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Original Article

# Sonographic criteria for the evaluation of dietary compliance of children with celiac disease

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**Abstract**

**Aim:** Although the only known way to avoid complications like iron deficiency anemia, short stature in celiac disease is a strict gluten-free diet, it is a known fact that not all patients follow the diet. Diet compliance is practically evaluated with serum antibodies, such as tissue transglutaminase antibody. The aim of this study was to evaluate the contribution of less invasive ultrasound and Doppler ultrasound in evaluating dietary compliance in celiac patients.

**Materials and Methods:** Twenty-five male and 47 female cases aged five to 17 years were included in the study. Seventy-two patients diagnosed with celiac disease and followed up were divided into two groups according to dietary compliance based on the results of tissue transglutaminase IgA antibody. Pericardial fluid, hepatosteatosis, mesenteric lymphadenopathy, intraabdominal free fluid, small intestine diameter, small intestine wall thickness and gallbladder volume, superior mesenteric artery (SMA) diameter, portal vein diameter, SMA peak systolic velocity, and portal vein velocity were measured on ultrasound. The differences between the groups were statistically compared.

**Results:** The frequency of mesenteric lymphadenopathy, superior mesenteric artery diameter, SMA peak systolic velocity, and portal vein velocity were increased in children who did not follow the recommended diet. There was no significant difference between the groups in terms of hyperperistalsis, gallbladder volume, and portal vein diameter. Pericardial fluid, fatty liver, small intestine dilatation, and increased intestinal wall thickness were not detected in either group.

**Conclusion:** Ultrasound can play an important role in the follow up of children with celiac disease. It can provide clinicians with an insight into the dietary compliance of these cases.

**Keywords:** Celiac disease; gluten-free diet; superior mesenteric artery; ultrasound

## INTRODUCTION

Celiac disease (CD) is a malabsorption syndrome that primarily affects the small intestine in patients with genetic predispositions. In CD cases exposed to gluten, villous atrophy, crypt hyperplasia and mucosal inflammation develop, and clinical and histological improvement is achieved by removing gluten from the diet. If CD is not treated, can cause iron deficiency anemia, short stature, dermatitis herpetiformis, dental problems, joint pain, neurological problems, and elevated liver enzymes (1). In these cases, osteoporosis and cancer may develop in the long term (1). Although the only known way to avoid such complications in celiac disease is a strict gluten-free diet, it is a known fact that not all patients follow the diet. It has been reported that 30-40% of celiac patients do not follow a strict diet (2). Serious structural changes in small bowel biopsies in patients with no symptoms or minimal symptoms suggest that the patient's clinic is inadequate in evaluating dietary compliance (3). Biopsy seems to be the best method to measure mucosal damage. However, serum antibodies which are less interventional are used more frequently in practice. Tissue transglutaminase Ig A antibodies return to normal in most of the cases in 1 year following a gluten-free diet (4). It becomes positive again in 3-12 months following the gluten diet (4). In addition, the diagnosis of celiac disease may be missed in cases with Ig A deficiency. Therefore, it is recommended to look for tissue transglutaminase Ig G antibodies. It was reported that tissue transglutaminase Ig A antibodies showed a better correlation than biopsy in evaluating dietary compliance (5). However, the percentage of false negative results is high in patients with low bowel damage (6). Therefore, more tools are needed that can be used in follow-up. Ultrasound is frequently used in seronegative cases despite clinical suspicion in the diagnosis of celiac

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disease (7). Also, there are some studies reporting the diagnostic effectiveness of ultrasound in celiac patients (8,9). In the follow-up of celiac cases, it is generally used in symptomatic conditions such as intussusception, elevated liver enzyme levels, exclusion of possible complications such as malignancy and abdominal pain. There is no data on the role of ultrasound in the follow up of celiac disease. The aim of our study is to determine the effectiveness of ultrasound in the follow-up of celiac patients to diet.

## MATERIALS and METHODS

### Patients

The patients followed up with a diagnosis of CD in the Pediatrics Outpatient Clinic of Adıyaman Training and Research Hospital between September 2013 and March 2020 were evaluated in terms of their ultrasound images obtained from the radiology archive. During patient screening from the system, those diagnosed with CD using upper gastrointestinal endoscopy without selective IgA deficiency were included in the study. Of the 186 cases included in the study, 114 were excluded from the study for various reasons (Figure 1). The remaining cases consisted of 25 boys and 47 girls whose ages ranged from 5-18, with an average age of 10.41 ± 3.30. The patients with tissue transglutaminase IgA positivity were divided into two groups as those that did not comply with a gluten-free diet (NoGFD) and those that followed a gluten-free diet (GFD). The sonographic findings of these two groups were statistically compared. The local ethics committee approval was obtained for the study.

