

Artículo Original



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TITLE: The effect of gluten-free diet on alanine aminotransferase (ALT) in celiac patients

TÍTULO: El efecto de la dieta libre de gluten en la alanina aminotransferasa (ALT) en pacientes celíacos

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UNITERMS:

Transaminases.

Celiac Disease.

Alanine Transaminase.

Aspartate Aminotransferases.

Diet, Gluten-Free.

ABSTRACT

Introduction: Celiac disease is an autoimmune disease triggered by gluten ingestion. It affects approximately 0.5-1% of the world population. Extra intestinal manifestations include elevated alanine aminotransferase (ALT) levels.

Objective: Evaluate the effects of a gluten-free diet on ALT levels in patients with celiac disease.

Methods: This cross-sectional study was conducted in the outpatient gastroenterology clinic of a university hospital.

Results: Twenty-six patients with celiac disease were included, with 34.1 ± 11.4 years; 15.4% were men. Study subjects had a mean ALT level of 54.6 ± 36.3 (median 40.5) U/L. Compared to subjects with ALT < 50 U/L, there was a higher proportion of individuals with hepatitis B in the group with ALT ≥ 50 U/L. Among patients tested after treatment with a gluten-free diet, we observed a significant reduction in ALT values (36.0 vs. 31.0 U/L; P = 0.008).

Conclusion: Thirty-five percent of celiac disease patients had ALT above the upper tertile. Higher ALT levels are found in patients with viral hepatitis B and in those who do not adhere to the diet. There was a reduction of aminotransferases with a gluten-free diet.

UNITERMOS:

Transaminasas.

Enfermedad celíaca.

Alanina transaminasa.

Aspartato aminotransferasa.

Dieta sin gluten

RESUMEN

Introducción: La enfermedad celíaca es una enfermedad autoinmune provocada por la ingestión de gluten que afecta a alrededor de 0,5-1% de la población. Manifestaciones extra-intestinales incluyen alanina aminotransferasa elevada (ALT).

Objetivos: evaluar los efectos de la dieta libre de gluten en el nivel de ALT de los pacientes con enfermedad celíaca.

Métodos: Estudio transversal, realizado en la clínica de gastroenterología de una universidad pública.

Resultados: Veinte e seis pacientes con enfermedad celíaca se incluyeron, con $34,1 \pm 11,4$ años, 15,4% eran hombres. Los sujetos del estudio tenían una media de $54,6 \pm 36,3$ ALT (mediana 40,5) U / L. Al comparar los sujetos con $ALT \geq 50$ U / L y $ALT < 50$ U / L, hubo una mayor proporción de la hepatitis B en el grupo de alto ALT. Entre los pacientes que se sometieron a control de laboratorio después del tratamiento de la enfermedad celíaca, hubo una reducción significativa en los niveles de ALT después de la dieta libre de gluten (36,0 vs. 31,0 U / l; $p = 0,008$). No hubo diferencia en los valores de AST, Hb, MCV y RDW.

Conclusión: el 35% de las personas con enfermedad celíaca mostró ALT por encima del tercil superior. Niveles de ALT más altas se encuentran en los pacientes que no se adhieren a la dieta. Una disminución de las aminotransferasas con una dieta libre de gluten.

INTRODUCTION

Celiac disease is an autoimmune disorder triggered by dietary gluten. Gluten is a protein complex found in wheat, rye, and barley. Celiac disease is characterized by a chronic inflammatory state of the proximal small intestinal mucosa that heals when foods containing gluten are excluded from the diet and returns when these foods are reintroduced.(1) The disorder is characterized by a diverse clinical heterogeneity that ranges from asymptomatic to severely symptomatic, and it manifests with frank malabsorption, chronic diarrhea, weight loss, and abdominal distention. Other manifestations include iron deficiency with or without anemia, recurrent abdominal pain, aphthous stomatitis, short stature, high aminotransferase levels, chronic fatigue, and reduced bone mineral density.(2) Unusual manifestations of celiac disease include dermatitis herpetiformis and gluten ataxia, even without symptoms of the gastrointestinal tract.(3)

Multicenter studies done in Europe and the United States showed that the prevalence of celiac disease is around 0.5% to 1%.(4, 5) Among European countries, the positivity of autoantibodies is described as 0.3% to 2.4% of the population, and it is less common in Germany and more so in Finland.(5-7) In São Paulo, the prevalence of celiac disease is 0.6%, which is similar to the rates reported in Portugal and Italy.(5, 7, 8)

