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Clinical Characteristic of Coeliac Disease in Adult Sudanese Patients and Gender Difference at Ibn Sena Specialized Hospital, Khartoum State, Sudan

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Abstract Introduction: The study was conducted at Ibn Sena Hospital during the period from October 2020 to February 2021. The study included 84 patients with celiac disease (CD), of which 28 (33.3%) were males and 56 (66.7%) were females. The average age among the study participants was 30.2±10.3 years. average BMI was 23.8± 3.8. Methodology: This study is a descriptive and analytical, cross sectional, hospital-based study, that went from October 2020 to February 2021 at Ibn Sena hospital. A structured questionnaire was used to collect data about demographic, clinical, and laboratory findings of patients. Then, the data was analyzed using SPSS version 25. Results: The most common GI symptoms were weight loss, diarrhea/steatorrhea, and bloating (61.9%, 58.3%, and 44%, respectively). On the other hand, the most common extraintestinal symptoms are bone and joint pain (58.3%), shortness of breath (52.4%), and anxiety (41.7%). Anemia was present in 86.9% and Calcium levels were low in 98.8% of patients. Depression was prevalent among 28.6% of CD patients. There was significant difference between genders and depression and anemia (P=0.04, P<0.001). Conclusion: Significant difference was found between genders when it comes to depression and anemia, with females having higher risks.

Keywords: *celiac disease, clinical characteristics, Sudanese patients*

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1. Introduction

1.1. Background

Epidemiology

Celiac disease (CD) is an autoimmune disease that cause enteropathy and is triggered by the ingestion of dietary gluten and other similar proteins in a genetically susceptible individual [1]. The disease was first described in children and for a while was thought to be only a pediatric disease, until later studies demonstrated that it can occur in all ages [2]. During the past years, CD has seen an upward trend in the prevalence among adults [3]. CD is more frequent among women and its general prevalence is 0.5-1% [2]. The prevalence of the disease keeps increasing over time and it varies according to sex, age, and geographic location [4].

Risk factors

The exact cause of CD is yet to be known. The disease is triggered by an excessive immune reaction due to the contact of intestinal mucosa with gluten. Gluten is a protein found in many foods containing any grains like wheat, barley and spelt. Other foods such as bread, baked food, pastas, some condiments (like ketchup), premade coffee drinks, and many processed foods (processed cheese, breakfast cereals, ice creams…). Other risk factors associated with CD are certain medications, alpha interferon, surgery, and gastrointestinal infections [5].

There is familial and genetic clustering present in CD leading to higher risk among CD patients' relatives [3]. Genetic mutations with possible correlation with CD were detected. These mutations were in genes situated near the ones controlling type 1 diabetes [6]. One of the well-documented and established genetic factors that increase the risk of CD is the presence of HLA-DQ2.5 which is encoded by two genes, DQA1*05:01 and DQB1*02:01 genes in either cis position (DR3 haplotype) or trans position (DR5 and DR7 haplotypes). Most patients with CD are DR3, DQ2 positive. Approximately 90% of persons with CD express HLA-DQ2.5, while 20% of patients possess HLA-DQ8 (DR4, DQ8 haplotype) [7]. These HLA haplotypes are necessarily present in CD but not sufficient for its development, as it found that 40% of

the population carry the HLA haplotypes without having the disease [8].

Immunology

Repeated exposure to gluten in the mucosa of the small intestines in susceptible people causes an increase in the permeability of the intestinal wall, then both the innate and the adaptive immune response are activated [9]. CD is an autoimmune disease and the autoantigen that plays a role in this immune reaction is the enzyme tissue transglutaminase (tTG). tTG is found in the lamina propria of the small bowel and it transforms the gulatimine residues found in gluten to glutamic acid. Glutamic acid is a negatively charged molecule that is recognized by the cells that express HLADQ2/DQ8 receptors for T lymphocytes. The gluten sensitive T cells then induce intestinal damage by releasing immunomodulators such as immunoglobulins, cytokines,interferons, tumor necrosis factor, interleukin 15 and 17 [10] [11].

The intestinal microbiota is different in those with CD when compared with those who do not have it. Furthermore there was a difference between those two groups (with or without CD) in relation to age [12].

When it comes to the clinical presentation of celiac disease, it can have either intestinal or extraintestinal manifestations. The intestinal manifestations are more common in children and they include, persistent diarrhea, abdominal pain, involuntaryweight loss, loss of appetite, failure to thrive, bloating, nausea,vomiting, and constipation. Malnutrition can be a presentation of CD, but so can overweight and obesity [12]. The extraintestinal manifestations of CD are many and some of them are, fatigue, anemia, hypoalbuminemia, hypertransaminasemia, deficiencies (vitaminsD, B12, folic acid, Fe, Cu, Zn, carnitine), tooth enamel disorders (enamel hypoplasia), aphthous stomatitis, bone metabolicdisorders (osteopenia, osteoporosis), abnormalities in coagulationfactors (hemorrhagic diathesis due to malabsorption of vitaminK), neurological disorders (headache, epilepsy, cerebellar ataxia,peripheral and central neuropathy due to decreased absorption of vitamins B1, B6 and B12 with muscle fatigue, altered reflexes,paresthesia, up to severe motor deficits), psychiatric disorders(anxiety, depression, apathy, irritability, eating disorders,attention-deficit/hyperactivity disorders, social phobia,schizophrenia, autism), endocrine and gynecologicalmanifestations (amenorrhea, infertility, late menarche, recurrentmiscarriages, premature birth, early menopause), dermatological conditions (dermatitis herpetiformis), autoimmune diseases [13,14].

