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Original Research Article

Correlation of Serum Anti Tissue Transglutaminase Immunoglobulin-A Levels with Weight, Height and Haemoglobin in Cases of Celiac Disease

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Abstract

Objective: Correlation of serum anti tissue transglutaminase immunoglobulin-A levels with weight, height and haemoglobin. Correlation of staging with weight, height and haemoglobin. Abdominal ultrasonography finding in cases of celiac disease.

Methods: This was a prospective analytical study conducted in Department of Pediatrics, Umaid Hospital, Dr. S.N. Medical College, Jodhpur in children attending outpatient department and patients admitted in wards. Patients of with age less than 18 years were included in the study. The study was conducted over period of one year from January 2014 to December 2014. Total 52 patients were enrolled in study.

Results: The most common finding on abdominal ultrasound was distended bowel loops which were present in fifteen (28.84%) cases on upper gastrointestinal endoscopy villous atrophy was seen in 33 (63.46%) cases. There was no correlation between serum tissue transglutaminase IgA levels and clinical parameters like weight, height, hemoglobin .There was no correlation between serum tissue transglutaminase IgA levels and abdominal ultrasonography finding.

Conclusion: There is significant correlation between serum anti tissue transglutaminase immunoglobulin A levels. Endoscopy and biopsy may not be necessary for diagnosis of celiac disease. Whenever levels of serum anti tissue transglutaminase immunoglobulin levels are inconclusive then endoscopy and biopsy is helpful in diagnosis. This will avoid an invasive procedure and lead to a more rapid diagnosis and earlier treatment of celiac disease.

Keywords: Celiac Disease (CD), Villous Atrophy, Serum Tissue Transglutaminase IgA.

Introduction

Celiac disease (CD) is a chronic, immunologically determined form of enteropathy affecting the small intestine in genetically predisposed children and adults. It is precipitated by the ingestion of gluten-containing foods. For symptomatic celiac disease patients, the introduction of a gluten-free diet leads to significant improvement in symptoms, and quality of life. Concerns remain about the long-term consequences in patients with asymptomatic celiac disease and whether maintaining a lifelong glutein free diet is necessary for all patients. Recent studies have suggested that patients who are detected during screening, most of whom can be regarded as asymptomatic, can

improve their quality of life in the longer term with a glutein free diet.

Patients with (long-term untreated) celiac disease have an increased risk for benign and malignant complicationsIn current practice, the diagnosis of celiac disease hinges on a diagnostic intestinal biopsy and the concomitant presence of a positive celiac disease–specific serology[11]. With increasing noumber of cases of celiac disease there are certain limiting factors for histological diagnosis of celiac disease, these are

- Limited noumber of centers doing pediatric endoscopy.
- Lack of expert pathologists for histopathological examination of biopsy samples.
- Risk associated with upper GI endoscopy and anesthesia used during procedure.
- High cost of endoscopy and histopathological examination of biopsy specimens.

Due to above mentioned factors a large number of patients with positive serum tissue transglutaminase antibody A levels do not get histopathological confirmation of celiac disease diagnosis. In recent past some studies showed that there is linear correlation between serum anti tissue transglutaminase immunoglobulin A levels and histological changes in celiac disease although patients with very high serum anti tissue tansglutaminase immunoglobulin A levels donot require histological confirmation for diagnosis of Celiac disease. In present study we will try to determine the correlation between serum anti tissue transglutaminase immunoglobulin A levels in suspected celiac disease patients and also to findout correlation between serum anti tissue transglutaminase immunoglobulin-A levels and clinical severity of disease.

Materials and Methods

The study was conducted in Department of Pediatrics, Umaid Hospital, Dr. S.N. Medical College, Jodhpur in children attending outpatient department and patients admitted in wards. Patients of with age less than 18 years were included in the study. The study was conducted over period of one year .

Type of study: It was a prospective analytical study.

Sample size(n): Total 52 patients were enrolled in study. According to this formula minimum of 26 cases will be required for the study with absolute precision of 5% and confidence level 99%.