A positive diagnosis of celiac disease is made by the presence in serologic tests of anti-tissue transglutaminase (tTG) antibodies and endomysial antibodies (EmA). When positive, these confirm immunologic damage; a biopsy of the small intestine is necessary to show tissue damage. The histological features include increased intraepithelial lymphocyte, villous atrophy, and crypt hyperplasia.(3)

Treatment consists of a gluten-free diet, which allows clinical remission and restores antibody negativity. Histologic healing occurs within 6 to 24 months after the diet has begun.(9)

Liver involvement in celiac disease has been studied for more than thirty years, but the impact of celiac disease in several etiologies of liver disease is yet to be determined.(10) Hepatic injury is often described in celiac disease and can occur in two

different ways: cryptogenic and associated with autoimmune liver diseases. Cryptogenic disorders are more common, typically asymptomatic, marked by mild elevation of aminotransferases, and partially reversible with a gluten-free diet.(11) In these cases, hepatic histopathology can show a nonspecific reactive hepatitis.(12) However, there are cases of individuals with celiac disease who were diagnosed with cryptogenic cirrhosis and portal hypertension of unknown etiology.(13, 14)

Celiac disease has previously been described as related to primary biliary cirrhosis, primary sclerosing cholangitis, and autoimmune hepatitis, where the hepatic injury is chronic and progressive.(11, 15-17) The effect of a gluten-free diet in these situations is controversial.(11, 18)

Because there is a lack of information about liver abnormalities related to celiac disease, this study aims to describe the behavior of transaminases in celiac disease, in order to identify factors associated with alanine aminotransferase (ALT) rates that are elevated beyond the superior tertile and to compare the serum rates before and after a gluten-free diet.

MATERIALS AND METHODS

We conducted a descriptive, retrospective, and cross-sectional study that evaluated the adult patients with celiac disease. The evaluations of subjects took place in the Gastroenterology Clinic of the University Hospital of the Federal University of Santa Catarina (HU/UFSC) from August 2013 to February 2014. Patients lacking clinical information or laboratory data in their medical records were excluded from this study, as were those who refused to participate.

In a routine medical appointment, individuals were invited to participate in the study; those who agreed signed an informed consent document in duplicate. Clinical, laboratorial, and histological data were then collected from the HU/UFSC medical records service.

Subjects were analyzed by the following clinical and epidemiological variables: genre, age, and the presence of diabetes mellitus, hypothyroidism, abdominal pain, diarrhea, anemia, and a family history of celiac disease.

The laboratorial variables were EmA, anti-tTG, hemoglobin, mean corpuscular volume (MCV), RDW, serum iron, ferritin, and albumin. The biochemical tests were expressed in absolute values. ALT and aspartate aminotransferase (AST) were analyzed using the Dimension® system (Siemens Healthcare Diagnostics, USA) with Flex reagent (Siemens Healthcare Diagnostics, USA) at a temperature of 37°C. The level of ALT is considered to be normal when it is under 78 U/L, and AST is considered normal when under 37 U/L. The ALT levels were characterized in tertiles.

Patients with confirmed celiac disease were put under lifelong gluten-free diet. No treatment other was offered to these patients in the present study. ALT was collected before treatment and one year after the initiation of treatment (\pm 6 months).

The screening for celiac disease was made by serologic tests of anti-tTG and EmA.(19, 20) For the identification of EmA, an immunofluorescence test was used; it consists of a rat liver imprint or Hep2 commercially acquired lamina. Anti-tTG was detected using a commercial enzyme-linked immunosorbent assay (ELISA; Quanta Lite, USA). Upper digestive endoscopy and duodenal biopsy were indicated for individuals with positive serology for celiac disease. Duodenal fragments were fixed in 10% formalin, processed with paraffin, and stained with hematoxylin and eosin (HE). For diagnoses of celiac disease, the following histological variables were analyzed: lymphocytic infiltrate, villous atrophy, and crypt hyperplasia.(1, 20)

Statistical analysis

The patients were evaluated according to ALT levels. A bivariate analysis was conducted to identify factors related to ALT levels above the upper tertile (\geq 50 U/L). Continuous variables were compared using Student's t-test or the Mann-Whitney test, as appropriate. Categorical variables were compared using the chi-squared test or Fisher's exact test. Numerical variables before and after treatment were evaluated using Student's t-test for normal distributions or the Wilcoxon test for nonnormal distributions. P values less than 0.05 were considered to be statistically significant. All tests were performed using the *Statistical Package for the Social Science* (SPSS, Chicago, Illinois, USA), version 17.0.

Ethical considerations

The study protocol conformed to the ethical guidelines of the 1975 Helsinki Declaration and was approved by the review board of the Universidade Federal de Santa Catarina as Study Number 358.045.

