Research Article

Normalization of Anti Tissue Trans-glutaminase Antibodies in Patients with Histologically Confirmed Celiac Disease: A Retrospective Analysis

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Abstract

Background: Frequent absence from classes may lead to improper learning and poor academic performance. Absenteeism can make teaching - learning environment unwelcoming and impacting those also who attend classes regularly. **Patients and Methods:** We conducted a retrospective analysis of all patients diagnosed with celiac disease based on histological criteria between 2013 and 2018 at King Abdulaziz University Hospital (KAUH). Baseline patient demographics, clinical, endoscopic, histological and follow up data was ascertained from the hospitals' electronic medical records. The main primary outcome of interest was rate of and time to normalization of anti TTG antibodies. Logistic and Cox proportional regression analysis were used to identify predictors of the main outcome. Odds Ratio (ORs) and Hazard Ratios (HR) with 95% confidence intervals (95% CI) were generated. **Results:** Seventy-six patients fulfilled the study criteria. Average age was 30.5 (± 12) years. Females comprised 58% of the cohort and 54% were Saudis. The most common presentation was anemia (46%) followed by abdominal pain (28%). Dermatitis herpetiformus was reported in 13%. While selective IgA deficiency was documented in 13%, other autoimmune diseases were noted in 32%. Mean anti TTG at baseline was 217 ± 457 IU/ml. Iron deficiency, vitamin B12 deficiency, and Folate deficiency were reported in 49%, 11%, and 11%, respectively. Osteopenia and Osteoprosis according to DEXA scan were found in 22.4% and 22.4%, respectively. Villous atrophy was reported in 74% (mild to moderate in 39% and severe in 47%) of biopsy samples. Mean follow up was 43.8 (± 35.1) months. Overall, anti TTG antibody normalization was achieved in 46% of patients. Anti TTG antibody concentration was less likely to normalize in the presence of villous atrophy (OR=0.50, 95%=0.26-0.95, p=0.03). Time to normalization was predicted by Folate deficiency (HR=14.30, 95% CI=1.88-108.68, p=0.01), osteoporosis (HR=0.07, 95% CI=0.009-0.51, p=0.009), and a positive Rheumatoid Factor (RF) (HR= 5731.3, 95% CI=34.69-946852, p=0.001). **Conclusion:** A significant proportion of patients diagnosed with celiac disease achieve normalization of previously documented high anti TTG antibody concentrations. Folate deficiency and osteoporosis are predictive of biochemical remission.

Keywords: Celiac; Anti TTG; Follow up; Normalization

Introduction

Celiac Disease (CD) is a lifelong autoimmune disease that is triggered by gluten uptake in genetically susceptible individuals and targets the small intestinal mucosa. The immune response leads to mucosal damage and subsequently loss of function. CD represents a global health problem, however, in Saudi Arabia, a recent study that conducted mass screening 7930 school aged-children for CD estimated a prevalence rate of 1.5%. The high prevalence of CD among the pediatric Saudi population has been linked to the common presence of CD-predisposing HLA-haplotypes -DQ2 and -DQ8. This is based on results of another cross sectional study of 192 healthy children with negative IgA-based anti-Tissue Transglutaminase (TTG) antibody testing. In this cohort, 52% had HLA-DQ genotypes that confer a high risk to develop CD. [1]

CD has a significant impact on lifestyle and health. Patients with CD can present with intestinal and non-intestinal manifestations. The commonest of which is chronic diarrhea and malnutrition. [2] CD requires close follow up and strict adherence to dietary restrictions to avoid major sequelae such