Inclusion criteria-There are two groups of patients

1. New patients with positive tissue transglutaminase immunoglobulin-A levels.
2. Patients with negative tissue transglutaminase immunoglobulin-A levels but strong clinical suspicion of celiac disease.

Exclusion criteria-Diagnosed cases of celiac disease who were on glutein free diet were not included in the study as in celiac disease glutein free diet causes reversal of mucosal changes in duodenum.

Parameters evaluated Detailed history was taken on predesigned pro-forma. Complete general physical and systemic examination was done, with special attention to anthropometry (weight, height/length, Upper segment to lower segment ratio, head circumference). Mucosal biopsy from second part of duodenum was taken with biopsy forceps and was sent in formalin for histopathological examination and Marsh staging. Ultrasonography abdomen was done with special attention to look for dilated bowel loops. Complete haemogram was done using automated cell counter. Erythrocyte Sedimentation Rate was done by Westergren method. Stool Examination

was done to see for pus cells, occult blood, PH, giardia, amoeba, steatorrhea etc.

Endoscopy in patients with suspected celiac Disease Upper gastrointestinal endoscopy has gained importance as a procedure allowing histological sampling of the mucosa, as it is less invasive and less time-consuming. The endoscopic procedure also allows incidental observation of typical duodenoscopic features that are highly predictive of the celiac disease. Although endoscopy may provide an indication for intestinal biopsy in patients who are being examined for other reasons than suspected celiac disease, it may not be sufficiently sensitive to detect the disorder. The characteristic findings of celiac disease on endoscopy include.

- Scalloped folds, fissures and a mosaic pattern
- Flattened folds
- Smaller size and/or disappearance of folds with maximum insufflation

If on endoscopy we see above mentioned findings, a duodenal biopsy becomes necessary. In contrast, a clinical suspicion of celiac disease requires a small-bowel biopsy even when there is a normal duodenoscopic appearance.

Observation Chart

Table 1: Distribution of cases according to age & sex

S. No.	Age(yr)	Male	Female	Total
		No.	No.	No.
1.	<5	06(23.07%)	06(23.07%)	12
2.	6-9	10(38.46%)	11(42.30%)	21
3.	10-18	10(38.46%)	09(34.61%)	19
4.	Total	26(50%)	26(50%)	52

Female ratio = 1:1

Maximum no. of patients were in the age group of 6-9 year.

Table 2: Distribution of cases according to religion

S. No.	Religion		Hindu	Muslim	Total
1.	Cases	No.	43	09	52
2.		%	82.69%	17.3%	100%

There were 82.69% Hindu cases compared to only 17.30% Muslims.

Table 3: Distribution of cases according to clinical presentation

S. No.	Clinical presentation	Total no. of cases	
		No.	Percentage
1	Abdominal pain	09	17.30%
2	Diarrhoea	19	36.53%
3	Constipation	07	13.46%
4	Vomiting	07	13.46%
5	Abdominal distension	17	32.69%
6	Anorexia	08	15.38%
7	Not gaining weight	17	32.69%
8	Not gaining height	09	17.30%

The most common presenting complaint was diarrhoea (36.53%) followed buy not gaining weight (32.69%) and abdominal distension (32.69%).

Table 4: Anthropometry

S. No.	Distribution	No. of cases	
		Height	Weight
1.	>2 SD	23(44.23%)	25(48.07%)
2.	<2 SD	29(55.76%)	27(51.92%)
3.	<3 SD	9(17.83%)	-
4.	Total	52(100%)	52(100%)

Short stature was present in 23 (55.76%), while 25 (51.92%) cases were underweight.

Table 5: Distribution of cases according to degree of anemia

S. No.	Anemia	Total no. of cases	
		No.	%
1.	No Anemia	14	26.92%
2.	Mild Anemia	03	5.76%
3.	Moderate Anemia	20	38.46%
4.	Severe Anemia	15	28.84%
5.	Total	52	100%

73.08% cases were having anemia, out of which maximum (38.46%) cases were having moderate anemia, followed by severe anemia (28.84%) and mild anemia (5.76%). Abnormal USG findings were noted in 29 (55.76%) cases.

