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Can Celiac Disease Affect Liver Enzymes in Patients with Gallstones? A Comparative Study

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ABSTRACT

Background: Gallstone disease is growth of a pebble-like substance as gallstones. Celiac disease is an autoimmune disease in genetically susceptible patients. The aim of the study is to investigate the liver enzymes among patients with gallstones in the presence of celiac disease once and the absence of disease again.
Methods: A comparative study was conducted on 280 people, 134 of them had gallstone disease, 6 patients who had celiac and gallstones disease, 12 asymptomatic celiac patients and 128 healthy persons were involved. All of participants had subjected to immunological investigations via Enzyme Linked Immunosorbent Assay technique. Biochemical investigations (Liver Function Test) were performed to check liver enzymes parameters fluctuations.
Results: The gallstones disease and active celiac disease cases mean age was 41.01 years. Six patients revealed a positive ultrasonography exam for having gallstones as well as a positive immunological test including anti-gliadin IgA, IgG and anti-transglutaminase IgA (greater than 10U/ml). Asymptomatic or silent celiac disease group comprised of 12 healthy persons with a seropositive immunological result and still with silent symptoms of celiac disease with positive anti-gliadin IgA and IgG only (greater than 10U/ml). Furthermore, the present research revealed that these two diseases together seemed to have a substantial or relatively significant influence on ALT, AST and ALP.
Conclusion: Active celiac disease produces disturbances in the AST liver enzyme, which have been related to both of the disorders that were investigated in this research, although Gallstones Disease alone had a possible influence on biliary system specific enzymes.
Key words: celiac disease, gallstones disease, Cholelithiasis, Cholecystokinin, liver enzymes

INTRODUCTION

Celiac disease (CD) is an autoimmune enteropathy defined by a lifelong sensitivity to eating gluten in people who are genetically predisposed to it (1). CD prevalence may approximately reach to affect one person every 100 persons worldwide and varies by gender, age, and geography (2). Inflammation and tissue injuries throughout the small intestine are caused by an abnormal immune response to gluten and the symptoms are diverse and can affect both intestinal and extra-intestinal locations (3).

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Respectively, Gallstones or (Cholelithiasis) are a pebble-like material that develop inside the gallbladder (GB), hepatic bile duct (HBD) and common bile duct (CBD). It is considered as one of the most common gastroenterological conditions (4). GSD is a major burden on healthcare systems across the world, and it is one of the most prevalent illnesses among people who arrive at emergency departments with abdominal pain (5). Gallstone disease has an estimated frequency of 5 to 22%, depending on risk factors (6). Although many gallstones remain asymptomatic, around one-third of them eventually produce symptoms and complications (7).

Fraquelli et al, stated the impact of CD on gallstone formation via reduced postprandial enteric peptide secretions and increased gallbladder volume (8). GB motility has been investigated in untreated celiac patients and the result confirms that decreased CCK secretion will affect intestinal and gallbladder motility (8). Diet with low-calorie content possibly induces GB stasis and consequently a reduction in GB stimulation (9). Fat intake plays a crucial role to induce GB contraction, this idea has been introduced by Gebhard et al (10). Additionally, GB stasis promotes the conversion of cholesterol into cholesteryl esters for deposition in the GB wall, exacerbating the already poor GB motor function. More specifically, a lengthy retention period of cholesterol supersaturated bile inside the biliary lumen commonly results in rapid cholesterol crystal development, crystallization, and aggregation as microlithiasis, and subsequently macroscopic gall stones, not just in CD patients but also in non- celiac individuals (11). Most importantly, in celiac patients, biliary cholesterol synthesis and secretion are substantially doubled, indicating increase biliary cholesterol secretion is a crucial component in the formation of supersaturated bile (12). Liver enzymes were not significantly linked with gallstone development, but may be changed dramatically as an impact of CD with Gallstones on the liver organ (5-12).

METHODS

Study participants

This comparative study has conducted on 280 participants (aged ≥ 15 years) in Basrah teaching hospital from December 2021 to August 2022. Totally, 140 patients were admitted into the surgical word, diagnosed, examined, investigated and followed up in outpatient clinic, all of those patients underwent to abdominal ultrasonography and the results indicated that they are diagnosed with gallstones and have prepared to performing laparoscopic cholecystectomy. Six patients among them who had celiac as well as gallstones disease. They have seropositive tests results of anti-gliadin autoantibodies IgA, IgG and anti-transglutaminase autoantibodies IgA. About 140 healthy control subjects were chosen randomly from the outpatient clinic of Basrah teaching hospital, those who visited the outpatient clinic for general health checkup. All of them were checked by ultrasonography consultant to exclude gallstones disease (GSD). Twelve patients among them had immunological seropositive biomarkers result and clinical presentations indicated the patients was asymptomatic celiac patients. All the 280 participants were subjected to a liver function test.

