic are in fact not, but are accustomed to living in a chronic health condition. In fact, after initiation of a gluten-free diet and subsequent development becoming apparent, these individuals are often able to recall and retrospectively recognize previous symptoms of their untreated disease that they mistakenly ignored [54]. The incidence of CD is increasing as it spreads throughout the world. There is a trend towards increased diagnosis of atypical presentations, and there is emerging evidence for accurate diagnosis other than biopsy among patients and particularly in children [49].

Conclusions

A high rate of CD was identified among gastrointestinal symptoms patients undergoing upper gastrointestinal endoscopy, arriving at the tertiary hospital in Sana'a, Yemen, and this demonstrates the importance of general practitioners in identifying patients with CD, especially in the absence of a medical facility for CD, and this was facilitated through the serological markers test. Our findings also indicate that celiac disease is more common in females, children and younger people, and there was an association between CD and the non-

gastrointestinal classic symptoms of this disease as hair loss, dry skin, itching, depression, and peripheral neuropathy which can be used for clinical diagnosis. However, more studies are needed to support and confirm our findings and conclusions. According to this high prevalence, clinicians should pay more attention to CD when examining huge different symptoms to avoid misdiagnosis or long-term delay diagnosis.

Acknowledgments

The authors acknowledge the Police Hospital for support this research and materials supply.

Authors' Contributions

All authors contributed to the study design, analysis and manuscript writing.

Ethical Approval

Ethical approval was obtained from the Ethics Committee from the Faculty of Medicine and Health Sciences, Sana'a University, Sana'a, Yemen.