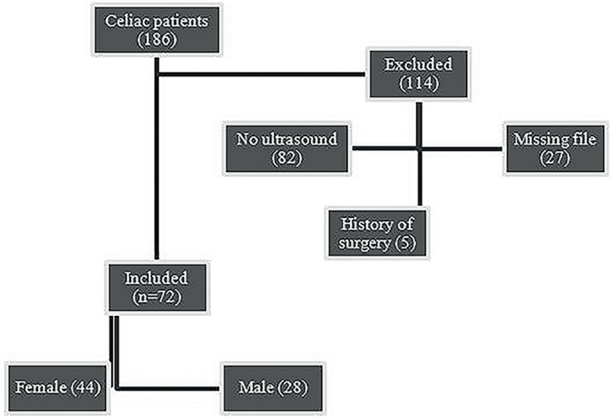


**Figure 1.** Flow chart of pediatric patients with celiac disease

### Ultrasound

The ultrasound examination was performed using MyLab Seven equipment (Esaote, Genova, Italy) with a convex probe AC2545 and linear probe SL1543. Ultrasound was routinely undertaken after fasting. Portal hypertension and cardiovascular disease have been reported in celiac patients (10,11). For this reason, Doppler US from portal vein and SMA are routinely checked in our clinic. The presence of pericardial fluid, hepatosteatosis, mesenteric lymphadenopathy, and intra-abdominal free fluid were investigated on ultrasound. In addition, gallbladder volume, superior mesenteric artery (SMA) diameter, portal vein diameter, SMA peak systolic velocity (PSV), and mean portal vein velocity were measured. Mesenteric lymph node diameter of more than 5 mm in the anteroposterior plane and cortex thickened lymph nodes were accepted as mesenteric lymphadenopathy (LAP) (9). In cases where the small intestine diameter was over 2.5 cm, there was dilatation of bowel loops, and the small intestine wall thickness was over 3 mm, the intestinal wall was considered to be thickened (8,12). It was noted whether there was free fluid in the abdomen. Portal vein Doppler ultrasound was performed using the right lateral intercostal approach. The mean portal vein velocity was obtained by using the Doppler angle of 60 degrees or less at the level of porta hepatis. Superior mesenteric artery Doppler examination was performed with patients in the supine position. The probe was first placed under the xiphoid process. After finding the aorta and then SMA, color mode examination was continued in the sagittal plane. Patients with intestinal gas superposition were examined in an inclined position. Doppler examination, SMA diameter and PSV were measured 2-3 cm distal from the origin of the vascular structure. In spectral examination, the Doppler angle used was equal or under 60 degrees. Mesenteric lymph node diameter of more than 5 mm in the anteroposterior plane and cortex thickened lymph nodes were accepted as mesenteric lymphadenopathy (LAP) (9), (Figure 2).

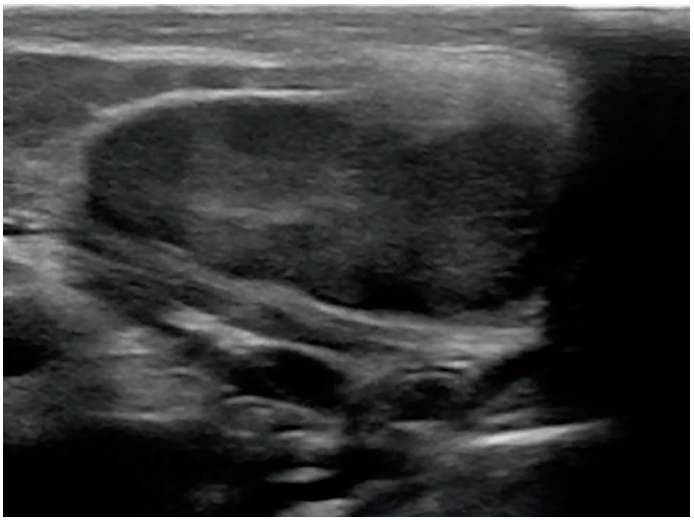

**Figure 2.** Ultrasound image showing mesenteric lymphadenopathy in the right lower quadrant of the abdomen

### IgA anti-tissue transglutaminase antibody assay

The analysis of tissue transglutaminase IgA antibody was performed using the enzyme-linked immunosorbent assay (ELISA) method, and the quantitative measurement was performed on a Triturus ELISA autoanalyzer (Grifols, Spain).