Ethical commitment

The study has conducted after obtaining the written consent of the participants, taking into account medical ethics.

Design of study

Patients and healthy control have assessed by questionnaire. All collected blood samples in this study were obtained from fasting patients for 12 hours at least. A fresh vein blood sample of 4 ml was taken by a laboratory technician using a sterilized syringe. Collected blood samples were putted into specific GEL tube (acid citrate dextrose) that helps the blood sample to coagulate rapidly and enhances the separation of the sample into two phases after centrifuging them. After 20 minutes, the Centrifuge process was conducted by an electrical centrifuge instrument for 5 minutes at speed of 4000 rpm. Beyond centrifuging process, we obtain serum sample using a micro pipette putting them into Eppendorf tubes, each tube containing (0.5 ml) and make ready for preservation. Serum samples were used to achieve the celiac biomarkers: (anti-tissue transglutaminase T/IgA and T/IgG, anti-gliadin-A, and anti-gliadin-G) and liver function tests. The samples were stored immediately in a sterile Eppendorf tube, then transported directly into a deep-freezing instrument at the BASRA BIOBANK to prevent serum sample damage. Samples were kept at -50°C that ensure the biomarkers and serum protein content were still undegraded and kept these contents active for 6 months (13). Serum samples were used to achieve the celiac biomarkers: (anti-tissue transglutaminase T/IgA and T/IgG, anti-gliadin-A IgA, and anti-gliadin-G IgG) and liver function test.

Immunological markers of CD

Anti-gliadin markers IgA and IgG were detected via indirect ELISA (Demeditec Diagnostic GmbH (Germany), cut off value for both isotypes markers were (10 U/ml) (14,15). Anti-tissue transglutaminase markers IgA and IgG were detected via indirect ELISA (Demeditec Diagnostic GmbH (Germany), cut off value for IgA isotypes markers were (10 U/ml) and for IgG isotypes markers were (7 U/ml) (16,17).

For a quantitative examination, the absorbances of both the standards as well as controls are graphed versus their levels. The level values for each specimen can then be obtained from the resulting reference curve in relation to their absorption spectra. It is also feasible to employ computer applications that run automatically (10-13).

Biochemical markers of LFT

Using a commercial kit from Sigma-Aldrich – USA, serum samples were tested for liver function test, liver enzymes Alanine aminotransferase enzyme (ALT) (references values for adults at 37°C up to (40 U/L) (0.67 kat/L) and 30°C up to (25 U/L) (0.42 kat/L), for plasma or serum) (18), Aspartate aminotransferase enzyme (AST) (references values for adults at 37°C up to (40 U/L) (0.67 kat/L) and at 30°C up to (25 U/L) (0.42 kat/L), for plasma or serum) (19) and Alkaline phosphatase enzyme (ALP) (references values for Serum or plasma in adults) (20). All of these tests depend on measured absorbance (A) of both the samples and standard compared to reagent blank.

Statistical analysis

The data were analyzed using the statistical software, SPSS-26.0 (SPSS Inc, Chicago, IL). Quantitative data were represented using basic measurements of mean and standard deviation. The significance of differences between means was assessed using the ANOVA test for differences between more than two independent means, followed by the Tukey test. Chi2 was used to investigate any association between qualitative variables. Statistical significance was regarded when the P value was less than 0.05 and highly significant when it was less than 0.01.

RESULTS

The demographic findings of participants enrolled in this study showed 134 patients (14 male and 120 female) with GSD only without CD of ages range (19-85 years) with a mean value (41.01) who have claimed clinical features of gallstones, 6 female patients of ages range (15-52) years with a mean of (34.33) revealed seropositivity of anti-gliadin and anti-transglutaminase autoimmune antibodies in a varying degree and appeared as overt CD in addition to GSD. 128 healthy control persons (14 male and 114 female) who didn't complain of any disease, age range (16-76) years with a mean of (40.99). 12 healthy female persons with a seropositive immunological result and still with silent symptoms of CD, ages range (17-68) years with a mean of (39.83), (*fig. 1*). Statistical analysis didn't show a significant association between age among study groups (P>0.05).