Table 6: Distribution of cases according to abdominal USG

S. No.	Abdominal ultrasonography finding	Total no. of cases	
		No.	%
1	Normal	29	55.76%
2	Distended bowel loops	15	28.84%
3	Hepatomegaly	04	7.69%
4	Mesentric Lymphadenopathy	04	7.69%
	Total	52	100%

Most common finding in abdominal ultrasound was distended bowel loops which were present in 15 (28.84%) cases.

Table 7: Distribution of cases according to duodenal endoscopy

S. No.	Endoscopy finding	No. of cases
1.	Villous atrophy	33(63.46%)
2.	Normal	19(36.53%)
3.	Total	52(100%)

Villous atrophy was present in 33 (63.46%) cases on duodenal endoscopy.

Table 8: Correlation between tissue transglutaminase IgA and weight

S. No.	Serum tTg (IU/ml)	Cases		
		Weight <3 SD	Weight > 3SD	Total
1.	0-70	13(44.82%)	16(55.17%)	29
2.	71-140	04(36.36%)	07(63.63%)	11
3.	141-210	08(88.88%)	11(1.11%)	19
4.	211-280	02(66.66%)	01(33.33%)	03
5.	Total	27(51.92%)	25(48.07%)	52

P value > 0.05

There was no correlation between serum tissue transglutaminase IgA levels and weight.

Table 9: Correlation between tissue transglutaminase IgA and height/length

S. No.	Serum tTg (IU/ml)	Cases		
		Height < 2 SD	Height > 2SD	Total
1.	0-70	14(48.27%)	15(51.72%)	29
2.	71-140	05(50%)	05(50%)	10
3.	141-210	08(88.88%)	01(11.11%)	09
4.	211-280	02(50%)	02(50%)	04
5.	Total	29(55.76%)	23(44.23%)	52

P value > 0.05

There was no correlation between serum tissue transglutaminase IgA levels and height/length

Table 10: Correlation between tissue transglutaminase IgA and abdominal ultrasonography

S. No.	Serum tTg (IU/ml)	USG in Cases		
		Normal	Dilated bowel loops	Total
1.	0-70	23(79.31%)	6(20.68%)	29
2.	71-140	06(60%)	04(40%)	10
3.	141-210	5(55.55%)	4(4.44%)	09
4.	211-280	03(75%)	01(25%)	04
5.	Total	37	15	52

P value is > 0.05

There was no correlation between serum tissue transglutaminase IgA levels and abdominal ultrasonography finding.

Results

The following are the salient observations of our study –

- In our study male female ratio was 1:1.
- Maximum number of patients were in the age group of 6-9 years.
- There were 82.69% Hindu cases compared to only 17.30% Muslims
- The most common presenting complaint was diarrhoea (36.53%) followed buy not gaining weight (32.69%) and abdominal distension (32.69%).
- Twenty-three (44.23%) cases were having short stature, while twenty-five (48.07%) cases were underweighted.
- Maximum number of cases (53.84%) were having serum tissue transglutaminase IgA level between 21-70 IU/ml.
- Anemia was present in 73.08% cases, out of which maximum (38.46%) cases were having moderate anemia, followed by severe (28.84%) and mild anemia (5.76%).
- Most of the cases (73.07%) were having microcytic red blood cells indicating iron deficiency anemia.
- Thrombocytosis was present in nine (17.33%) cases while two (3.84%) cases were having thrombocytopenia. Majority of the patients (78.84%) were having normal platelet counts.
- No abnormal abdominal USG finding was noted in 29(55.76%) cases. The most common finding on abdominal ultrasound was distended bowel loops which were present in fifteen (28.84%) cases.
- On upper gastrointestinal endoscopy villous atrophy was seen in 33 (63.46%) cases.