References

1. Lebwohl B, Ludvigsson JF, Green PH. "Celiac disease and non-celiac gluten sensitivity". BMJ 2015; 351: h4347. .
2. Fasano A, Catassi C. "Clinical practice. Celiac disease". The New England Journal of Medicine (Review) 2012; 367 (25): 2419–26.
3. Rewers M. "Epidemiology of celiac disease: what are the prevalence, incidence, and progression of celiac disease?" (PDF). Gastroenterology 2005; 128 (4 Suppl 1): S47–51.
4. Guandalini S, Assiri A. "Celiac disease: a review". JAMA Pediatrics 2014; 168 (3): 272–8.
5. American Gastroenterological Association medical position statement: Celiac Sprue". Gastroenterology 2001;120 (6): 1522–5.
6. Tonutti E, Bizzaro N (2014). "Diagnosis and classification of celiac disease and gluten sensitivity". Autoimmun Rev 2014; 13 (4–5): 472–6.
7. Niveloni S, Fiorini A, Dezi R, et al. "Usefulness of videoduodenoscopy and vital dye staining as indicators of mucosal atrophy of celiac disease: assessment of interobserver agreement". Gastrointestinal Endoscopy 1998; 47 (3): 223–29.
8. Husby S, Koletzko S, Korponay-Szabó IR, et al. "European Society for Pediatric Gastroenterology, Hepatology, and Nutrition guidelines for the diagnosis of coeliac disease". J Pediatr Gastroenterol Nutr 2012; 54 (1): 136–60.
9. Mee AS, Burke M, Vallon AG, et al. "Small bowel biopsy for malabsorption: comparison of the diagnostic adequacy of endoscopic forceps and capsule biopsy specimens". The BMJ 1985; 291 (6498): 769–72.
10. Redondo-Cerezo E, Sánchez-Capilla AD, De La Torre-Rubio P, De Teresa J. "Wireless capsule endoscopy: Perspectives beyond gastrointestinal bleeding". World J. Gastroenterol 2014; 20 (42): 15664–73.
11. Tovoli F, Masi C, Guidetti E, et al. "Clinical and diagnostic aspects of gluten related disorders". World Journal of Clinical Cases 2015; 3 (3): 275-84.
12. Al-dossary OAI, Ahmed RA, Al-Moyed KAA, Al-Ankoshy AAM, Al-Najhi MMA, Al-Shamahy HA. Celiac disease among gastrointestinal patients in Yemen: its prevalence, symptoms and accompanying signs, and its association with age and gender. Universal Journal of Pharmaceutical Research 2021; 6(5):1-6.
13. Al-Anesi M, Hu Q, Al-Eryani E, Al-Amrani M, Al-Shamahy H. The association of adult male and female infertility with celiac disease patients in Yemen. Universal J Pharm Res 2017; 2(6): 21-23.
14. Othman A, Alyosfi E, AL-Shamahy H. The association of epstein-barr virus antibodies with rheumatoid arthritis among Yemeni patients in Sana'a city. Universal J Pharm Res 2017; 2(4).
15. Othman A, Hamzah E, Almughales J, Al-Mikhlafy A. Serum positivity of ana and asma among khat and nonkhat chewers as markers for autoimmune hepatitis type 1. Universal J Pharm Res 2017; 2(4), July 2017.
16. El-Aghbary D, Al-Jaaidi A, Al-Moyed K, Al-Robasi AA, Othman A. Seroprevalence of anti-mannose binding lectin autoantibodies in patients with rheumatoid arthritis in Sana'a city- Yemen. Universal J Pharm Res 2018; 3(2):34-37.
17. Al-Shamahy HA, Ishak AA. Trends and causes of morbidity in part of children in the city of Sana'a, Yemen 1978-2018: findings of single children's health center. Universal J Pharm Res 2021; 5(6).
18. Shamsan ENA, De-ping C, Al-Shamahy HA, *et al*. Coccidian intestinal parasites among children in Al-Torbah city in Yemen: in country with high incidence of malnutrition. Universal J Pharm Res 2019; 4(4).
19. Sheiban A, Al-Shamahy H, Alattab N, Abbas AK. Epidemicity of Vibrio cholera in Sana'a city, Yemen: prevalence and potential determinants. Universal J Pharm Res 2018; 2(6).
20. Al-Moyed KA, Harmal NH, Al-Harasy AH, Al-Shamahy HA .Increasing single and multi-antibiotic resistance in Shigella species isolated from shigellosis patients in Sana'a, Yemen. Saudi medical journal 27 (8), 1157-1160.
21. Al-Shamahy HA . Seroprevalence of *Helicobacter pylori* among children in Sana'a, Yemen Annals of Saudi medicine 25 (4), 299-303.
22. Nassar MY, Al-Shamahy HA, Masood HAA. The association between human leukocyte antigens and hypertensive end-stage renal failure among Yemeni patients. Sultan Qaboos University Medical Journal 15 (2), e241.
23. 23-Al-Shamahy HA, Al-Robasi A, Al-Moyed KA. Epidemiology, clinical features and antibiotic susceptibility of *Campylobacter* infections in Sana'a, Yemen. Journal of Chinese Clinical Medicine 2 (8), 455-463
24. Ogaili MAO, Al-gunaid EA, Al-Shamahy HA, Jaadan BM. Survey of safety practices in diarrheal treatment centers: cholera treatment centers in Yemen. Health 2020, 51,49.
25. Ishak AA, Al-Shamahy HA. Traveling Through Life with Arthritis Mutilans: Humanity Joins All Medical Practitioners in Treating and Supporting the Condition of Chronic Arthritis Mutilans Case. Ann Case Report 2021; 7, 729.
26. AL-Rrobasi AA, AL-Shamahy AA. Defect in cellular immunity (CD4, IL2) in persistent pulmonary tuberculosis. Journal-Bahrain Medical Society 17 (3):150.
27. Koning F, Schuppan D, Cerf-Bensussan N, Sollid LM. "Pathomechanisms in celiac disease". Best Practice &