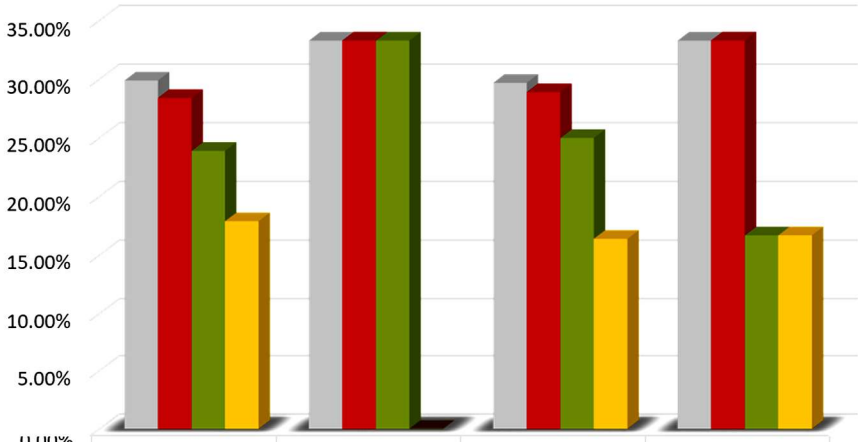
Our study has showed the female/male ratio for gallstone prevalence was 9:1. Residence distribution of study groups indicated that most of the patients and healthy control were of urban residence and the little percentage were of rural residence. The residence of patients in GSD group was distributed as (120, 89.6%) urban and (14, 10.4%) rural. The residence of patients in dual disease group was distributed as (6, 100%) urban. The distribution of residence in healthy control group was (106, 82.8%) urban and (22, 17.2%) rural and finally the distribution of residence in asymptomatic Celiac disease group was (7, 58.3%) urban and (5, 41.7%) rural (*table 1*).

Gliadin autoantibody G/IgA

Results showed a highly significant differences in gliadin autoantibody G/IgA titers (P<0.01) among study groups. Dual disease group showed the highest mean value (85.5833 U/ml ± 128.05484) greater than upper limits (≥10 U/ml), indicating the peoples in this group have CD with GSD. Healthy control group revealed the lowest mean value (2.3539 U/ml ± 1.39199). GSD group showed G/IgA with a mean value (2.6373 U/ml ± 1.57917) and the mean value of CD group is (17.4 U/ml ± 8.74) (*fig. 2a*).

Gliadin specific immune marker (G/IgG) results indicated a substantial variation (P<0.01) between research groups. Dual disease group showed mean value (36.9167 U/ml ± 20.87165) greater than upper limits (≥10 U/ml), indicating that these patients have celiac disease (CD) with Gallstone disease (GSD). GSD group showed G/IgG with a mean value of (2.6873 U/ml ±1.65309), healthy control group revealed the lowest mean value (2.3789 U/ml ±1.56), and CD group showed mean value (13.7583 U/ml ±11.06) with a slight elevation more than upper limits (≥10 U/ml), (*fig. 2b*).

Figure 1 - Study groups stratified by age



	Gallstone	Celiac disease+ Gallstone	Control	Celiac disease
Age group (Year) 15-29	29.90%	33.30%	29.70%	33.30%
Age group (Year) 30-44	28.40%	33.30%	28.90%	33.30%
Age group (Year) 45-59	23.90%	33.30%	25.00%	16.70%
Age group (Year) 60-85	17.90%	0.00%	16.40%	16.70%

Age group (Year) 15-29 Age group (Year) 30-44 Age group (Year) 45-59 Age group (Year) 60-85

Table 1 - Study groups stratified by sex and residence

		Category				Total
		Gallstone disease	Silent Celiac disease	Celiac disease + Gallstone	Control	
Sex	Male	14 10.4%	0 0	0 0	14 10.9%	28 10.0%
	Female	120 89.6%	12 100.0%	6 100.0%	114 89.1%	252 90.0%
Residence	Urban	120 89.6%	7 58.3%	6 100.0%	106 82.8%	239 85.4%
	Rural	14 10.4%	5 41.7%	0 0	22 17.2%	41 14.6%
Total		134 100.0%	12 100.0%	6 100.0%	128 100.0%	280 100.0 %