Types of CD

Classic celiac disease; it includes malabsorption signs andsymptoms such as diarrhea, weight loss, failure to thrive, bloating. This type is present in children and adults. Non-classic celiac disease, on the other hand, does not include malabsorption signs and symptoms. Patients with this type present reflux, dyspepsia, abdominal pain, vomiting, bloating, constipation or extraintestinal manifestations such as fatigue, anemia, dental enamel hypoplasia, osteoporosis/osteopenia, vitamin deficiencies, hypertransaminasemia, dermatological,gynecological, neurological, psychiatric conditions. The non-classic CD is present in later childhood or adulthood. The third type is Potential celiac disease; which includes, positive CD serology and normal small bowel biopsy. This type may be asymptomatic or may have classic/non-classic symptoms. The fourth types is Non-responsive celiac disease; in which symptoms persist after 6 – 12 months on a gluten-free diet (GFD). In this type accidental gluten ingestion is the most common cause. The fifth and last type is Refractory celiac disease (RCD). Dagnosis of RCD requires the persistence of symptoms in spite of a gluten-free diet for 12 months or longer, and implies the exclusion of other causes of villous atrophy. CD diagnosis depends on a combination of many methods which include: clinical evaluation which is based mainly on symptoms, serological evaluation which detect the presence of high level of IgA and IgG isotypes of anti-TG2, but the most sensitive test is IgA anti- tissue transglutaminase and IgA endomysial antibody tests-, and histopathological findings (endoscopic biopsy)-which depend on the histological changes of intestinal mucosa and it is considered as the more accurate method to detect celiac disease- [15,16,17]. Regarding endoscopic examination, the celiac disease patients usually present with lesions in small intestine, villous atrophy, crypt hyperplasia, and increased intraepithelial lymphocytosis.

1.2. Literature Review

Many studies address the clinical presentation of celiac disease. One paper found that the demographic characteristic and clinical presentation of celiac disease were similar in both older and younger participants with a little difference in body mass index [18]. Ethnic variation might play a role in the rate of duodenal villous atrophy in patients with CD [18]. This difference in ethnicity can be applied to Sudan as well. This suggest that diagnosing CD should not be restricted to the textbook definition of it, since the pathophysiology of it is not well understood and the genetic and ethnic variations can affect how the disease manifest itself. The presentation of CD can range from gastrointestinal manifestations to depression and sleep deprivation [19,20].

Another interesting finding of a study conducted in red sea state has found an equal effect of celiac disease on both males and females, which indicates that gender does not affect the clinical presentation of the disease [19]. Another study by Ganji et al. found that sex can affect the prevalence of a study in Northeastern Iran, indicating that celiac disease was more common in females [20].

Jansson-Knodell et al. found that CD has a higher risk in females among the undiagnosed population as there are more undiagnosed females than males [21]. They concluded that this might be due to gender role in disease development and severity of intestinal damage [21]. In a study at a single UK center among Caucasian patients, the researchers did not find any difference in frequency of symptoms or anemia among males and females [22].

Celiac can manifest as gastrointestinal symptoms (like diarrhea, stomach pain, constipation.) or extraintestinal symptoms (like anemia, arthritis, infertility, neurological symptoms) [23]. Many studies have addressed this clinical presentation in order to narrow the wide range of the disease. One of them is a study in the red sea state, which illustrates that celiac disease's most common symptom is chronic diarrhea. This finding is aided by another study in

Mexico and also two studies in Sudan [19] [24] [25]. Another study by Ganji et al. in Northeastern Iran counteract these findings as it found that the main symptom was dyspepsia and then diarrhea [20].

In a celiac disease study in the red sea state by Ageep in Sudan, the most common symptoms were chronic diarrhea, weight loss, and stunted growth [19]. Ramírez-Cervantes et al. conducted a study in Mexico and found the most common symptoms were chronic diarrhea, bloating, abdominal pain, fatigue, weight loss, constipation, headache, skin rashes, and another symptom [24]. In another similar study in Soba University Hospital and Fedail Hospital in Sudan, many celiac disease cases present with iron deficiency anemia (41.7% of the participants).

A study found that patients with celiac disease have lower bone mineral density than patients without celiac disease. Patients with celiac disease who are not taking a gluten-free diet had even lower bone mineral density than those who have celiac and are following the diet. They also found lower levels of calcaemia, calciuria, and 25(OH) vitamin D in celiac disease patients when compared with the controls [21]. Another study done in Ibn-Sina hospital, that included 42 (81% of whom were females), investigated vitamin D levels and bone mineral density in CD patients. They found a significant positive moderate relationship and bone mineral density ($r = 0.437$, $P < 0.04$). They also found a significant positive correlation between vitamin D levels and the BMI of the participants($r = 0.328$, $P< 0.034$). They, however, found no relation between vitamin D levels and adherence to gluten free diet, but instead between bone mineral density and adherence to gluten free diet ($P < 0.012$) [22].