RESULTS

Characteristics of the sample

From August 2013 to February 2014, twenty-nine patients with celiac disease and who were being treated in this institution were considered for enrollment. Three patients were excluded due the lack of aminotransferases.

Twenty-six patients with celiac disease were included; the mean age was 34.1 ± 11.4 (median 32.0) years, and 15.4% of the patients were men. The clinical features were as follows: 70.8% had abdominal pain, 50.0% had diarrhea, 47.8% had iron deficiency with or without anemia, and one patient had dermatitis herpetiformis. A family history of celiac disease was known for 35% of the patients. EmA values were positive in 72.7% of the patients, and anti-tTG IgA antibodies were positive in 91.3%. No patient had an IgA deficiency. Histologic patterns suggestive of celiac disease were exhibited in 91.67% of the patients. Upper digestive endoscopy and duodenal biopsy were positive in two patients (latent celiac disease).

During the evaluation, seventeen patients (65.4%) followed a gluten-free diet. Of these, there was a reduction of symptoms in 88.2% of the patients, but only 82.3% tested negative for antibodies.

The clinical and laboratorial characteristics are summarized in Table 1. The individuals in this study showed an average ALT value of 54.6 ± 36.3 (median 40.5) U/L. Nine patients showed ALT values above the upper tertile ($ALT \geq 50$). Of the four patients that presented positive for hepatitis B surface antigen (HBsAg), all of them had ALT levels above the upper tertile. Two patients were positive for HBsAg, anti-HBe reactive and both presented low viral load ($< 2,000$ IU/L) featuring, therefore, inactive carriers that did not need antivirals. And the two other patients were anti-HBe reactive with high viral load, advanced fibrosis characterizing chronic hepatitis by precore mutants, and they were under antiviral treatment, one with tenofovir and the other entecavir.

Comparative analysis according above the upper tertile of alanine transaminase

When patients with ALT \geq 50 U/L were compared with those with ALT < 50 U/L (Table 1), we observed a higher proportion of hepatitis B infection in the ALT \geq 50 U/L group (data not shown). No differences were found between the groups in gender, age, diabetes, dyslipidemia, hypothyroidism, abdominal pain, diarrhea, anemia, family history of celiac disease, positive EmA, or positive anti-tTG between ALT \geq 50 U/L group and ALT<50 U/L group. Similarly, no difference was observed when we assessed the following laboratory variables: hemoglobin, MCV, RDW, iron serum, ferritin, and albumin.

In the group with ALT \geq 50 U/L, there was a higher proportion of individuals who did not adhere to a gluten-free diet (42.9% vs. 93.3; P = 0.021), remission of symptoms (50.0% vs. 100%; P = 0.021), and autoantibodies remission (50.0% vs. 91.7%; P = 0.035). No correlation among ALT, age, weight, hemoglobin, MCV, RDW, iron, ferritin, or albumin was observed.

Evaluation of laboratory variables before and after a gluten-free diet

Among patients who were tested following treatment of celiac disease, we observed a significant reduction in ALT values after a gluten-free diet (36.0 vs. 31.0 U/L; P = 0.008). No differences in AST, Hb, MCV, or RDW were observed (Table 2).

DISCUSSION

Studies of blood donors were performed in different regions of Brazil to determine the seroprevalence of celiac disease in this country. Based on levels of EMA and anti-tTG, the prevalence of celiac disease in Sao Paulo was 0.6%, and in Curitiba, the prevalence was 0.3%.(8, 21) In Brasilia, among 2045 blood donors, 62 showed positive gliadin antibody tests and two presented positive EMA.(22)

In individuals with celiac disease, the average age varies between 32 and 37 years, similar to that found in the present study.(23-25) It is known that this disease is more common in females, reaching from 73% to 80%, and this pattern has been described by many authors.(23, 25, 26) However, occasionally, celiac disease has been

described as being more frequent among men, particularly when evaluating trials using blood banks; this occurs because the majority of blood donors are male.(27, 28)

In this study, at the time of diagnosis, 34.6% of the patients showed ALT levels elevated above the upper tertile ($ALT \geq 50$ U/L). Hypertransaminasemia has been found in 9.18% to 40.4% of individuals with celiac disease.(23-26, 29) The behavior of ALT in this group of patients, after a gluten-free diet, has been analyzed in various studies.(23-26, 29, 30) This is the first Brazilian study to evaluate this.