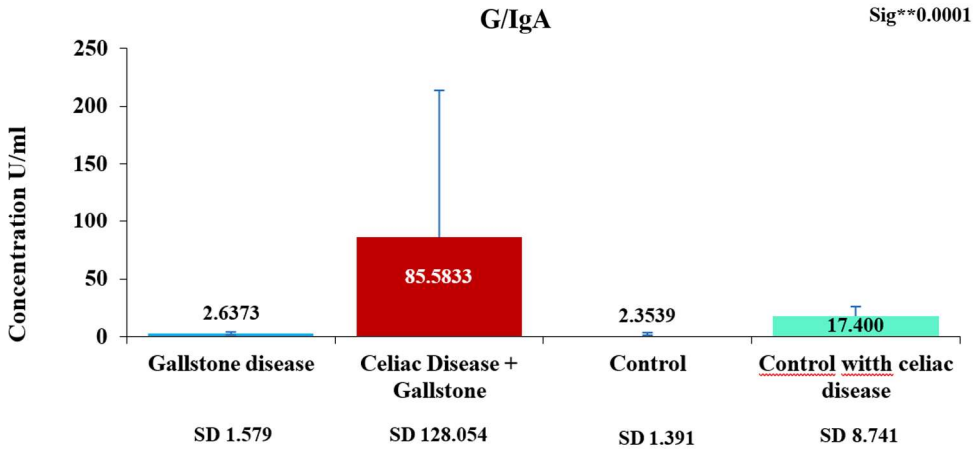


Figure 2 a - Level of G/IgA (U/ml) among study groups Gliadin autoantibody G/IgG

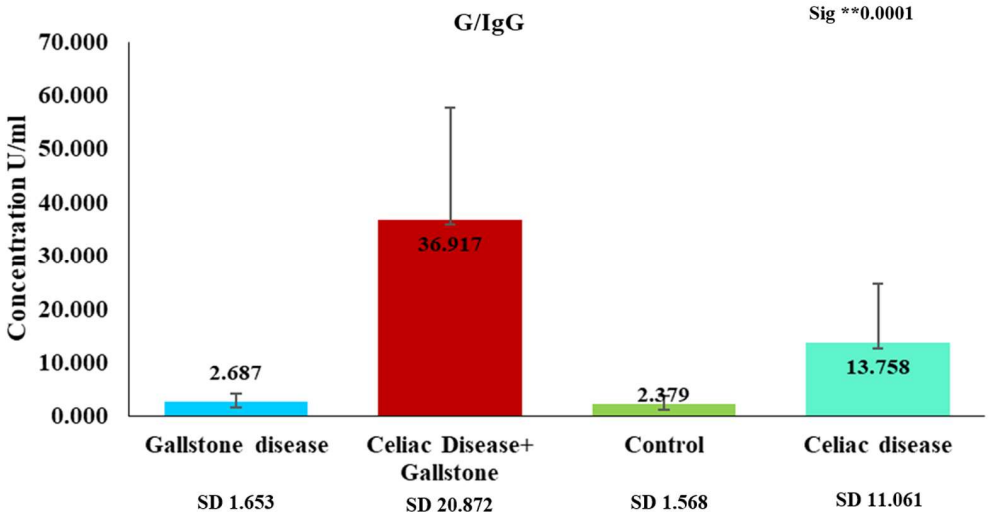


Figure 2 b - Level of G/IgG (U/ml) among study groups

Transglutaminase autoantibody T/IgA

Transglutaminase specific antibody marker (T/IgA) results revealed highly significant difference (P<0.01) between study groups. Dual disease group showed the highest mean value (74.85 U/ml ± 148.55) greater than upper limits (≥10 U/ml), indicating the people in this group have CD with GSD. GSD group showed the lowest mean value of tTG/IgA (2.05 U/ml ± 1.40) and silent CD group showed mean value of (8.73 U/ml ± 8.09), subsequently, healthy control group showed mean value of (2.46 U/ml ± 1.46) which are stay below upper limits of normal values (*fig. 3a*).

Transglutaminase autoantibody T/IgG

The results of (T/IgG) transglutaminase specific antibody markers revealed a highly significant difference (P<0.01) between study groups. Dual disease group showed a mean range greater than 7 U/ml, indicating that the T/IgG titer is slightly elevated more than the normal range below 7 U/ml (35). GSD group revealed T/IgG with a mean value of (2.06 U/ml ±1.34), dual disease group showed a mean value (8.61 U/ml ± 10.30), the control subjects group showed mean value (2.36 U/ml ±1.45), and asymptomatic Celiac disease group revealed mean value (6.40 U/ml ±8.36). Also,