After finding the aorta and then SMA, color mode examination was continued in the sagittal plane (Figure 3).

### Statistical analysis

Categorical variables were compared with chi-square test

and numerical values with student t test. P <0.05 was considered statistically significant. The receiver operating characteristic (ROC) analysis was used to determine the cut-off value. The sensitivity, specificity, positive likelihood ratio, negative likelihood ratio, positive predictive value, and negative predictive value were calculated to evaluate the diagnostic performance of ultrasound and Doppler ultrasound findings in the prediction of dietary compliance.

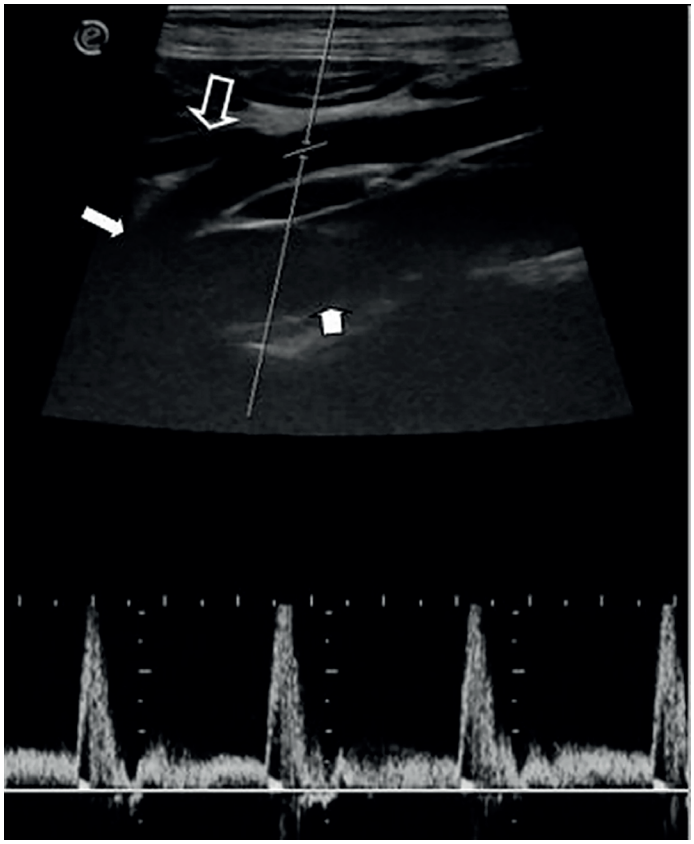

**Figure 3.** Measurement of the peak systolic velocity from the superior mesenteric artery (SMA). The origin of SMA is shown by a filled arrow, the aorta by a short arrow, and the right hepatic artery originating from SMA by a blank arrow

## RESULTS

The mean age was calculated as 10.47 ± 2.68 years for the NoGFD group and 10.46 ± 3.67 years for the GFD group. There were seven boys and eight girls in the NoGFD group. In the same group, mesenteric lymphadenopathy was more common (Table 1). The SMA diameter and SMA peak systolic velocity were statistically significantly increased in the NoGFD group (p=0.001 and p=0.0005, respectively).There was no significant difference between the two groups in terms of the portal vein diameter (p=0.488), but the portal vein velocity values were significantly higher in the NoGFD group (p=0.005).

**Table 1. Ultrasound finding of the patients with celiac disease according to their dietary compliance**

| | NoGFD | GFD | p |
|---|---|---|---|
| Increased peristalsis | 7/15 | 17/57 | 0.21* |
| Hepatosteatosis | 0 | 0 | |
| Pericardial fluid | 0 | 0 | |
| IFF | 5/15 | 9/57 | 0.15*** |
| Gallbladder volume | 10.55 ± 4.26 | 9.33 ± 5.99 | 0.46 |
| Mesenteric LAP | 10/15 | 16/57 | 0.004*** |
| ISWT | 0 | 0 | |
| ISD | 0 | 0 | |
| SMA diameter | 5.13 ± 0.85 | 4.38 ± 0.79 | 0.001*** |
| PSV of SMA | 101.99 ± 18.23 | 87.48 ± 21.24 | 0.005*** |
| PV diameter | 7.70 ± 1.54 | 7.10 ± 3.20 | 0.488* |
| PV velocity | 33.42 ± 5.90 | 25.74 ± 9.69 | 0.005* |

NoGFD: the group that did not comply with a gluten-free diet; GFD: the group that followed a gluten-free diet; p:significance; IFF: Intra-abdominal free fluid; LAP: lymphadenopathy; ISWT: Increased small intestine wall thickness; ISD: Increased small intestine diameter; SMA: superior mesenteric artery; PSV: peak systolic velocity; PV: portal vein *Pearson,***Fisher's exact test