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as micro- and macronutrient deficiencies and osteoporosis. [3,4] The IgA-based anti TTG antibody test is used to screen for, diagnose and monitor CD activity. Anti TTG antibody titer can also be used to monitor the success of therapy; with a typical target of normalization. [5] However, Anti TTG antibody concentration should be documented at the time of diagnosis as exclusion of gluten from the diet typically results in a gradual decline in serum IgA TTG antibody levels with an average half-life of six to eight weeks. A normal baseline value, which is the conventional target of treatment, is typically reached within 3 to 12 months depending upon the pre-treatment concentrations. [6] According to previous studies, 4 months of compliance to gluten free diet, can result in ≥ 50% reduction in anti-TTG antibody concentration. [7] Lower anti TTG antibody concentration at the time of diagnosis has been shown to be one of the predictors of earlier normalization. [8]

In relation to villous atrophy, anti TTG antibody has a strong negative predictive value in predicting mucosal healing when combined with anti DGP serology. [9] Mean anti TTG titer increases in cases of severe mucosal damage. [5] Anti TTG levels can be used to predict endoscopic findings as well. According to a study that involved 945 CD patients, anti TTG levels >5-fold the upper limit of normal had 100% specificity for duodenal atrophy, and using this cut-off point, duodenal biopsies were avoided in one third of patients. [10,11] In contrast, persistently elevated anti TTG antibody levels are significantly associated with abnormal duodenal histology. [7]

We aimed to evaluate the relationship between the degree of histological villous damage at the time of diagnosis and normalization of anti-Tissue Trans-Glutaminase antibody (anti TTG) and to identify predictors of time to normalization.

Material and Methods

We conducted a retrospective analysis of all adult patients (>14 year old) diagnosed with celiac disease between 2013 and 2018 at King Abdulaziz University Hospital (KAUH). Baseline patient demographics, clinical, endoscopic, and histological and follow up data was ascertained from the hospitals' electronic medical records. Board certified gastroenterologists completed all endoscopic assessments and a single specialized GI pathologist performed histological assessments. All patients were started on Gluten Free Diet (GFD) following diagnosis.

Definitions

A diagnosis of celiac disease was based on the presence of the following histological criteria in the duodenal mucosa: 1. Increased chronic inflammatory cells within the lamina propria; 2. Crypt hyperplasia; 3. Intra-Epithelial Lymphocytosis (IEL) at the tip of the villi (>20 lymphocytes/100 enterocytes); 4. Villous blunting [Figure 1]; as well as an abnormally elevated serum anti TTG antibody concentration. Normalization of anti TTG antibody concentration was defined as a reduction below 20 IU/ml. Villous atrophy was classified into none (no evidence of atrophy), mild to moderate (atrophy with some preservation of villous height), and severe (total villous loss) [Figure 2].

Outcomes

The main primary outcome of interest was normalization of anti TTG and the main secondary outcome was time to anti TTG normalization in weeks.

Statistical analysis

We used standard statistical approach to summarize baseline demographics including student t-test to compare means of normally distributed continuous variables and chi square test to compare frequencies of categorical variable. Association between baseline villous height and time to anti TTG normalization was assessed using logistic regression analysis; an Odds Ratio (OR) with 95% confidence intervals (95% CI) was generated. To identify predictors of time to anti TTG normalization, we utilized cox proportional regression analysis, where appropriate. Hazard Ratios (HR) with 95% CI were generated. A statistical threshold of 5% was used for significance.

Results

Baseline characteristics

A total of 76 patients fulfilled the study criteria. Baseline characteristics are summarized in [Table 1]. Average age was