Moreover, in Italy, another study by Casella et al. in Italy found that weight loss, dyspepsia, and lymphoma due to celiac disease were more common in older participants compared to young ones despite that 10% of the participants had it [18].

The duration of having CD without dietary restriction can be a useful indicator for disease prognosis. Decreased quality of life could be predicted by a longer duration of CD symptoms before a diagnosis is made. The presence of psychiatric, neurologic, or gastrointestinal comorbidities could also predict the quality of life of CD patients [23]. On the other hand, the earlier the diagnosis, the better the prognosis and outcomes of the disease, less risk of refractory CD, and fewer complications like unexplained infertility [24]. In North America, it is known that the unexplained infertility is women is due to celiac more than any other region [25].

Screening for CD should be considered among the first-degree relatives of celiac patients, given the high prevalence of CD in these groups. Sudan has a very huge rate of consanguine marriages that inherit HLA antigens to new generation increasing the risk and of course the disease incidence rate in them [25,26,27,28].

European Society of Pediatric Gastroenterology and Nutrition modified the guidelines of the diagnostic pathway of CD in children. The clinical suspicion of CD should be raised in children with unexplained chronic gastrointestinal symptoms, as well as extra-intestinal manifestations such as growth retardation, iron deficiency anemia, weight loss, chronic fatigue, delayed puberty, amenorrhea, recurring bone fractures or alterations of liver function tests. Children and adolescents with Down's syndrome, Turner's syndrome, Williams syndrome, IgA deficiency, autoimmune thyroiditis, type-1 diabetes, or autoimmune disorders of the liver, first-degree relatives of celiac patients, should also be screened.. And we should also follow the track and do more researches to know the wide range of the extra-intestinal manifestations and clinical characteristic according to our race, gender, age, and geographic background in order to reach the current new line of vaccination, especially in a disease like this when the negative test screening cannot rule out the disease. By doing this actually we are not only grantee a better quality of life for the Sudanese patients by earlier diagnosis but also decreasing total morbidity and mortality rates due to the disease [29,30,31].

One of the most accurate ways to detect celiac disease, and it detects the presence of a high level of IgA and IgG isotypes of anti-TG2 [17]. They are both antibodies produced by B cells in response to celiac disease, and they are specific to TG2 (transglutaminase), a specific enzyme that is typically found in the tissue matrix and has many benefits for the body. In the case of CD patients, the lamina propria in the intestine increases their secretion of TG2, making the glutamine from gluten acquires a negative charge. This negative charge in glutamine makes it binds with HLA DQ2/DQ8 and induces autoimmune reactions resulting in celiac disease manifestation and elevated antibodies [17]. So, it is believed that HLA DQ2 and -DQ8 have a role in the presence of celiac disease, but it is still controversial with the theory that says they do not cause celiac disease alone [26].

Many studies talk about the serological findings of celiac disease like a study in Soba University Hospital and Fedail Hospital in Sudan, which found that hemoglobin level, albumin level, calcium level, and vitamin D level were significantly lower in older participants compared to IgA level, which was higher in young participants [18]. Moreover, in Northeastern Iran, they found a decrease in vitamin D3 level in celiac patients [20].

A study in Bangladesh found that IgA deficiency was not found in celiac patients indicating that it cannot detect celiac disease. Also, only a small percent of the participants was positive in tTG-IgA, and 0% of participants positive in tTG-IgG and gliadin IgG [27]. Another study in Northeastern Iran say the exact things about anti-tTG level as it found no correlation between anti tTG level and histological severity of the small intestine [20].

Serological tools are useful diagnostic tools as most celiac disease patients have elevated aspartate aminotransferase, alanine aminotransferase, anti-endomysial antibodies anti-transglutaminase. The same paper also finds that nearly half of the celiac disease patients have intestinal villi atrophy [28].

In addition to this, there may be an association between other autoimmune diseases and celiac disease as autoimmune diseases like type 1 diabetes and Rheumatoid arthritis have a high prevalence (30%) among people with celiac disease, and this according to a specific study on celiac disease and inflammatory bowel syndrome [29].

1.3. Problem Statement

Unfortunately, there is a huge lack of data about celiac disease specially in Africa and other developing countries [32]. And which amplify the danger is the wide range of presenting symptoms of celiac patients as mentioned before. Also, there is lack of awareness about the clinical presentation of the disease which cause delay in diagnosis and make the patient's condition worse [33] [34]. As there is study in Mexico that illustrate the positive association between poor quality of life and delay of celiac disease diagnosis [35].

People used to believe that celiac disease is uncommon in adults which result in ignorance by the researchers to study its manifestation in adults as but many papers find that this is not true as older adults represents 5% of all celiac disease patients in the clinic [33] [36]. Beside all this, it was found that celiac disease can be manifested as silent disease asymptomatic in type 1 diabetes patients which represent a major risk to their lives [37].