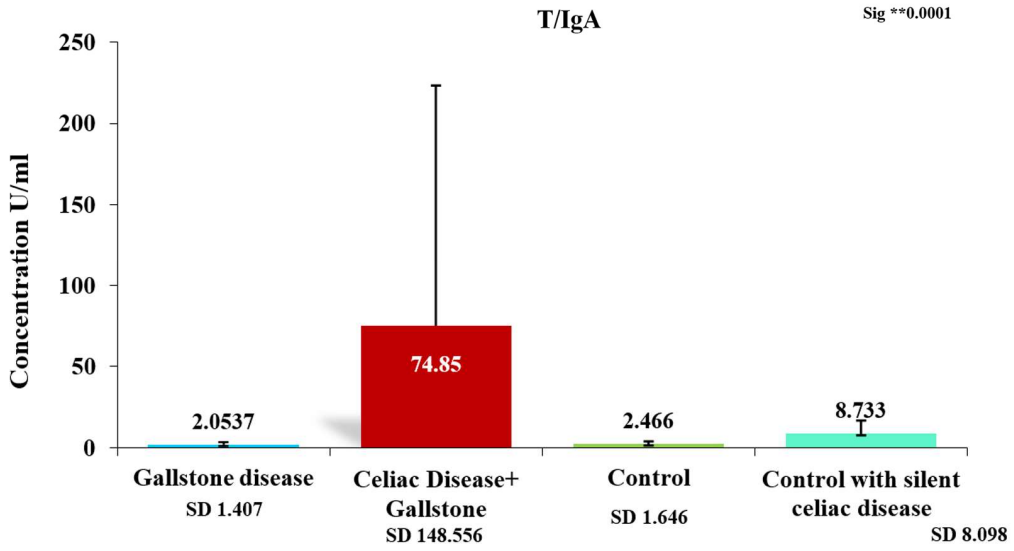


Figure 3 a - Level of T/IgA (U/ml) among study groups

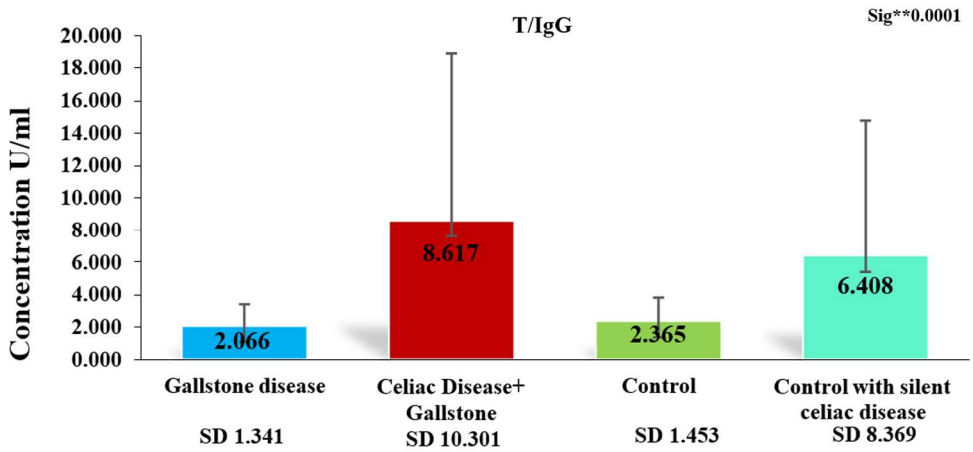


Figure 3 b - Level of T/IgG (U/ml) among study groups

dual disease group showed the highest mean value (8.61 U/ml ±10.30) while GSD group revealed the lowest mean value (2.06 U/ml ±1.34) (*fig. 3b*). Also, dual disease group showed the highest mean value (8.6167 U/ml ± 10.30134) while GSD group revealed the lowest mean value (2.0664 U/ml ± 1.34063).

Alanine aminotransferase enzyme (ALT)

Gallstones disease (GSD) group revealed Alanine aminotransferase enzyme (ALT) enzyme with a lowest mean value of (25.4552 U/L ± 29.30488), dual disease group showed a highest mean value (30.1667 U/L ± 13.57080), healthy control group showed a mean value (26.1016 U/L ± 13.26818), finally asymptomatic CD group revealed a mean value (29.25 U/L ± 20.66233). There was a very significant difference (P<0.01) between the research groups. The ALT enzyme was found to be within normal levels in all research groups, with really no evidence of an increase, (*fig. 4 a*).

Aspartate aminotransferase enzyme (AST)

The Gallstones disease group seemed to have an AST mean value of (31.9776 U/L ± 45.85929), the dual disease group seemed to have a mean value of (54.3333 U/L ± 50.85928), the control subjects' group had a mean value of (23.6563 U/L ± 12.84090), as well as the silent celiac disease group had an average value of (26.0 U/L ± 11.64630).

Collected data that explained in *fig. 4 b* was demonstrated insignificant differences (P>0.05) by comparison between study groups together. All study groups showed that AST enzyme have be within normal value and no one of them showed elevation except dual disease group that showed a slight elevation.