- There was no correlation between serum tissue transglutaminase IgA levels and clinical parameters like weight, height, haemoglobin.
- There was no correlation between serum tissue transglutaminase IgA levels and abdominal ultrasonography finding.

Statistical Analysis:

The collected data was summarized by using frequency, percentage, mean & S.D. To compare the qualitative outcome measures Chi-square test or Fisher's exact test was used. To compare the quantitative outcome measures independent t test was used. If data was not following normal distribution, Mann Whitney U test was used. SPSS version 22 software was used to analyse the collected data. p value of <0.05 was statistically significant. Box plot, receiver operating characteristic *(*ROC) curve, Analysis of variance (ANOVA), Chi square test and student t test were applied.

Discussion

Thorvardur R. Halfdanarson et al studied haematological parameters in celiac disease and find out that 46% cases of celiac disease were having anemia.In our study 73.07% case were having microcytic red blood cells . This microcytic picture of red blood cells can be explained by high prevalence of iron deficiency anemia in celiac disease. Lombardo T et al studied hypochromic microcytic anemia as a clinical presentation of celiac disease. Total 207 women with microcytic hyochromic anemia were studied. They find out celiac disease as a very common cause of microcytic hypochromic anemia. They reviewed hematologic manifestations of celiac disease. They find out that 46 % cases of celiac disease were suffering from microcytic hypochromic anemia. As we can see in above mentioned studies there is high prevalence of thrombocytosis in cases of celiac disease and same results were seen in our study. This association can be attributed to iron deficiency anemia in celiac disease. [1,2]

Abdullah Altıntas et al. screened 74 cases of chronic idiopathic thrombocytopenic purpura for celiac disease with 162 controls. Serum anti tissue transglutaminase IgG positivity was found in 17, and IgA was present in 5 out of 74 celiac disease cases. These results show that there is high prevalence of celiac disease in patients of idiopathic thrombocytopenic purpura. In our study we have not investigated cases for idiopathic thrombocytopenic purpura so we can't comment on association of these two diseases but as compare to general population there was definitely high prevalence of thrombocytopenia in our cases and it needs to be further investigated for underlying-cause.In present study 55.76% cases were having distended bowel loops on abdominal ultrasonography. [3]

Mirella Fraquelli et al studied role of abdominal ultrasonography in celiac disease. Total 162 cases with suspected celiac disease were enrolled, out of them 12 were having positive serology for celiac disease. All of them underwent abdominal ultrasonography. An increased gallbladder volume, the presence of free fluid in the abdominal cavity, and enlarged mesenteric lymph nodes showed a specificity of 96%, 96%, and 97%, respectively (95% confidence intervals 92%-99%, 93%-99%, and 95%-99%), whereas the presence of dilated small bowel loops with increased fluid content and increased peristalsis had a sensitivity of 92% and 83%, respectively (95%, 76%-100% and 62%-100%). Eleven (92%) of the 12 patients with celiac disease and 35 (23%) of the 150 patients who did not have the disease had at least one ultrasonography sign (P = .001); All of the ultrasonography signs were concomitantly present in 4 patients with celiac disease (33%) and 1 patient without disease (0.6%) (P = .001). [4]

Riccabona M et al studied role of abdominal ultrasonography in celiac disease. They

studied 43 case of suspected celiac disease out of them 7 were positive for celiac disease serology. The common findings in cases of celiac disease were hyperperistalsis, slight ascites, pericardial fluid, or liver tissue texture changes. On relating the findings of abnormal small-bowel wall structures to the data of the small-bowel biopsy, they found a sensitivity of 94% and a specificity of 88% for sonographic detection of changes related to celiac disease. [5]