Research. Clinical Gastroenterology 2005; **19** (3): 373–387.
28. Mowat AM. "Coeliac disease – a meeting point for genetics, immunology, and protein chemistry". Lancet 2003; **361** (9365): 1290–1292.
29. Landman M, Theuns SDM, van Wering HM *et al.* Evaluation of the implementation of the 2012 ESPGHAN guideline of Coeliac disease in children: Results of a retrospective study in the Netherlands. Arch. Dis. Child. 2020; 105: 413.
30. Husby S, Koletzko S, Korponay-Szabó I *et al.* European Society Paediatric gastroenterology, Hepatology and Nutrition Guidelines for Diagnosing Coeliac Disease 2020. J. Pediatr. Gastroenterol. Nutr. 2020: 70:141–156.
31. Mills JR, Murray JA. Contemporary celiac disease diagnosis: Is a biopsy avoidable? Curr Opin. Gastroenterol 2016; 32: 80–85.
32. Kurien M, Ludvigsson JF, Sanders DS. The Authors of the BSG Guidelines. A no biopsy strategy for adult patients with suspected coeliac disease: Making the world gluten-free. Gut 2015; 64:1003-1004.
33. Silvester JA, Kurada S, Szwajcer A, *et al.* Tests for Serum Transglutaminase and Endomysial Antibodies Do Not Detect Most PatientsWith Celiac Disease and Persistent Villous Atrophy on Gluten-free Diets: A Meta-analysis. Gastroenterology 2017; 153: 689–701.e1.
34. Lebwohl B and Rubio-Tapia A. Epidemiology, Presentation, and Diagnosis of Celiac Disease. Gastroenterology 2021;160:63–75.
35. Al Attas RA. How common is celiac disease in Eastern Saudi Arabia. Ann Saudi Med, 2002: 22(5-6):315-319.
36. Sanders DS, Patel D, Stephenson TJ *et al.*, A primary care cross-sectional study of undiagnosed adult coeliac disease. European journal of gastroenterology & hepatology, 2003; 15(4): 407-413.
37. Hadithi M, Mary E von Blomberg, Crusius JBA, *et al.*, Accuracy of serologic tests and HLA-DQ typing for diagnosing celiac disease. Annals of internal medicine, 2007; 147(5): 294-302.
38. Catassi C, Kryszak D, Louis-Jacques O, *et al.*, Detection of celiac disease in primary care: a multicenter case-finding study in North America. The American journal of gastroenterology, 2007; 102(7):1454.
39. Dickey W S, McMillan, Hughes D. Identification of coeliac disease in primary care. Scandinavian journal of gastroenterology 1998; 33(5): 491-493.
40. Hopper AD , Cross SS, Hurlstone DP *et al.*, Pre-endoscopy serological testing for coeliac disease: evaluation of a clinical decision tool. Bmj 2007; 334(7596): 729.
41. Shahbazkhani B, Forootan M, Merat S *et al.*, Coeliac disease presenting with symptoms of irritable bowel syndrome. Alimentary pharmacology & therapeutics 2003; 18(2):231-235.
42. Carroccio A, Vitale G, DiPrima L *et al.*, Comparison of anti-transglutaminase ELISAs and an anti-endomysial antibody assay in the diagnosis of celiac disease: a prospective study. Clinical chemistry 2002; 48(9):1546-1550.
43. King JA, Jeong J, Underwood FE, *et al.* Incidence of celiac disease is increasing over time: a systematic review and meta-analysis. Am J Gastroenterol 2020; 115:507–525.
44. Jansson-Knodell CL, Hujoel IA, West CP, *et al.* Sex difference in celiac disease in undiagnosed populations: a systematic review and meta-analysis. Clin Gastroenterol Hepatol 2019;17:1954–1968.
45. Rubio-Tapia A, Kyle RA, Kaplan EL, *et al.* Increased prevalence and mortality in undiagnosed celiac disease. Gastroenterology 2009;137:88–93.
46. Katz KD, Rashtak S, Lahr BD, *et al.* Screening for celiacdisease in a North American population: sequential serology and gastrointestinal symptoms. Am J Gastroenterol 2011;106:1333–1339.
47. Lebwohl B, Tennyson CA, Holub JL, *et al.* Sex and racial disparities in duodenal biopsy to evaluate for celiac disease. Gastrointest Endosc 2012;76:779–785.
48. Collin P, Vilppula A, Luostarinen L, et al. Review article: coeliac disease in later life must not be missed. Aliment Pharmacol Ther 2018;47:563–572.
49. Liu E, Dong F, Barón AE, et al. High incidence of celiac disease in a long-term study of adolescents with susceptibility genotypes. Gastroenterology 2017;152:1329–1336.
50. Andrén Aronsson C, Lee H-S, Hård Af Segerstad EM, et al. Association of gluten intake during the first 5 years of life with incidence of celiac disease autoimmunity and celiac disease among children at increased risk. JAMA 2019;322(6):514–523.
51. Schuppan D, Zimmer KP. "The diagnosis and treatment of celiac disease". Deutsches Ärzteblatt International 2013; 110 (49): 835–46.
52. Vriezinga SL, Schweizer JJ, Koning F, Mearin ML. "Coeliac disease and gluten-related disorders in childhood". Nature Reviews. Gastroenterology & Hepatology 2015;12 (9): 527–36.
53. van Heel DA, West J. "Recent advances in coeliac disease". Gut 2006; 55 (7): 1037–46.
54. Lionetti E, Gatti S, Pulvirenti A, Catassi C. "Celiac disease from a global perspective". Best Practice & Research. Clinical Gastroenterology 2015; 29 (3): 365–79.