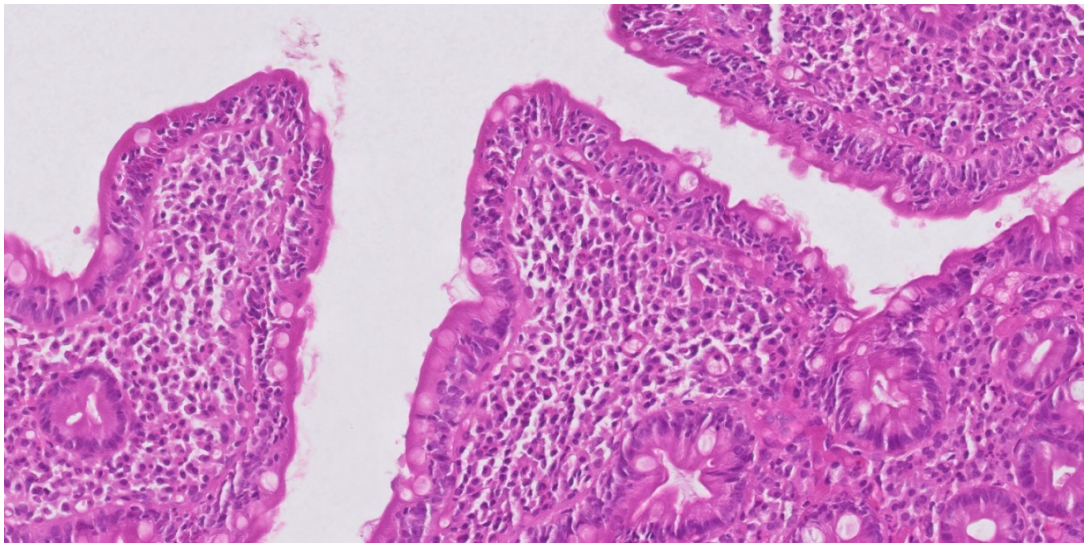

Figure 1: Villous blunting

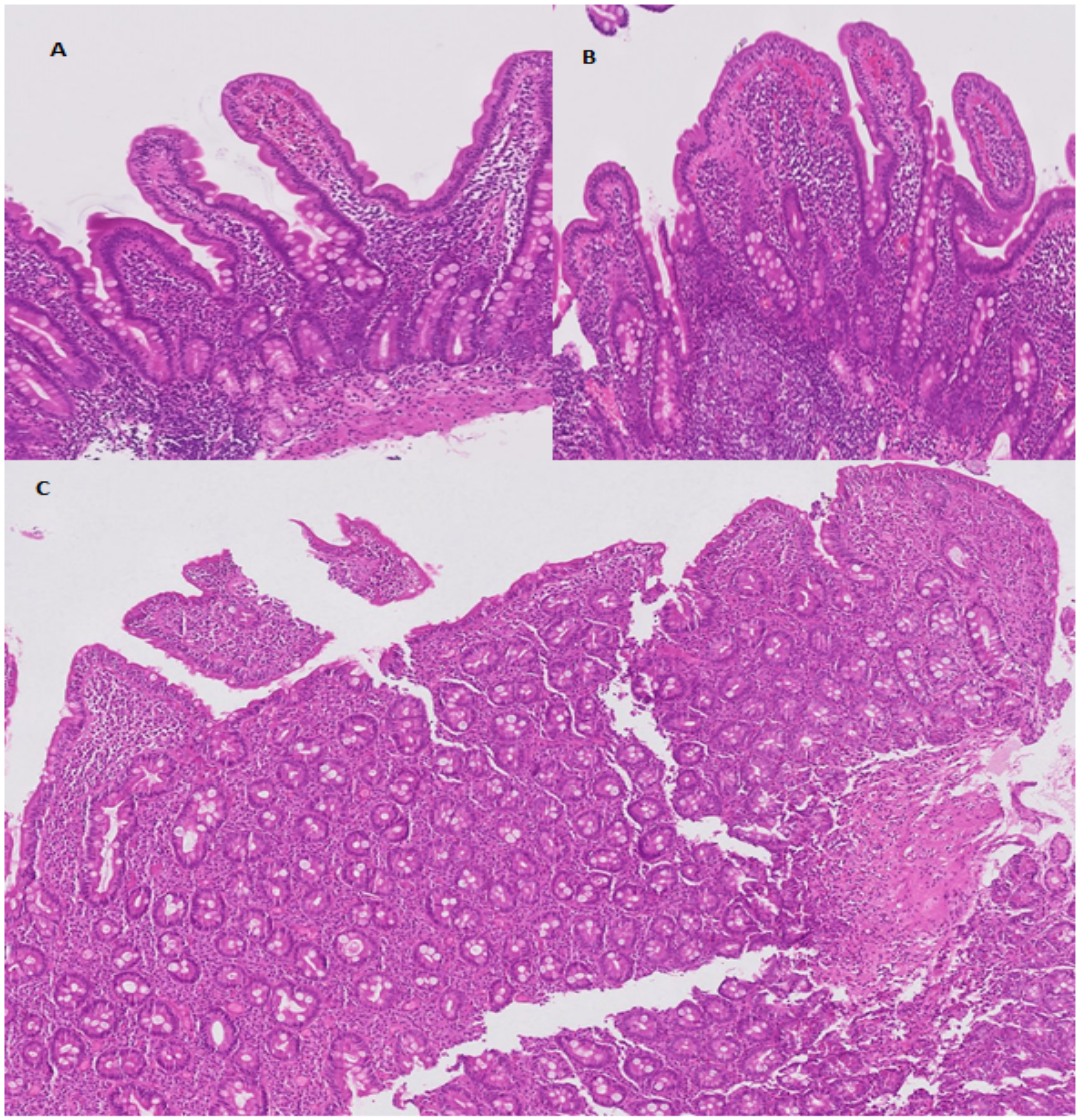

Figure 2: Classification of Villous atrophy A) None, B) Mild to moderate and C) Severe

30.5 (± 12) years. Females comprised 58% of the cohort and 54% were Saudis. First and second-degree family history of celiac disease was reported in 5% and 1.3%, respectively.

The most common presentation was anemia (46%) followed by abdominal pain (28%) and weight loss (20%). Mean Body Mass Index (BMI) was 22.3 ± 6. Dermatitis herpetiformus was reported in 13% and 4% of the cohort had Down syndrome. While selective IgA deficiency was documented in 13%, other autoimmune diseases were noted in 32%; type 1 DM in 21%, thyroid disorders in 18%, Inflammatory Bowel Disease (IBD) in 8%, psoriasis in 3%, and SLE in 1%. Iron deficiency, vitamin B12 deficiency, and Folate deficiency were reported in 49%, 11%, and 11%, respectively. Vitamin D and calcium were deficient in 90% and 41% of the cohort, respectively. Osteopenia and Osteoporosis according to DEXA scan were found in 22.4% and 22.4%, respectively.