Thomas Rettenbacher et al studied abdominal ultrasonography findings in celiac disease. The authors found several ultrasonographic pathologic signs in patients with untreated disease, including abnormal fluid-filled small intestine in all eleven patients, flaccid and moderately dilated small-bowel loops (2.5–3.5 cm) in eight, slight diffuse thickening of the small-bowel wall (3–5 mm) in seven, increased peristalsis of the small intestine in eight, enlarged mesenteric lymph nodes (anteroposterior diameter 5–10 mm) in nine, dilated calibre of the superior mesenteric artery or portal vein in seven, free fluid in the abdominal cavity in five, and increased echogenicity of the liver in six. None of these signs was present in the control group. They concluded that there are several ultrasonography signs associated with celiac disease. None of the signs identified is specific, but a combination of signs is characteristic and indicates suspicion of this disease in a high percentage of cases. Ultrasonography could helps in avoiding diagnostic delay, especially in patients who have atypical clinical presentations. [6]

Soresi M et al studied 524 consecutive patients with symptoms of suspected celiac disease underwent an extensive diagnostic workup. A diagnosis of celiac disease with negative serum antibodies was probable in 71 patients who underwent abdominal US and duodenal biopsy for histology evaluation. Intestinal histology and subsequent clinical and histological follow-up confirmed the celiac disease diagnosis in 12 patients (GROUP 1) and excluded it in 59 subjects (GROUP 2). They conclude that abdominal USG is useful in the diagnostic workup of patients with a high clinical suspicion of celiac disease but with negative serology. After looking at current study and studies done in past we can conclude that there are certain findings on abdominal ultrasonography which are seen in celiac disease patients, but they all are nonspecific and more studies are needed to define the ultrasonographic findings of celiac disease. [7]

Amy S Oxentenko et al studied endoscopy findings in celiac disease. Loss of folds was the most sensitive marker of villous atrophy, present in 47% with celiac disease, with 97% specificity. The mosaic pattern was much less sensitive (12%), with 100% specificity. Nodularity and scalloping had low sensitivities (6%), but specificities of 95% and 100%, respectively. A finding of any endoscopic marker yielded a sensitivity of 59% and specificity of 92% for celiac disease. These results are different from results of our study but still supports good predictive value of villous atrophy for diagnosing celiac disease. [8]

Vivas S et al studied celiac disease in both adult and pediatric population. Total 66 children and 54 adult cases of celiac disease were enrolled. Histological analysis revealed a marked atrophy in 86% children versus 52% adults ($P < 0.001$). The degree of villous atrophy was inversely correlated with age ($P < 0.001$). In pediatric population maximum number of cases were having Marsh stage III (48.26%) followed by Mash stage II (37.74%) and Marsh stage I (14%). [9]

Prasad KK et al studied histological lesion variability in patients of celiac disease in pediatric population. Total 67 cases of celiac disease were studied. Forty-three celiac disease children (64.2%) had a "mixed" type 3 lesion characterized by a different degree of villous atrophy at different biopsy sites. Eight children

(11.9%) showed two different types of histologic lesions in the same patient at different biopsy sites. The overall variability of histologic lesion (variability in the grade of villous atrophy [type 3a, 3b, or 3c], and coexistence of villous atrophy and type 2 lesion) was seen in 51 (76.1%) of the celiac disease patients. The results of this study were just opposite to our study. [10]

As per Datta Gupta S et al the reference values of normal duodenal biopsies are lacking in Indian subcontinent and there is large variability in histology of different patients of celiac disease there is need to collect more data or histological variability in patients of celiac disease. In our study there was no correlation between serum tissue transglutaminase IgA levels and clinical parameters like anemia, short stature. [11]

Dahlbom et al conducted a study for prediction of clinical severity and mucosal damage in celiac disease and dermatitis herpetiformis by quantification of IgA and IgG serum antibodies to tissue transglutaminase. One hundred seventy patients with celiac disease and 131 controls were studied. Cases were divided in three groups according to clinical severity of disease. The control subjects had a lower median level of IgA and IgG serum antibodies to tissue transglutaminase than the other patient groups ($P < 0.0001$) and group I (group with severe symptoms) had a higher IgA-TGA level than all other groups. He concluded that high levels of IgA and IgG antibodies against tissue transglutaminase were associated with the high grade of mucosal damage and more severe clinical presentation. [12]