The prevalence of celiac disease in Sudan is still unknown [38]. Moreover, there is a lack of awareness among citizens and doctors about celiac disease in Sudan as celiac disease study in red sea state emphasize that many doctors in rural areas don't know the clinical presentations of the diseases and that it doesn't always follow the typical pattern [39]. Also serological tests aren't used mainly in Sudan in spite its effectiveness in determination of celiac disease [32].

In addition to lack of data, lack of awareness which all work together to cause delay in diagnosis and worthening the patient condition, there is no effective treatment to end celiac disease but patients with it can only undergo a healthy diet which is free of gluten to minimize the symptoms [40].

1.4. Justification/Rationale

As mentioned above, there is still a huge gab regarding celiac disease specially in Sudan which there are very few published papers regarding it. Also, researchers tend to focus on celiac disease that affect children only which emphasize the need of such a study that address celiac disease in adults. Moreover, the different manifestation and absence of diagnostic standards require a huge effort to explore the clinical characteristic of celiac disease and its association with demographic data and that is the gab this research come to fill.

1.5. Objectives

1.5.1. General Objective

To determine the Clinical characteristic of coeliac disease in adult Sudanese patients and their association with sociodemographic characteristic.

1.5.2. Specific Objectives

1. To measure the prevalence of celiac disease among different sociodemographic groups (specially age, gender, geographical data).
2. To identify both intestinal and extra intestinal manifestations of Celiac disease in Sudanese patients.
3. To determine and interpret serological and histopathological findings among celiac disease patients.
4. To determine the correlation between serological and histopathological findings with Hb level, Liver function test, serum Ca and Vit D level.
5. To determine the association between clinical characteristic of celiac disease and gender.

2. Methodology

2.1. Study Design

This study is a descriptive and analytical, cross sectional, hospital-based study.

2.2. Study Area

The study will be conducted in the coeliac refer clinic of Ibn Sena Teaching hospital which is considered as one of the main references teaching hospital in Sudan, it had specialized coeliac clinic, main lap-rotary, blood bank, ICU, renal unit, refer clinics, private rooms and medical director office. Totally, it has building that contain many wards for long admissions. Teaching and training opportunities offered for medical students, house officers and registrars. This hospital provided services to the general population from surrounding residential areas and for referred patients from all over the country.

2.3. Study Period

The study will be conducted with in the period from October 2020 to February 2021.

2.4. Study Populatio

All patients who diagnosed with coeliac disease who underwent for refer clinic at Ibn Sena Teaching hospital within the study period and fulfill the following criteria.

2.4.1. Inclusion Criteria

Adults (age 18 or above)
diagnosed with Celiac disease
Visit refer clinics in Ibn Sena Teaching Hospital within the study time period.
Accepted to participate in the study.

2.4.2. Exclusion Criteria

Patients with non-coeliac gluten sensitivity
Non-Sudanese patients
Asymptomatic celiac disease patient
Not fulfill the inclusion criteria

2.5. Sample Size and Technique

Simple random sampling technique will be applied to

recruit the study participants from the population by the following formula:

$$n = \left(Z^2 \times (p \times q)\right) / e^2$$

- n: sample size required by the study
- Z: the determined area under the normal curve by the desired confidence interval (CI: 95%)
- P prevalence of the disease =0.05 (as it is unknown)
- q=1-P
- e=desired precision =0.05
- n=1.96X1.96X0.5X0.5/(0.05X0.05) = 384 patients

2.6. Research Tools and Method of Data Collection

Consent/permission

A formal written permission will be taken from administration of the study area (Ibn Sena Teaching Hospital)

Questionnaire.

The questionnaire is comprehensive structural close ended that contain data regarding all demographical, clinical, investigation, findings for all study participants. And It will be filled by direct interview

2.7. Study Variables

Study variable can be classified as shown in the following table:

Independent
Demographical characteristics
Age
Sex
Education
Occupation
Residence
Socioeconomic status
Other clinical characteristics
Dependent:
Coeliac diagnostic tools:
Hemoglobin level
TTG AB [IgA, IgG]
Anti-endomysial Ab
Antigliadin Ab
Duodenal /jejunal biopsy
Biopsy
CD presentation:
Intestinal [GIT upset, bloating …]
Extraintestinal [anemia, coeliac hep….]
Others [lymphoma, osteoporosis]

Association with other autoimmune [DM1, thyroiditis, RA, SLE, AIH, IBD] Process of implementation:

The questionnaire will be developed and tested in In Ibn sena hospital before data collection. Quality checks will be done by the supervisors and the researcher through all the work from the questionnaire writing and data collection until writing of the report. After completing data collection, the report will be written by the researcher.

2.8. Plan of Analysis Data Entry, Analysis and Presentation

Data will be entered, cleaned, and analyzed using SPSS version 25.0 Descriptive statistics in term of frequency tables with percentages and graphs. Means and standard deviations will be presented with relevant graphical representation for quantitative data.

Bi-variable analysis to determine the associations between the main outcome variable and the other relevant factors with Chi square test (for categorical variables) and t- test (quantitative variables) statistical tests.

P value of 0.05 or less is considered statistically significant.