During analysis, it was found that villous atrophy were statistically significant correlated with patients with dyspepsia (p=0.001) which account for 30% in patients without villous atrophy and 3% in patients with villous atrophy, also correlated with IgA deficiency (p=0.01) which account for 30% in patients with no villous atrophy and 7% in patients with villous atrophy, Crypt hyperplasia (p=0.04) and intraepithelial lymphocytes ($p \leq 0.001$).

Serological markers

All patients had an abnormally elevated IgA or IgG based serum anti TTG antibody concentration at the time of diagnosis. Mean IgA based anti TTG antibody concentration at baseline was 217+-457 IU/ml. 8/76 (11%) had an elevated serum anti EMA antibody concentration, 4/76 (5%) patients had an elevated IgG based serum anti TTG antibody concentration and 4/76 (5%) had an elevated serum anti DPG antibody concentration at the time of diagnosis.

Additionally, 19/67 (25%) had positive ANA, 9/67 (11%) had positive thyroid antibodies, 5/76 (7%) had positive AMA, and 2/76 (3%) had positive anti SMA,

Baseline histological findings

Crypt hyperplasia and IEL were documented in 59% and 71% of biopsy samples, respectively. Villous atrophy was reported in

Table 1: Baseline characteristics of 76 patients with histologically confirmed celiac disease