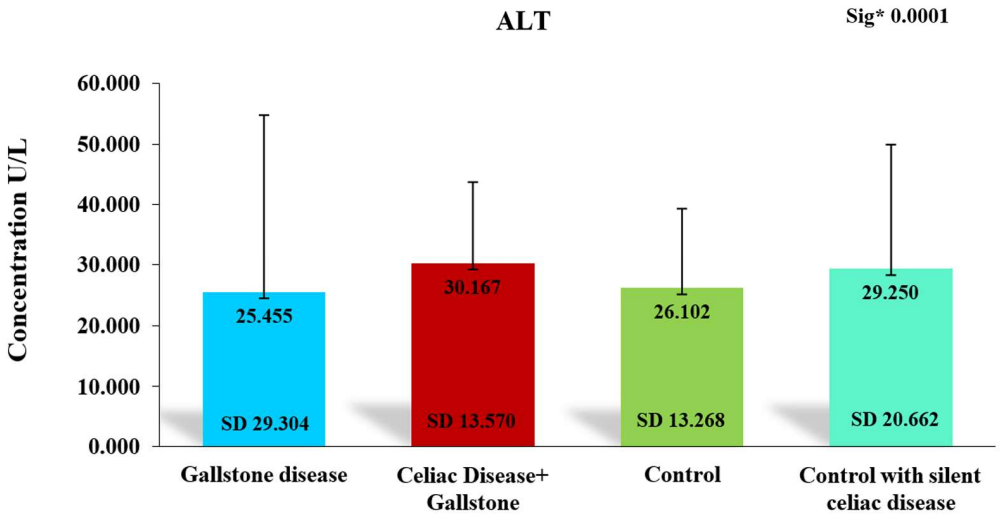


Figure 4 a - Level of ALT (U/L) among study groups

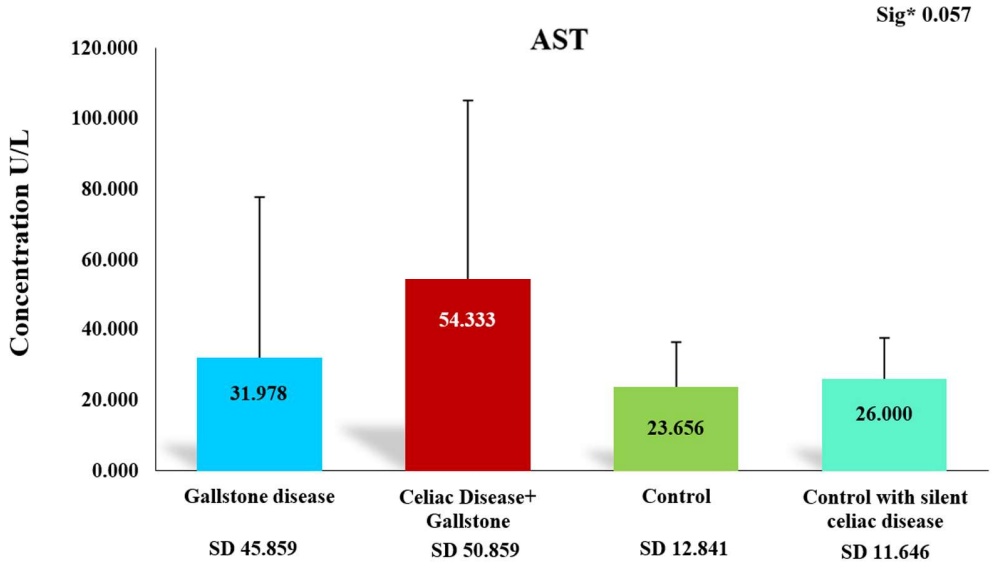


Figure 4 b - Level of AST (U/L) among study groups

Alkaline phosphatase enzyme (ALP)

The data obtained, as described in *fig. 4c*, showed statistically significant variations among research groups (P<0.01). Gallstones disease group had an ALP with a greatest mean value of (263.8134 U/L ± 123.91976), the dual disease group seemed to have a mean of (214.3333 U/L ± 69.54.327), the control patients' group seemed to have a mean of (136.6719 U/L ± 82.61705), and the silent celiac disease group seemed to have the lowest mean of (135.2500 U/L ± 71.64448), (*fig. 4c*). All study groups showed that ALP enzyme have be within normal value and no one of them showed elevation except GSD group that showed a light elevation. ALP enzyme elevation indicated biliary system injury.

DISCUSSION

According to Celiac disease-specific antibodies, a significant number of patients appear having atypical symptoms (asymptomatic CD) or even without symptoms (potential CD) (21).