Data will be represented after analysis in form of univariable tables, cross tabulation (bi variable tables), figures and narrative illustration.

Table 1. Demographic characteristics of the participants

Variable	Count	Percent
Age	30.2± 10.3	
Gender		
Male	28	33.3%
Female	56	66.7%
Weight	64.3± 13.4	
Height	163.5± 8.1	
BMI	23.8± 3.8	
Underweight	4	4.9%
Average	47	57.3%
Overweight	25	30.9%
Obese	6	7.3%
Marital status		
Single	43	53%
Married	36	44.4%
Divorce	2	2.5%
Widow	-	0.0%
Education		
Illiterate	-	0.0%
Primary	-	0.0%
Secondary	16	21.9%
University	57	78.1%
Socioeconomic status		
Low	4	5.2%
Moderate	51	66.2%
High	22	28.6%
Origin		
North	14	19.2%
East	23	31.5%
West	9	12.3%
Middle	27	37%

2.9. Ethical Considerations

Written ethical clearance and approval for conducting this research will be obtained from Sudan Medical Specialization Board Ethical Committee.

Written permission will be obtained from the administrative authority of Ibn Sena Teaching Hospital.

Study data/information will be used for the research purposes only. The privacy issues will be intentionally considered.

A written consent will be taken from the patients (if they can) or from their care taker.

3. Results

The obtained sample size was 84 patients with CD, and of those 28 (33.3%) were males and 56 (66.7%) were females. The average age among the study participants was 30.2 years with a standard deviation of 10.3 years.

The weight was taken for all participant and the average was 64.3± 13.4 Kg. The height of the participants was also taken to measure the body mass index (BMI) and the average BMI was 23.8± 3.8. Obese patients were 7.3%, while underweight patients were 4.9%. Details for demographic data are in Table 1.

Independent sample T test revealed no statistically significant age difference between those with each manifestation and those who haven't expressed the manifestation except for depression; patients with depression were 5.8 years younger than patients who haven't experienced depression (p-value 0.19).

The average duration of illness was 4.4± 5.8 years and duration of illness after diagnosis 2.8± 2.8 years. This disparity shows that late diagnosis is a common theme among CD patients.

The most common GI symptoms were weight loss, diarrhea/steatorrhea, and bloating (61.9%, 58.3%, and 44%, respectively). on the other hand, the most common extraintestinal symptoms are bone and joint pain (58.3%), shortness of breath (52.4%), and anxiety (41.7%). More details about the symptoms are found in Table 3.

Table 2. Frequency of depression

	Depression	N	Mean	Std. Deviation	Mean difference	p-value
Age	No	60	31.93	10.891	1.406	
	Yes	24	26.13	7.520	1.535	

Table 3. Duration of CD

	Range	mean± SD
Duration of illness	From 1 week- 28 years	4.4± 5.8 years
Duration since diagnosis	from 3 weeks- 12 years	2.8± 2.8 years

Table 4. Symptoms associated with celiac disease

	variable	count	percent
GI symptoms	Abdominal pain	36	42.9%
	Diarrhea/ steatorrhea	49	58.3%
	Constipation	26	31%
	Bloating/ gases	37	44%
	Nausea/ vomiting	23	27.4%
	Wight loss	52	61.9%
Extra-intestinal manifestations	Anemia		
	Palpitation	24	28.6%
	Shortness of breath	44	52.4%
	fatigability	30	35.7%
	Bone		
	Bone and joint pain	49	58.3%
	Pathological fracture	5	6%
	Peripheral neuropathy		
	Tingling	11	13.1%
	Numbness	22	26.2%
	Imbalance	17	20.2%
	Dermatitis		
	Itchy rash	31	36.9%
	Blistery rash	12	14.3%
	Psychiatric		
	Depression	24	28.6%
	Anxiety	35	41.7%

Table 5. Diagnostic tests for CD

Test	Count	Percent
TTG Ab		
Not performed	6	7.2%
Negative	1	1.2%
Positive	77	91.7%
Tissue Endomysial Ab		
Not performed	64	76.2%
Negative	1	1.2%
Positive	19	22.6%
Antigliadin Ab		
Not performed	36	42.9%
Negative	1	1.2%
Positive	47	56%
Histopathology		
Not performed	26	31%
Negative	13	15.5%
Positive	45	53.6%

Table 6. Hematological findings in CD patients

Parameter	Count	Percent
HB		
Low	73	86.9%
Normal	11	13.1%
Albumin		
Low	2	2.5%
Normal	78	97.5%
AST		
Normal	75	94.9%
High	4	5.1%
ALT		
Normal	80	98.8%
High	1	1.2%
ALP		
Low	2	2.4%
Normal	79	96.3%
High	1	1.2%
Ca		
Low	82	98.8%
Normal	1	1.2%
Vit D		
Low	6	7.2%
Normal	77	92.8%

Table 7. Association between gender and Hb levels among CD patients

		gender		Total	p-value
		males	females		
Hb	**Low**	18	55	73	<0.001
		24.7%	75.3%	100.0%	
	Normal	10	1	11	
		90.9%	9.1%	100.0%	
Total		28	56	84	
		33.3%	66.7%	100.0%	