Novacek and colleagues (1999) conducted a retrospective study of 178 patients with celiac disease. In 40.4% of these individuals, AST and/or ALT levels were elevated. Following one year on a gluten-free diet, ALT and AST levels were normalized in all but eight cases (4.6%). Four patients were considered to be noncompliant, and the others had hepatic steatosis due to poorly controlled diabetes mellitus, autoimmune liver disease, or alcoholic fatty liver disease.(23)

The prevalence of hypertransaminasemia and the effect of a gluten-free diet were evaluated by Bardella and colleagues (1995) in 158 adult celiac patients. At diagnosis, 67 patients (42%) had elevated aspartate and/or alanine transaminase levels (mean, 47 IU/L, range, 30 to 190; and 61 IU/L, range, 25 to 470, respectively). At one year, a highly significant improvement in intestinal histology was observed in both groups ($P < .0001$), and transaminase levels had normalized in 60 individuals (95%). In cases where ALT remained high, liver biopsy showed fatty infiltration, chronic active hepatitis, chronic infection with hepatitis B virus, hepatitis C virus, or an autoimmune condition.(25)

Casella and colleagues (2013) studied data from 245 untreated patients with celiac disease, and they found that 43/245 (17.5%) patients had elevated values of one or both aminotransferases; the elevation was mild (< 5 times the upper reference limit) in 95% and marked (> 10 times the upper reference limit) in the remaining 2 (5%) patients. Following one year on a gluten-free diet, aminotransferase levels normalized in all but four patients with hepatitis C infection or primary biliary cirrhosis.(26)

Recently, Korpimaki and colleagues (2011) and Moghaddam and colleagues (2013) evaluated celiac patients and also observed transaminases reductions following a gluten-free diet.(29, 30) In the Korpimaki study, although the serum transaminase

values were within the normal range in the majority of untreated patients, the liver enzyme levels initially decreased significantly following the initiation of a gluten-free diet.(30)

Zanini and colleagues (2013) assessed the factors affecting hypertransaminasemia in 683 patients with celiac disease and 304 with functional syndromes. Hypertransaminasemia was detected in 20%, and it was associated with malabsorption and increasing severity of mucosal lesions. Hypertransaminasemia was detected in 7% of the functional gastrointestinal syndrome group and was associated with the World Health Organization's BMI categories. The transaminase level was significantly higher in celiac patients at baseline (25.2 ± 16.9 U/L AST) than in patients with functional syndromes (20.6 ± 9.9 AST, $p < 0.0001$). While following a gluten-free diet, the serum AST levels decreased from 25.2 ± 16.9 U/L at baseline to 19.9 ± 6.6 U/L ($P < .0001$). A similar effect was observed for ALT (28.1 ± 21.7 vs. 20.4 ± 9.5 U/L, $P < .0001$), and there was a reduced prevalence of hypertransaminasemia, from 13% to 4%.(24)

As in the studies described above, this study also showed that ALT receded following a gluten-free diet, but the same behavior was not observed with AST. A possible limitation could be due to the lack of control on factors that affect the levels of ALT and AST, such as day of collection, body mass index, physical activity, collection storage, hemolytic anemia, and muscle injury.(31-34) Since this was a retrospective study, the ALT and AST levels were not measured at specific times relative to diagnosis or the beginning of the diet, but both aminotransferases were measured in the same collection, which reflects the daily basis of the clinical assistance of these patients.

It has been noted in the medical literature that patients with celiac disease and coexisting liver disease from other causes do not show a reduction in ALT levels after beginning a gluten-free diet.(25) In this study, a patient with hepatitis B showed a reduction in ALT following a gluten-free diet; this individual had a pre-diet levels of ALT of 51 U/L and AST of 26 U/L, and the post-diet levels were reduced to 46 U/L and 25 U/L, respectively. There are no similar examples in the medical literature, since studies that evaluate aminotransferases before and after a gluten-free diet exclude individuals who are serum positive for hepatitis B, since it is a confounding factor for

hypertransaminasemia. Further studies are necessary to determine whether a gluten-free diet can also improve aminotransferases levels in patients with chronic liver disease.

The mechanism of hepatic injury in individuals with celiac disease is poorly understood. The serum aminotransferases normalize with a gluten-free diet, which suggests a causal relation between gluten ingestion and injuries to the liver and intestine. Patients with hypertransaminasemia have an increased intestinal permeability when compared to those with normal levels.(23) This increased intestinal permeability can lead to augmented absorption of toxins or antigens into portal blood, and this can lead to the hepatic injury observed in these individuals.(35) Additionally, tTG is present in the liver and in other tissues besides the intestinal basal membrane, which suggests the possibility of a pathological role of humoral immunity (anti-tTG) in the hepatic injury observed in those with celiac disease.(36)