Barbara Zanini et al concluded that severity of certain clinical and laboratory parameters correlate with histology (Marsh Stage) while some shows no correlation. They compared demographic, clinical, and laboratory characteristics among patients with celiac disease who were classified based on the severity of duodenal lesions. Only anemia was having statistically significant correlation with degree of mucosal damage. They concluded that only some of the clinical and laboratory parameters correlate with degree of mucosal involvement in celiac disease. They found correlation between degree of mucosal involvement and severity of anemia which was not seen in our study. [13]

As per P. Brar and G.Y. Kwon, et al there is lack of correlation of degree of villous atrophy with severity of clinical presentation of celiac disease. The cohort consisted of 499 patients. The majority had silent celiac disease (56%) and total villous atrophy (65%). There was no correlation of mode of presentation with the degree of villous atrophy ($p = 0.25$). Sixty-eight percent of females and 58% of males had a severe villous atrophy ($p = 0.052$). There was a significant trend over time for a greater proportion of patients presenting as atypical/silent celiac disease and having partial villous atrophy, though the majority still had total villous atrophy. These results are similar to the results of our study. [14]

Antonella Diamanti et al conducted a study in pediatric hospital in Rome. Total 277 cases underwent upper gastrointestinal endoscopy and biopsy. Case with negative serology showed no histological changes of celiac disease on biopsy while 161 cases were having histological changes of celiac disease. This study found a strong correlation between anti-tissue transglutaminase immunoglobulin A levels and stage of mucosal injury. According to Shivani Kalhan et al mean baseline hemoglobin, and endoscopic findings were having correlation with increasing severity of mucosal damage. Esophagogastroduodenoscopy was performed in 229 cases of celiac disease. Marsh stage, serum anti tissue transglutaminase and clinical parameters were compared with each other, there was strong correlation between serum anti tissue transglutaminase Marsh stage, and

haemoglobin levels with P value of < 0.005. Anti-tissue transglutaminase immunoglobulin A levels of grades 1, 2 and 3a were significantly different from levels of grades 3b and 3c and grade 4. [15,16]

Antonio tursi, M.D, et al concluded that the mean serum value of anti-tissue transglutaminase immunoglobulin A in celiac disease with severe enteropathy (marsh IIIb-c lesions) was higher than in those with only slight enteropathy (marsh I-IIIa). Further, serologic test results in the absence of histopathologic evaluation may "underestimate the real prevalence of celiac disease," thus delaying a proper diagnosis and putting patients at risk for a large variety of serious health problems. [17]

P. G. Hill et al studied need of biopsy in patients of celiac disease and found that all patients with transglutaminase antibody levels >30 U/ml, i.e. 10 × upper limit of normal had characteristic small bowel mucosal lesions. They have shown that a transglutaminase antibody level can be defined which gives a positive predictive value of 100% for celiac disease. Their data provide further evidence that diagnostic guidelines could be modified so that small bowel biopsy is no longer regarded as mandatory in patients with such high transglutaminase antibody levels. This will avoid an invasive procedure and lead to a more rapid diagnosis and earlier treatment for over half of the new patients with celiac disease. [18,19]

Conclusion

We have concluded from this study that there was statistically significant correlation between serum anti tissue transglutaminase immunoglobulin A levels. Endoscopy and biopsy may not be necessary for diagnosis of celiac disease. Whenever levels of serum anti tissue transglutaminase immunoglobulin levels are inconclusive then endoscopy and biopsy is helpful in diagnosis. This will avoid an invasive procedure and lead to a more rapid diagnosis and earlier treatment of celiac disease.

Declarations:

Funding: None

Availability of data and material: Department of Pediatrics, Umaid Hospital, Dr. S.N. Medical College, Jodhpur

Code availability: Not applicable

Consent to participate: Consent taken

Ethical Consideration: There are no ethical conflicts related to this study.

Consent for publication: Consent taken

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