**Table 2. Diagnostic performance of four ultrasound parameters in predicting dietary compliance in celiac disease**

| | Sensitivity | Specificity | +LR | -LR | PPV | NPV |
|---|---|---|---|---|---|---|
| Mesenteric LAP (short diameter<0.5 mm) | 66.7 | 77.2 | 4.26 | 0.63 | 43.5 | 89.8 |
| SMA diameter (<4.95 mm) | 66.7 | 78.9 | 4.54 | 0.60 | 45.5 | 90 |
| PSV of SMA (<103.5 cm/sec) | 53.3 | 84.2 | 3.70 | 0.61 | 47.1 | 87.3 |
| PV velocity (<25.9 cm/sec) | 93.3 | 47.4 | 10.58 | 0.58 | 34.1 | 96.8 |

+LR: positive likelihood ratio; -LR: negative likelihood ratio; PPV: positive predictive value; NPV: negative predictive value; LAP: lymphadenopathy; SMA: superior mesenteric artery; PSV: peak systolic velocity; PV: portal vein

No significant difference was observed between the dietary compliance groups in terms of the gallbladder volume (p=0.46). There was also no statistically significant increase in peristalsis in the NoGFD group. No pericardial fluid or hepatosteatosis was detected in either group. According to the ROC curve analysis, the cut-off values were determined as 4.95 mm for the SMA diameter, 103.5 cm/sec for the PSV of SMA, and 25.9 cm/sec for the velocity of portal vein (Table 2).

## DISCUSSION

In this study, the most sensitive finding that showed dietary incompliance was increased portal vein velocity (93%), while mesenteric lymphadenopathy, increased SMA diameter, and increased SMA peak systolic rate were found to be less sensitive (67%, 67%, and 53.3%, respectively). Increased portal vein velocity can help exclude dietary compliance (NPV 96%). However, it was determined that intra-abdominal free fluid, hyperperistalsis, gallbladder volume, and portal vein diameter did not change according to the presence/absence of dietary compliance. Interestingly, pericardial effusion, hepatosteatosis, small intestine dilatation, and small intestinal wall thickness increase were not detected in either group.

In celiac patients, mesenteric lymphadenopathy is frequently encountered as a result of increased immune response to gluten. Mesenteric lymphadenopathy was found between 24% and 82% of cases in adult celiac cases (7-9,13). However, there are differences in lymphadenopathy measurements in these studies. Soresi et al. (7), Rettenbacher et al. (9) accepted lymph nodes with anteroposterior diameter more than 5 mm as lymphadenopathy. In contrast, Fraquelli et al. (8) accepted lymph nodes with a long axis greater than 5 mm and Tomei et al. (13) greater than 10 mm as lymphadenopathy. In this study, lymph nodes more than 5 mm in the anteroposterior diameter were accepted as lymphadenopathy. The difference between the frequency of lymphadenopathy in the studies may result from differences in measurement methods. In this study, the rate of mesenteric lymphadenopathy was 22.8% in the group following the gluten-free diet and 66.7% in the group that did not comply with the dietary recommendations ($p = 0.004$). This may be related to the decrease in immune response as a result of decreased antigenic stimulation. In celiac patients, as a result of chronic mucosal inflammation in the small intestine, the normal capillary structure is lost and replaced by a vascular network presenting with tortuosity and arterio-venous shunts (14). This disease leads to the impaired physiological autoregulation of blood flow in the mesenteric vascular bed (15). SMA blood flow, SMA diameter and peak systolic velocity values are significantly increased in celiac patients compared to healthy individuals (16-18). In this study, SMA diameter and SMA PSV values were found to be significantly higher in the group that did not comply with the diet compared to the group with dietary compliance ($p < 0.05$). Improvement in the autoregulation of blood flow in the mesenteric vascular bed may have been achieved by the gluten-free diet. Portal vein velocity is observed to be increased in celiac patients (17). In addition, improvement in portal hypertension through a gluten-free diet has been reported in this patient group (19). Although it is not known why portal hypertension develops, it is considered that it may develop as a result of immune response against antigenic stimulation. In our study, while the PV diameter did not significantly differ between the groups, the PV velocity values were found to be significantly higher in the group that did not comply with the gluten-free diet. PV velocity was the most sensitive (93.3%) sonographic parameter in predicting dietary compliance. On the other hand, the negative predictive value of PV velocity was 96.8, indicating that it is the most important parameter in excluding dietary compliance. The positive predictive values of mesenteric lymphadenopathy, SMA diameter, and SMA peak systolic velocity were poor in predicting dietary compliance.