	Total N=76	No Villous Atrophy N=20	Villous Atrophy N= 56	P value
Mean age ± SD	30.5 ± 12.0	31.8 ± 12.1	30.0 ± 12.0	0.6
Female gender (%)	44 (58)	12 (60)	32 (57)	0.83
Saudi nationality (%)	54 (71)	14 (70)	40 (71)	0.82
Mean height in cm ± SD	156.1 ± 12.2	158 ± 8.5	155.4 ± 13.3	0.42
Mean weight in kg ± SD	55.6 ± 17.6	55.4 ± 18.1	55.7 ± 17.6	0.96
Mean BMI ± SD	22.3 ± 0.71	21.9 ± 7.0	22.4 ± 5.6	0.8
Symptoms				
Chronic diarrhea (%)	19 (25)	8 (40)	11 (19)	0.07
Weight loss (%)	15 (19)	5 (25)	10 (17)	0.5
Abdominal pain (%)	21 (27)	5 (25)	16 (28)	0.8
Bloating (%)	13 (17)	4 (20)	9 (16)	0.7
Constipation (%)	9 (11)	4 (20)	5 (9)	0.19
Dyspepsia (%)	8 (10)	6 (30)	2 (3)	0.001
GERD (%)	7 (9)	3 (15)	4 (7)	0.3
Dysphagia (%)	5 (6)	2 (10)	3 (5)	0.47
Arthritis (%)	6 (7)	2 (10)	4 (7)	0.68
Fatigue (%)	10 (13)	4 (20)	6 (10)	0.29
Dysmenorrhea (%)	9 (11)	4 (20)	5 (9)	0.19
Dermatitis Herpetiformus (%)	3 (4)	1 (5)	2 (3)	0.79
Recurrent fetal loss (%)	3 (4)	0 (0)	3 (5)	0.29
Headache (%)	3 (4)	1 (5)	2 (3)	0.78
Anemia (%)	35 (46)	8 (40)	27 (48)	0.53
Family history of celiac disease				
First degree (%)	5 (6)	1 (5)	4 (7)	0.73
Second degree (%)	1 (1)	0 (0)	1 (1)	0.55
Comorbidities				
DM1 (%)	16 (21)	4 (20)	12 (21)	0.89
DM2 (%)	8 (10)	3 (15)	5 (8)	0.45
Thyroid disorders (%)	14 (18)	4 (20)	10 (17)	0.83
IBD (%)	6 (7)	1 (5)	5 (9)	0.76
Psoriasis (%)	2 (2)	1 (5)	1 (1)	0.44
SLE (%)	1 (1)	0 (0)	1 (1)	0.55
Epilepsy (%)	6 (7)	1 (5)	5 (9)	0.58
Down syndrome (%)	3 (4)	0 (0)	3 (5)	0.29
Laboratory investigations				
IDA (%)	37 (48)	11 (55)	26 (46)	0.51
Folate deficiency (%)	8 (10)	3 (15)	5 (9)	0.45
Vitamin B12 deficiency (%)	8 (10)	3 (15)	5 (9)	0.45
Calcium deficiency (%)	31 (40)	10 (50)	21 (37)	0.33
Vitamin D deficiency (%)	68 (89)	20 (100)	48 (85)	0.07
Thrombocytosis (%)	10 (13)	3 (15)	7 (12)	0.78
Thrombocytopenia (%)	2 (2)	1 (5)	1 (1)	0.44
Leukopenia (%)	10 (13)	2 (10)	8 (14)	0.63
Transaminitis (%)	31 (40)	5 (25)	26 (46)	0.09
Imaging				
DEXA scan (%)	33 (43)	4 (20)	29 (51)	0.01
Osteoprosis (%)	17 (22)	4 (20)	13 (23)	0.77
Osteopenia (%)	17 (22)	2 (10)	15 (26)	0.12
Abdominal US (%)	17 (22)	4 (20)	13 (23)	0.77
Hyposplenism (%)	5 (6)	1 (5)	4 (7)	0.74
Fatty liver (%)	2 (2)	0 (0)	2 (3)	0.39
Serological markers				
Mean anti TTG antibody concentration ± SD	216.9 ± 456.7	139.4 ± 91.1	244.6 ± 527.8	0.38
IgA deficiency	10 (13)	6 (30)	4 (7)	0.01
Elevated anti TTG antibody concentration (IgG) (%)	4 (5)	1 (5)	3 (5)	0.95
Elevated anti DPG antibody concentration (IgG) (%)	4 (5)	2 (10)	2 (3)	0.27
Elevated anti EMA concentration (IgG) (%)	8 (10)	3 (15)	5 (9)	0.45
Positive thyroid antibodies (%)	9 (11)	1 (5)	8 (14)	0.27