Table 8. Association between gender and depression

		gender		Total	p-value
		males	females		
Depression	**No**	24	36	60	0.04
		40.0%	60.0%	100.0%	
	Yes	4	20	24	
		16.7%	83.3%	100.0%	
Total		28	56	84	
		33.3%	66.7%	100.0%	

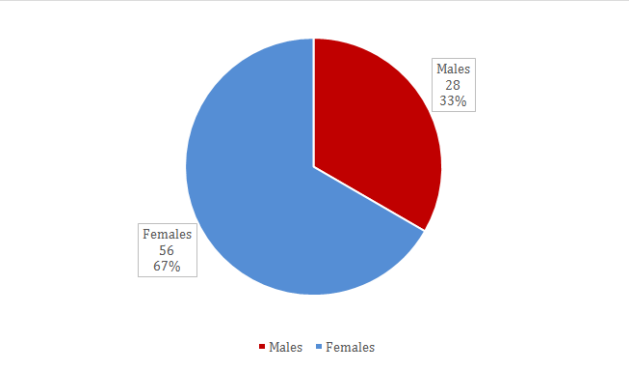

Figure 1. Gender of the participants

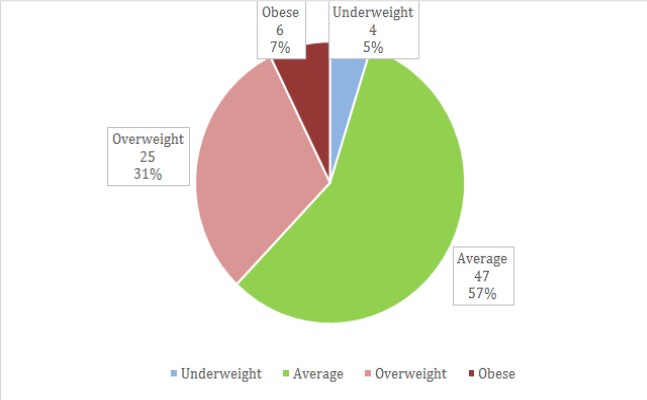

Figure 2. BMI of the participants

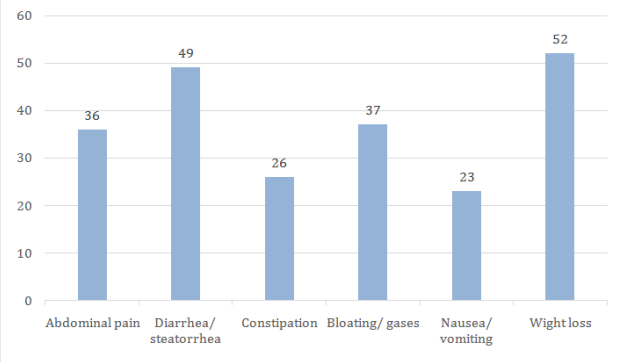

Figure 3. Intestinal symptoms among CD patients

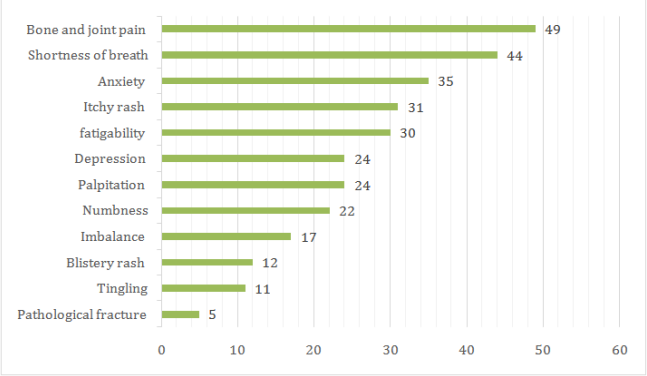

Figure 4. Extra-intestinal symptoms among CD patients

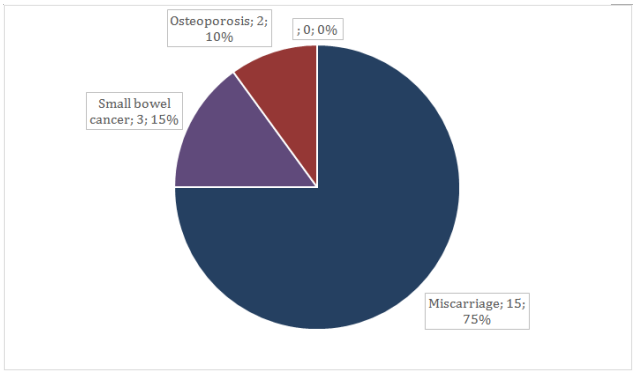

Figure 5. Frequency of complications in celiac patients

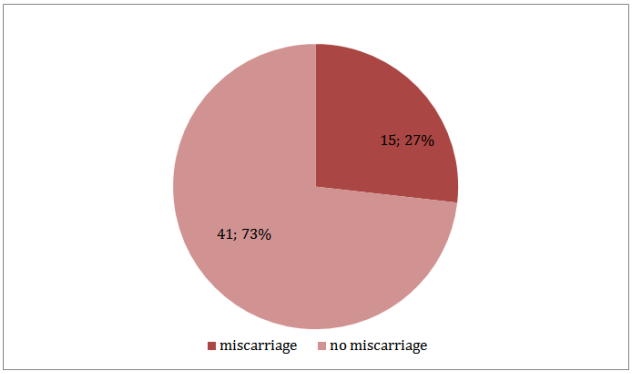

Figure 6. Frequency of miscarriage among female participants

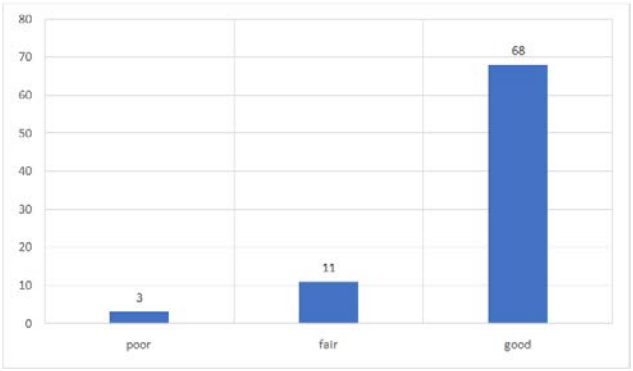

Figure 7. Adherence to gluten free diet

The most common complication we found was miscarriage 15 (17.9%). Small bowl cancer is was also a complication and it was adenocarcinoma type, as is shown in Figure 5. Miscarriage was a complication present in 26.7% of all female participants as is shown in Figure 6.

When serological tests were done 91.7% were positive for tTG Ab, while 56% were positive for Antigliadin Ab. Anemia was present in 86.9% of patients. A very high 98.8% of patients had low calcium levels. More details about hematological findings can be found in Table 6.

most of the patients were adherent to a diet free of gluten as shown in Figure 7.

Crosstabulation for clinical manifestations across gender revealed no significant proportional distribution difference between males and females except for depression and hemoglobin level; depression was more

proportionate among females (83.3% of depressed patients were females) with prevalence of depression in female patients of 35.7% compared to 14% in males (p-value 0.04). Also, low hemoglobin was more proportionate among females (75.3%).

4. Discussion, Limitations, Conclusion, and Recommendation

4.1. Discussion

This study was conducted at Ibn Sena Teaching hospital and included 84 subjects diagnosed with CD. The study was conducted from October 2020 to February 2021. Demographic data was taken and the patients were asked about their presenting symptoms. Varies hematological results were recorded and taken into consideration.

The majority of CD disease patients were females (66.7%) and the rest were males. This is consistent with other studies which found females to be generally more likely to have the disease than males [41,42]. The average age of the participants in our study was 30.2± 10.3 years. This higher than a study conducted in Ibn Sena hospital, which found that participants mean age was 27.3095 ± 9.47780SD [22]. Another study done by C. Ciacci et al. found an average age of 38.1±16.9 in males and 35.5±11.6 among females [43]. In a survey conducted by Mcmahon et al., they estimated an average age of 53 (range 18–88), which is significantly higher than our population [43].