It is clear that the age is considered as a predisposing

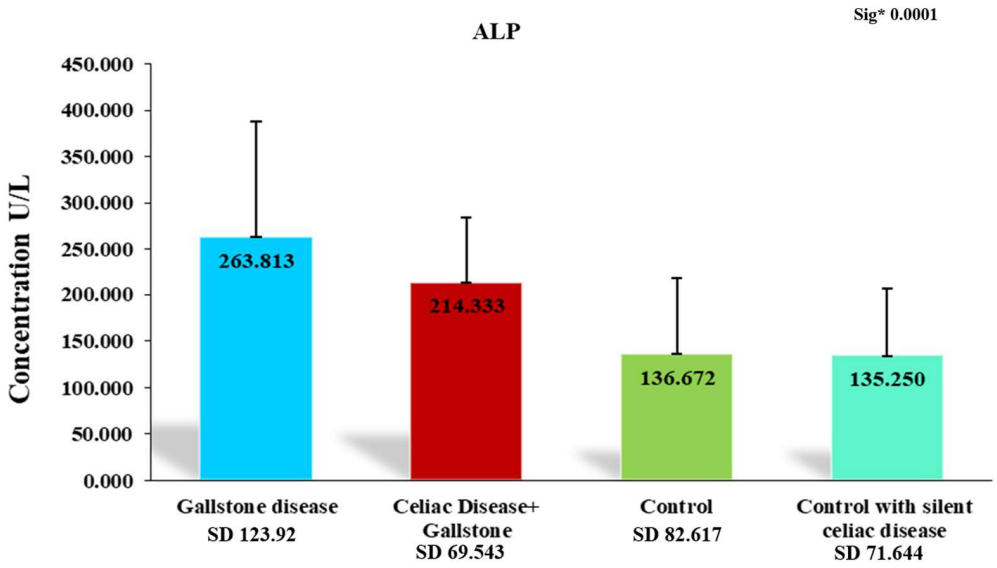


Figure 4 c - Level of ALP (U/L) among study groups

factor to the risk of gallstones and celiac disease incidence (22,23). The results of present study revealed age is closely related to gallstones disease (GSD) occurrence and show high frequency at patients younger than 50 years and the number of patients decreased in older age, but we noticed in our study, all patients have equal chance to get Celiac disease (CD) regardless the age. This may be related to the small population of CD group (24-28).

Some studies have proven different results, the prevalence of disease increase with age especially more than 60 years old with a Positive association between GSD trend and age has been revealed (29).

Age as a risk factor in population has a little effect on CD incidence; however, children population showed a significant disease occurrence relatively to adults (30, 31). In the present study, all age groups have equal chance to get CD and no correlation between age and disease, consequently, the effect of age may be related to metabolic disorder which synergized with CD. Moreover, CD occurred equally in all age groups approximately and decreased or not detected in old ages more than 60 years old.

Demographic parameters represented by the sex variation, the commonest sex that prone to have Gallstones disease (GSD) is female and the incidence in female more than male due to increasing bile cholesterol excretion and endogenous synthesis via female reproductive hormones that can induce gallstone development, as demonstrated by animal research and recently, testosterone has been linked to gallstone production in men. Number of births can increase the chance to get gallstones (32,33). This is in acceptance with our findings.

As a consequence, estrogens may increase the likelihood of GSD by increasing hepatic biliary cholesterol synthesis, which raises bile cholesterol saturation (34,35). Undiagnosed CD is more common in women than in men and increased risk of CD for female participants compared to male people involved is greater in children than in adults (36). By reviewing the previous results, we noticed sex as a predisposing factor plays a crucial role in GSD incidence and the sex effect on CD it is difficult to admit because of the number in this group was only 6 patients and healthy control group give rise only 12 asymptomatic patients. The ratio of female/male in healthy group was selected according to the ratio of female/male in GSD group.

By rechecking the residence findings in demographic results in this figure, 13 patients with CD, 7 patients (58.3%) from celiac group and 6 patients from dual disease group are residing in urban regions versus only 5(41.7%) patients are residing in rural regions. Also 126 patients with GSD, 120 patients (89.6%) from GSD group and 6 patients (100%) from dual disease group are residing in urban regions versus only 14 patients (10.4%) are residing in rural regions.

Patients with GSD in rural locations are frequently underserved and could not have the same access as their urban counterparts particularly health care (37). It was proposed that greater engagement to a Modern lifestyle, particularly increasing saturated fat with decreased fiber consumption, might be a potential factor for this. Increased BMI, in conjunction with increased urbanization, appears to be a significant potential factor in the genesis of GSD (37).

Rural populations have more disparities in health care because it has been founded that individuals who live in rural regions would be less likely to have healthy meal retail outlets and grocery stores, so it may be a requirement that comes with rural regions and is therefore not as widely reported as a restriction for such areas compared to urban areas (38).

The effect of residence on the disease was reviewed by previous studies (37,38) and these were in agreement with our study findings, it could reflect the impact of environment, nature of life, may be nature of nutrition and the level of education via the direct influence of these factors on disease discovering or progressing.

The findings of G/IgA indicated the patients in dual disease group have CD, while, asymptomatic CD group showed false seropositive result of gliadin autoantibody G/IgA due to negative result of T/IgA and this explained why patients in this group was asymptomatic. Another explanation for asymptomatic Celiac group they have slightly elevated titer and still asymptomatic, patients in this group may have the disease recently and need more time for titer elevation or they have gluten sensitivity without symptoms. By focusing on the mentioned results, elevation of anti-gliadin antibodies G/IgA, Multifoods more than its upper limits may precipitate GSD as a complication of CD.

Deamidated gliadin peptide-IgG (DGP-IgG) test is frequently used for CD screening. Tissue transglutaminase-IgA antibody is more sensitive and selective than DGP-IgG antibody (39). DGP-IgG is a sensitive method for CD discovering, especially in IgA deficient people. A positive DGP-IgG with presence of a negative T/IgA seems to have a low diagnostic accuracy for CD in children, although it can be increased in a number of non-celiac gastrointestinal diseases for unknown causes. Conjunction with digestive problems or biochemical signs of malabsorption or

inflammation (39). Positive G/IgG is difficult to be interpreted especially with negative T/IgA, Endoscopic duodenal biopsy was performed on forty individuals who tested positive for gliadin peptide G/IgG but negative for T/IgA, only one of those patients had CD verified by biopsy and this patient lacked IgA antibodies. Regarding separated G/IgG positive serology, this results in a positive predictive value about 2.5% (40). These studies were in agreement with our study findings.