There are some limitations to this study. It is a retrospective study and includes a limited number of individuals considering the high prevalence of European descendants in Southern Brazil and the celiac disease prevalence in this population. However, the University Hospital is a referral center for gastrointestinal disorders and serves individuals throughout the state of Santa Catarina, which is one of the smallest states in Brazil. Additionally, the study sample is similar to other samples of patients with celiac disease(37). However, this reflects the reality observed in our medical practice, and the study has a design similar to others that have previously been published.(23, 26, 30) In the present study, we did not perform a liver biopsy on patients in order to define which individuals presented with histological lesions. However, the causal relation between hypertransaminasemia and celiac disease is well known, and at the current time, a liver biopsy is only recommended for patients in which aminotransferase levels are not normalized following initiation of a gluten-free diet. There were no individuals in this study who maintained high ALT levels.

A multivariable analysis was not performed, due to the limited number of patients with ALT above the upper tertile ($n = 9$). Although this is not a rigid rule, most authorities recommend a minimum of ten events per variable when performing logistical regression analysis. This is based on studies that show that fewer than ten

events (and especially, fewer than five) lead to an increase in polarization and variability, nonreliable confidence-interval coverage, and problems with convergence.

CONCLUSION

Among patients with celiac disease, 34.6% presented with ALT levels above the upper tertile. Higher ALT levels were found in individuals who did not adhere to a gluten-free diet. Specific studies are needed to establish the mechanism of hepatic damage in celiac patients.

Table 1. Clinical and laboratorial characteristics associated with alanine aminotransferase (ALT) values above the upper tertile (ALT \geq 50 U/L)

Characteristics	Total n = 26	ALT \geq 50 n = 9	ALT < 50 n = 17	p
Male sex (%)	15.1	22.2	11.8	0.591 ^t
Age (years)*	34.1 \pm 11.4 (32.0)	38.9 \pm 7.4 (40.0)	31.4 \pm 12.9 (27.0)	0.121 ^t
Diabetes mellitus (%)	18.2	9.1	9.1	0.345 ^f
Dyslipidemia (%)	13.0	0.0	20.0	0.526 ^f
Hypothyroidism (%)	16.7	0.0	22.2	1.000 ^f
Abdominal pain (%)	70.8	77.8	66.7	0.069 ^f
Diarrhea (%)	50.0	55.6	46.7	1.000 ^f
Anemia (%)	47.8	55.6	42.9	0.680 ^f
Familiar record (%)	35.0	14.3	46.2	0.329 ^f
EMA positive (%)	72.7	75.0	71.4	1.000 ^f
anti-tTG positive (%)	91.3	100.0	85.7	0.502 ^f
Hemoglobin*	13.2 \pm 1.8 (13.4)	13.8 \pm 1.8 (13.2)	13.3 \pm 1.1 (13.5)	0.441 ^t
MCV*	85.9 \pm 7.5 (86.0)	88.7 \pm 4.9 (90.5)	86.0 \pm 5.3 (84.1)	0.248 ^t
RDW*	13.2 \pm 1.3 (13.0)	13.7 \pm 1.6 (13.5)	12.9 \pm 1.1 (12.8)	0.246 ^t
Serum iron*	78.3 \pm 31.3 (67.0)	70.7 \pm 36.7(50.0)	82.2 \pm 31.2 (72,5)	0.636 ^t
Ferritin*	45.3 \pm 58.7 (27,6)	84.7 \pm 130.2 (10.8)	39.1 \pm 30.5 (28.3)	0.607 ^t
Albumin [#]	3.4	3.4	3.6	0.885 ^m

EMA = Endomysial antibody; anti-tTG = Anti-tissue transglutaminase; MCV = Mean Corpuscular Volume; RDW = Red Cell Distribution Width; *mean \pm standard deviation; [#]median; ^tStudent's t-test; ^mMann-Whitney; ^fFisher's exact test.

Table 2. Comparative analysis of laboratory variables of patients before and after initiating a gluten-free diet

Characteristics	Before	After	P
ALT [#] (n = 16)	36.0	31.0	0.008 ^m
AST [#] (n=16)	20.0	20.5	0.753 ^m
Hemoglobin [#] (n = 17)	13.7	13.4	0.477 ^m
MCV [#] (n=14)	87.2	87.8	0.551 ^m
RDW* (n = 11)	13.2 ± 1.1 (12.8)	13.0 ± 1.0 (12.8)	0.551 ^t

ALT = Alanine aminotransferase; AST = Aspartato aminotransferase; MCV = Mean Corpuscular Volume; RDW = Red Cell Distribution Width; *mean ± standard deviation; [#]median; ^tStudent's t-test; ^mMann-Whitney; ^fFisher's exact test.

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