In celiac patients, mucosal damage in the small intestine may affect intestinal motility (20). In addition, these motility disorders may continue despite a gluten-free diet, which has been attributed to the ongoing low-level inflammation (20). In the current study, increased peristalsis was found at a rate of 29.8% in the group with dietary compliance and 46.7% in the group that did not follow the gluten-free diet ($p=0.21$). In this study, the increase in peristaltism in the group that did not follow the diet, although not statistically significant, supports the idea that mucosal inflammation caused by gluten exposure causes increased peristalsis. In celiac disease, intestinal permeability (15) and inflammatory cytokines (16) increase, similar to steatohepatitis. Grieco et al. detected celiac disease in four of 30 patients with non-alcoholic steatohepatitis and reported that hepatosteatosis improved based on laboratory and sonographic findings the patients started to follow a gluten-free diet (21). However, this study was conducted in adults and in a relatively small group of patients. In addition, patients with steatohepatitis are obese and increased cytokines such as increased TNF-alpha in obesity have been reported (22). In the current study, which was conducted with children, hepatosteatosis was not sonographically detected in 15 cases in the NoGFD group and 57 cases in the GFD group. It was previously reported that gallbladder volume was increased in adult patients with celiac disease (8). The probable pathological mechanism underlying this finding was explained with the idea that the increased volume of somatostatin in patients with untreated celiac disease was parallel to their gallbladder volumes (23). However, in another study, plasma somatostatin levels were not shown to change in children on a gluten-free diet (24), which may also explain why the gallbladder volume did not significantly differ between the two groups in the current study. The effect of dietary compliance on somatostatin levels is another study subject.

Increased intestinal wall thickness seen in 9 and dilated small bowel loops seen in 11 of 12 adult non-treated celiac patients were reported (9). In this study, dilated small bowel loops were reported as the most sensitive finding. However, this study was conducted in adults and in a relatively small group of patients. There is a need for a study in children with more and newly diagnosed patients. Interestingly, in the current study, no child with celiac disease had increased intestinal wall thickness or dilated small bowel loops. It has been suggested that pericardial effusion in celiac patients may result from the accumulation of immune complexes originating

from the small intestine in other organs (25). Pericardial effusion was reported in 13 of 26 pediatric celiac cases by Riccabona et al. (26) and four of 22 pediatric celiac cases by Grasso et al. (27). These two studies were conducted with children aged 12 to 24 months and seven to 36 months, respectively. In our study, the age range of the cases was five to 17 years, which can explain the different results compared to the previous studies. Further studies are needed to evaluate pericardial effusion according to age groups in children with celiac disease. The incidence of intra-abdominal free fluid in celiac patients has been reported to vary between 45 and 76% (8,9,28). In our study, we found intraabdominal free fluid in 15.8% of the patients in the GFD group and 33.3% of those in the NoGFD group ($p > 0.05$). It is known that intestinal permeability increases in celiac patients and this responds rapidly to a gluten-free diet (29). In this study, although the intra-abdominal fluid was lesser as expected in the group following the diet, the etiology of the fluid in 15.8% of the cases could not be determined. In the group that does not comply with its diet, the detection of free fluids in fewer cases compared to the new diagnosis celiac patients can be explained by partial dietary compliance.

Our study has some limitations. For example, ultrasound findings were compared to tissue transglutaminase Ig A antibodies, not biopsy findings, which is the gold standard. Comparison with biopsy is more valuable, but its use in follow-up cases is impractical. Due to the retrospective design of the study, it was made from file and image records. Mild findings are likely to be missed, and more detailed evaluation will be more valuable on ultrasound, where detailed evaluation takes time. Since the cases under the age of five are not in our study, it does not cover the entire childhood.

## CONCLUSION

Ultrasound provides some remarkable findings in the follow-up of pediatric celiac patients and determination of their compliance with treatment. Increased portal vein velocity is the most sensitive sonographic parameter in detecting cases that do not comply with a gluten-free diet. The positive predictive values of mesenteric lymphadenopathy, increased SMA diameter, and increased SMA peak systolic rate are poor. Being an inexpensive and easily available modality containing no radiation, ultrasound is a useful tool for clinicians in the follow-up of celiac patients.

*Conflict of interest : The authors declare that they have no competing interest.*

*Financial Disclosure: There are no financial supports.*

*Ethical approval: This study was approved by the Adiyaman University Ethics Committee. (protocol number:2019/7-14).*

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