The G/IgG assay had no effect on the diagnostic performance of the T/IgA test. The serology of T/IgA was favorably linked both for IgG and IgA gliadin peptide antibodies, with significant agreement with T/IgA and G/IgG and moderate correlation with G/IgA. G/IgG, but not IgA, was equivalent to T/IgA, indicating that it might be used as a reliable option for CD diagnosis and follow-up in case of T/IgA was positive (15).

Silent CD group showed insignificant difference with a slightly elevation of G/IgG titer with negative T/IgA that confirmed they are free of CD and they have either gluten sensitivity with non-inflammatory changes or patients have recently the disease without enteropathy or intestinal damage and no presence of histological modification like villous atrophy and crypt hyperplasia. It needs more time for titer elevation and induce bowel damage and make the symptoms obviously to appear in these group. Previous researches (39,40) that explored the association between anti-gliadin IgA and IgG with gallstones occurrence revealed a negligible correlation between them. Many studies included GIT and liver disorders such as IBS but did not include this correlation (41). Anti-gliadin autoantibodies (AGA) might be detected in non-celiac gluten sensitivity cases and considered as indicator of gluten sensitivity without giving any imagine about intestinal damage and enteropathy. GSD occurrence is closely related to intestinal dysmotility, intestinal enteropathy and villous atrophy as a result of CD and CCK neuropeptide secretion disturbance (41).

ALT level within dual disease group demonstrated insignificant difference and this pointing to a slightly effect of CD on aminotransamine enzyme. These findings contradicted previous research (42-44) that examined the effect of CD on aminotransamine enzymes. Gallstones effect is almost non-existent on ALT enzyme due to GSD group didn't show a significant difference with dual disease group and control group.

Obviously, hypertransaminemia refer to the elevation of hepatic transamine enzymes in multiple illness cases such as CD, sclerosing cholangitis and autoimmune hepatitis that may be associated with CD (44). Transaminase enzymes levels are higher in 9-42% of adult persons with CD and 24-40% of children with CD, according to studies. Furthermore, the incidence of unknown aminotransferase height in adults is proven to be 4% and 1.8% in kids. Increased liver enzymes could be the only result in Celiac disease; this could combine with non-alcoholic fatty liver disease (NAFLD), non-specific hepatitis, immunologic illness, and cholestatic liver problems (42). Elevated transaminases owing to CD are described as gluten-induced liver abnormalities hat often revert to baseline after 12 months of rigorous gluten-free eating (44). The liver is influenced to varying degrees in CD. Due to increased liver enzymes are remarkably common at the time of CD diagnosis, all clinically diagnosed cases with CD should be evaluated for hypertransaminemia (42).

When these patients were given a gluten-free diet (GFD), their ALT levels recovered to normal in (2.7%) of patients. After liver histopathology, hepatic cells didn't show pathognomonic findings rather than nonspecific or mild changes observed. Previous study conducted on 149 children of newly diagnosed with CD, liver pathological changes was found in 17 children and only 10 children had ALT enzyme elevation. Hepatic pathology represented as steatosis or liver enlargement that was detected at 12 patients. This study has documented there is a significant relation between IgA autoantibody against Transglutaminase 2 TG2 and ALT serum level (43).

Elevated value of ALP in the serum predicts the presence of stones, whereas elevated levels of liver testing process do not demonstrate disease because ALP is unique to the biliary system (44). Alkaline phosphatase (ALP) values might be normal or high in 4-20% of Celiac patients (45). ALP enzyme may be closely related to vitamin D level and parathyroid hormone PTH, since it inversely related to them and our study didn't asses vitamin D and PTH (46). The biliary system, in additional to the liver, can be significantly disrupted among CD patients; in addition, gallbladder function might vary in these individuals (47).

It is noticeable that ALP levels within the dual disease group revealed a significant correlation with CD, suggesting that CD has a little influence on enzyme levels and that gallstones have a direct effect on the biliary system.

CONCLUSION

Gallstones Disease had a potential effect on biliary system specific enzyme (ALP). Liver enzymes disturbances can be observed which associated with one of

diseases or both. We can distinguish between celiac and non-celiac gluten sensitivity by exclusion the immunological test. Anti-Gliadin test give an indication of gluten sensitivity and not for intestinal damage, also it has 95% sensitivity for CD and low specificity due to overlapping with another autoimmune disease.

Conflict of interests

The authors declare no conflict of interests.

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