Positive ANA (%)	19 (25)	4 (20)	15 (26)	0.55
Positive AMA (%)	5 (6)	3 (15)	2 (3)	0.08
Positive ASMA (%)	2 (2)	0 (0)	2 (3)	0.39
Positive RF (%)	1 (1)	0 (0)	1 (1)	0.55
Positive anti DsDNA (%)	1 (1)	0 (0)	1 (1)	0.55
Endoscopic findings				
Abnormal mucosa	38 (50)	12 (60)	26 (46)	0.3
Histological findings				
Crypt hyperplasia (%)	45 (59)	8 (40)	37 (66)	0.04
Intraepithelial lymphocytes (%)	54 (71)	8 (40)	46 (82)	<0.001
Follow up				
Mean duration ± SD	43.8 ± 35.1	38.4 ± 36.3	45.6 ± 34.9	0.48
Dietitian referral (%)	42 (55)	9 (45)	33 (58)	0.28
Follow up visit (%)	51(67)	11 (55)	40 (71)	0.18
Follow up anti TTG antibody test (%)	65 (85)	16 (80)	49 (87)	0.41

Table 2: Study outcomes

	Total N=76	No Villous Atrophy N=20	Villous Atrophy N=56	P value
Anti TTG antibodies normalization (%)	35 (46)	9 (45)	26 (46)	0.91
Anti TTG antibodies normalization within 1 year of follow up (%)	14 (18)	4 (20)	10 (17)	0.83
Vitamin B12 normalization (%)	4 (5)	2 (10)	2 (3)	0.47
Folate normalization (%)	5 (6)	2 (10)	3 (5)	0.53
IDA normalization (%)	18 (23)	4 (20)	14 (25)	0.28
Hospitalization (%)	17 (22)	2 (10)	15 (26)	0.12

74% (Mild to moderate in 31% and severe in 51% of cases) of biopsy samples.

Baseline endoscopic findings

Endoscopic findings suggestive of celiac disease were reported in 38/76 (50%) of cases. Most reported features was scalloping of mucosa in 20/76 (26%), flattening of mucosa in 11/76 (14%), diffuse nodular mucosa in 5/76 (6%), cobblestone appearance in 3/76 (3%), diffuse inflammation in 3/76 (3%) and duodenal hemorrhage in 1/76 (1%) However, no follow up endoscopic biopsy was reported to assess for improvement.

Follow up

Mean duration of follow up was 43.8 months (± 35.1). Referral to a dietitian was completed in 55% of cases and 67% of patients were seen in clinic after diagnosis within (of which 86% had anti TTG repeated). 17/76 (22%) of patients required hospitalization during follow up. No cases of lymphoma or small bowel adenocarcinoma were reported.

Outcomes

Overall, anti TTG antibody normalization was achieved in 46% of patients of whom 18% occurred during first of year of follow up. Mean time to anti TTG antibody normalization was 110.1 ± 92.4 weeks. IDA normalized in 18/26 (50%) patients, Folate deficiency in 5/10 (50%) patients, and vitamin B12 in 4/8 (50%) patients [Table 2].