The average BMI was 23.8± 3.8. Overweight patients were 30% and Obese patients were 7.3%, while underweight patients were 4.9%. This seems to be the trend found in other studies. A study conducted in the USA found that the average BMI of 371 celiac patients diagnosed over a 10-yr period to be 24.6 kg/m2. They found 5% to be underweight, 57% were normal, and 39% were overweight, including 13% (of all patients) in the obese range [44]. Another study conducted at Ibn Sena hospital had a BMI mean of 19.7588 ± 4.40561 SD[22]. This is in contrast to another study among 201 patients, which found that 36.2 % of the patients were underweight, 54.8 % were normal weight, 6.2 % were overweight, and 2.9 % were obese [45].

Celiac disease prevalence might be related to socioeconomic class of the person. A study conducted in Sweden found that there is a significant decrease in risk among low socioeconomic status compared with other groups, despite free health care in Sweden [46]. CD may be under-recognized in this population due to socioeconomic factors that possibly include lower rates of health-seeking behavior [47]. Another possible explanation involves a different infant feeding pattern (including amount and timing of gluten introduction) in families with low socioeconomic position [46].

In our study subjects, the most common GI symptoms were weight loss, diarrhea/steatorrhea, and bloating (61.9%, 58.3%, and 44%, respectively), followed by abdominal pain, constipation, and nausea/vomiting (42%, 31%, and 27%, respectively). The most common extraintestinal symptoms are bone and joint pain (58.3%), shortness of breath (52.4%), and anxiety (41.7%). Anemia was found in 86% of our study subjects. In another study, weight loss and diarrhea were the major mode of presentation in CD although that was in less than 50% of the adult population[48]. Another study which compared the differences in clinical presentation between adults and children, found that 42% of the adults had anemia compared with children (19%)[49]. Anemia in CD is usually iron-deficiency anemia and this is caused by the localization of CD in the proximal part of the small intestine, where enterocytes uptake of iron in the duodenum is hindered. This makes iron deficiency anemia an independent manifestation of CD and sometimes can even lead to its initial recognition [50,51].