According to logistic regression analysis, anti TTG antibody

Table 3: Results of the Cox regression analysis for time to anti TTG antibody concentration normalization

Predictor	Hazard Ratio	P value	(95% Conf. Interval)	
Villous atrophy	0.26	0.214	0.03	2.18
Age	1.04	0.196	0.98	1.11
Female gender	0.39	0.271	0.07	2.08
Body mass index	0.84	0.168	0.66	1.07
Crypt hyperplasia	1.82	0.396	0.46	7.20
Lymphocytosis	2.09	0.537	0.20	21.72
Iron deficiency anemia	0.22	0.054	0.05	1.02
Folate deficiency	14.30	0.010	1.88	108.68
Vitamin B12 deficiency	1.35	0.916	0.01	372.22
Calcium deficiency	0.18	0.054	0.031	1.03
Vitamin D deficiency	1.38	0.786	0.14	13.75
Osteopenia	2.67	0.154	0.69	10.26
Osteoporosis	0.07	0.009	0.01	0.51
Thyroid antibodies	5.59	0.125	0.62	50.22
RF positive	5731.33	0.001	34.69	946852
SMA positive	0.13	0.236	0.005	3.73
AMA positive	0.01	0.128	0.00001	3.75
GI clinic visit after diagnosis	0.05	0.060	0.002	1.13
Dietitian referral	0.98	0.979	0.17	5.76

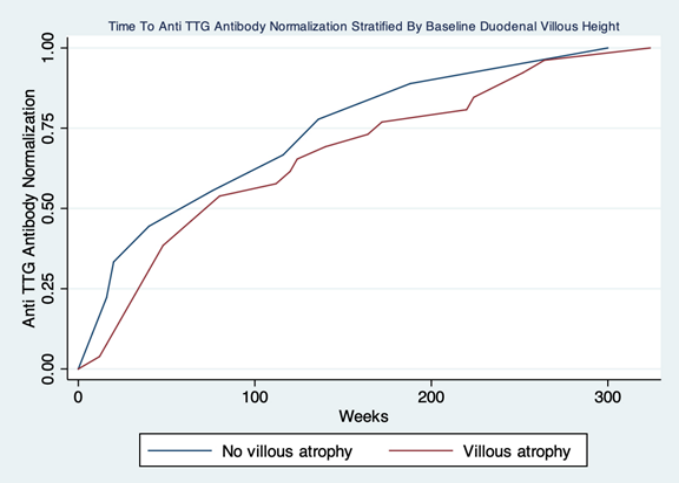

Figure 3: Cox proportional regression analysis of Time to anti TTG normalization

concentration was less likely to normalize in the presence of villous atrophy (OR=0.50, 95%=0.26-0.95, p=0.03).

Time to anti TTG normalization

According to cox proportional regression analysis, no difference in time to normalization of anti TTG antibodies was observed between patients with villous atrophy at baseline and those with preserved villous height (HR=0.26, 95% CI=0.03-2.18, p=0.21) [Figure 3]. Time to normalization was predicted by Folate deficiency (HR=14.30, 95% CI=1.88-108.68, p=0.01), osteoporosis (HR=0.07, 95%CI=0.009-0.51, p=0.009), and a positive Rheumatoid Factor (RF) (HR=5731.3, 95% CI=34.69-946852, p=0.001) [Table 3].

Discussion

CD reportedly affects 1% of the population and historically patients with CD have been known to present with classic symptoms such as diarrhea, weight loss, and growth failure. [12] Other atypical presentations such as IDA, bloating, fatigue, and metabolic bone disease can also be seen but are less common. Given the wide range of symptoms, the National Institute for Health and Care Excellence (NICE) recommends testing for CD in the following conditions: persistent abdominal or GI symptoms, faltering growth, prolonged unexplained fatigue, unexpected weight loss, severe or persistent mouth ulcers, unexplained iron, B12, and or Folate deficiency, type 1 DM, irritable bowel syndrome, autoimmune thyroid disease, and having a first degree relative with CD. [13] The ideal test to use is anti TTG antibody due to its high accuracy and relative cheap price compared to other tests such as anti EMA. In our cohort, the commonest presentation to be reported by patients with CD was anemia (46%) followed by abdominal pain (28%) and weight loss (20%) and only 7% of the cohort reported having a first-degree relative with CD.

The IgA-based anti TTG antibody test is used to screen for, diagnose and monitor for the success of therapy in CD. [5] Persistently elevated anti TTG antibody concentration following GFD typically reflects non-compliance, dietary contamination with gluten, or less commonly GFD refractory CD, which occurs in 20% of cases.[14] This has been linked with poor outcomes such as the development of enteropathy-associated lymphoma. [15,16] Accordingly, documenting normalization of anti TTG normalization during follow up and identifying predictors of normalization is a necessity. In our study, we addressed this important question by collecting data retrospectively of a total of 76 patients with a mean duration of follow up of 43.8 months. All patients had an abnormally elevated IgA or IgG based serum anti TTG antibody concentration at the time of diagnosis. Mean IgA based anti TTG antibody concentration at baseline was 217 ± 457 IU/ml. Overall, anti TTG antibody normalization was achieved in 46% of patients of whom 18% occurred during first of year of follow up. Mean time to anti TTG antibody normalization was 110.1 ± 92.4 weeks. Time to normalization was predicted by Folate deficiency and osteoporosis. This is in line with results from a previous study that identified malabsorption (55% *vs.* 41%, P=0.003), elevated EMA (46% *vs.* 25%, P<0.001), and severe mucosal damage (total villous atrophy 32% *vs.* 19%, P<0.001) at the time of diagnosis as predictors of incomplete biochemical recovery. [17]

Histological examination of the duodenal mucosa is gold standard for diagnosing CD. Confirming a diagnosis of CD is contingent on documenting the presence of chronic inflammatory cells, mainly IEL, and villous damage in the duodenal mucosa. [15] In our cohort, villous atrophy was the most commonly observed histologic findings (74%), followed by IEL (71%) then crypt hyperplasia (59%). Healing of villous atrophy couldn't be assessed, as re-evaluation of the proximal intestinal mucosa is not standard of care at our Center. However, we sought to examine the association between the degrees of villous damage at baseline with anti TTG antibody normalization and to identify predictors of time to normalization. According to logistic regression analysis, anti TTG antibody concentration was less likely to normalize in the presence of villous atrophy and there was no difference in time observed between patients with villous atrophy at baseline and those with preserved villous height. Data from a study by Pekki *et al.* that involved 760 patients with confirmed CD reported that 58% of patients had reached morphological small-bowel mucosal recovery, while 42% it remained incomplete. Their analysis identified malabsorption (55% *vs.* 41%, P=0.003), high serum EMA titre (46% *vs.* 25%, P<0.001) and severe mucosal damage (total atrophy 32% *vs.* 19%, P<0.001) at diagnosis as factors that were associated with incomplete recovery. [17] Other studies have also correlated the anti TTG antibody concentration with the degree of duodenal villous damage. [10] Zanini *et al.* conducted a cross sectional analysis of 945 patients suspected of having CD and identified an anti-TTG concentration >5-fold ULN as a cut-off point with 100% specificity for duodenal atrophy. Our study failed to show a difference in mean anti TTG antibody concentration between patients with duodenal atrophy and those with preserved duodenal architecture (244.6 ± 527.8 *vs.* 139.4 ± 91.1, p=0.38).

We acknowledge that our study carries several limitations including its retrospective design and absence of follow up histopathology; other limitations include the small sample size, single center source of data, and absence of measures of compliance to GFD. Conversely, the study is strengthened by the fact that all patients had confirmed diagnosis based on histology, and a long duration of follow up.

Conclusion

A significant proportion of patients diagnosed with celiac disease achieve normalization of previously documented elevated anti TTG antibody concentrations. Patients with duodenal villous atrophy at the time of diagnosis are less likely to reach normal anti TTG antibody concentration. Micronutrient deficiencies such as Folate deficiency and osteoporosis are predictive of biochemical remission.

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