Another important symptom which we found in our subjects is bone and joint pain (58%) and pathological fractures (6%). Those two symptoms are related to osteoporosis which in the case of CD is related to the low calcium level (which we found to be low in 98.8%). Calcium and phosphate malabsorption, hormones, and local factors (e.g., growth factors, cytokines) may all be involved in determining the loss of bone minerals [52]. The exact mechanism is not well understood but two factors are thought to be related to decreased bone density in CD. The first is an impaired intestinal malabsorption, which leads to calcium deficiency and general malnutrition. The other factor is the presence of inflammation and the chronic release of cytokines [52]. A case control study among 77 CD patients and 157 controls found that CD patients had significantly lower bone mineral density (BMD) than the control subjects at the lumbar spine and femoral neck. They also found that BMD did not differ significantly between different disease severity. They found at the end that, 26% of all celiac patients having osteoporosis (T score ≤ -2.5 SD) at the lumbar spine ($p = 0.03$), compared with only 5% of control subjects. On the other hand, they found that, osteoporosis was rare at the femoral neck in both groups (3% vs. 1%, $p = 1.00$) [53].

Peripheral neurological symptoms in our study were, numbness, imbalance, and tingling (26.2%, 20.2%, 13.1%). Another study covering a total of 176 CD patients and 52 age-matched controls found peripheral neurological symptoms to be present in 50% of CD patients [54]. In yet another study that compared the prevalence of neurological manifestation of CD between 149 young adults and 125 older patients (more than 65 years) found that neuropathy was more common in elderly patients (11%) when compared with young adults (4%, p value 0.023) [55].

Depression and anxiety were common findings in our study, with prevalence of 28% and 41%, respectively. Another study in CD patients that investigated depression, found that apathy, excessive anxiety, and irritability were the most common symptoms of depression among CD patients [56]. The mechanism of maybe related to intestinal malabsorption and deficiency of nutrients, especially, vitamin B6 and tryptophan, in associated with other autoimmune diseases [57]. Another study found that there were Decreased plasma levels of tryptophan, decreased cerebrospinal fluid levels of serotonin, dopamine and nor-epinephrine metabolites in untreated CD patients [58]. Another study concluded that, Impaired absorption of tryptophan, a precursor to serotonin, leads to serotonin deficiency and consequent mental Illness [58].

In our study we found significant difference between males and females regarding the prevalence of depression, with females having more depression than males (p value 0.04). this is in contradiction with another study which 441 patients of CD and found significant difference between genders in anxiety, with female gender being a risk factor (P = 0.01). They could not predict depressive episode base on gender or any other demographic characteristics [59].

Vitamin D levels in our study was low in 7% of the patient. This is lower than what was found by another study of 133 CD patients, which found that 25% of patients had low vitamin D levels [60]. The role of parathyroid hormone (PTH) and 1,25-dihydroxy vitamin D should be noted here. In the presence of low calcium levels (in CD it can be caused by vitamin D deficiency, malabsorption or steatorrhea), the parathyroid glands increase the secretion of PTH, which in turns increases the circulating levels of 1,25-dihydroxy vitamin D, by stimulating the renal production of 1alpha-hydroxylase, the enzyme responsible for the conversion of 25-hydroxy vitamin D (the main circulating metabolite of vitamin D) to the final hormone 1,25-dihydroxy vitamin D. For this reason, increased 1,25-dihydroxy vitamin D levels may be observed in CD. Moreover, since 1,25-dihydroxy vitamin D is also involved in the catabolism of 25-hydroxy vitamin D, a sustained increase in serum 1,25-dihydroxy vitamin D may lead to an accelerated depletion of vitamin D stores, and to a worsening of vitamin D deficiency [52,61].

4.2. Limitations

The number of patients was low because despite it being a total coverage, that included patients that were referred to the clinic, which is most likely due the pandemic of COVID 19. The study did not go into enough details, regarding the clinical symptoms of CD. For example, neurological symptoms in CD disease are not just peripheral symptoms like numbness and imbalance but other central neurological symptoms like cerebellar ataxia, sensory neural hearing loss, epilepsy, and migraine are other symptoms that may be found in CD patients.

4.3. Conclusion

Among 84 patients with CD, 28 (33.3%) were males and 56 (66.7%) were females. The average age among the study participants was 30.2±10.3 years. average BMI was 23.8± 3.8. Obese patients were 7.3%, while underweight patients were 4.9%. The most common GI symptoms were weight loss, diarrhea/steatorrhea, and bloating (61.9%, 58.3%, and 44%, respectively). On the other hand, the most common extraintestinal symptoms are bone and joint pain (58.3%), shortness of breath (52.4%), and anxiety (41.7%). Depression was prevalent among 28.6% of CD patients. There was significant difference between genders and depression and anemia.

Calcium levels were low in 98.8% of patients. No ignificant difference between gender and any other clinical symptoms.

4.4. Recommendation

To Screen every patient presenting with vague abdominal pain since there is increase in the prevalence of celiac disease nowadays. To do large cohort study to see the risk factors and effects of gluten free diet and compliance on disease prognosis.

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