The relation between ischemia modified albumin level and autoimmunity/chronic inflammation in celiac disease

Çölyak Hastalığında iskemi modifiye albumin düzeyi ile otoimmunite/kronik inflamasyon arasındaki ilişki

**Objective:** We established an expectation that ischemia-modified albumin (IMA) levels are higher in the celiac disease since it is an autoimmune/chronic inflammatory disease. In this study, we determined the level of IMA and its relation to autoimmunity/chronic inflammation in celiac disease.

**Material and methods:** The level of IMA of 65 patients diagnosed with celiac disease and 65 healthy volunteers, was measured with the serum ELISA kit. C-reactive protein (CRP), anti-gliadin antibodies immunoglobulin A (AGA-IgA), anti-gliadin antibodies immunoglobulin G (AGA-IgG), anti-tissue transglutaminase immunoglobulin A antibodies (Anti-t TGA), anti-tissue transglutaminase immunoglobulin G antibodies (Anti-t TGG) levels were studied.

**Results:** IMA (30.8 ng/mL vs. 20.1 ng/mL, \( p = 0.006 \)) levels in celiac patients were higher than the control group. In celiac patients who were antibody positive, IMA level was found to be higher compared to antibody negative patients. A positive correlation was determined between IMA level and AGA-IgA (\( r = 0.504, \ p < 0.001 \)), AGA-IgG (\( r = 0.445, \ p < 0.001 \)), Anti-t TGA (\( r = 0.485, \ p < 0.001 \)), Anti-t TGG (\( r = 0.477, \ p < 0.001 \)) and CRP (\( r = 0.385, \ p = 0.011 \)) levels.

**Conclusion:** Chronic inflammation and autoimmunity were found to be associated with high levels of IMA. To use IMA as a diagnosis and follow-up criterion in celiac disease, IMA levels must be compared before and after treatment of active celiac disease.

**Keywords:** Autoimmunity; Gluten enteropathy; Ischemia modified albumin; Oxidative stress.

**Özet**

**Giriş ve Amaç:** Çölyak hastalığı otoimmün/kronik inflamatuvar bir hastalık olduğu için, iskemi modifiye albumin (IMA) düzeylerinin çölyak hastalığında normalden daha yüksek çıkmasını bekleriz. Bu çalışmada çölyak hastalığındaki IMA düzeyini belirlemeyi ve otoimmunite/kronik inflamasyon ile olan iliskisini incelemeyi amaçladık.

**Yöntem ve Gereçler:** Çölyak tanısal alan 65 hastada ve 65 sağlıklı güçlüde IMA düzeyleri ELIZA kit ile ölçüldü. C-reactive protein (CRP), anti gliadin antikor immunoglobulin A (AGA-IgA), anti gliadin antikor immunoglobulin G (AGA-IgG), anti-tissue transglutaminase immunoglobulin A antikoru (Anti-t TGA), anti-tissue transglutaminase immunoglobulin G antikoru (Anti-t TGG) düzeyleri çalışıldı.

**Bulgular:** Çölyak hastalarında IMA (30.8 ng/mL vs. 20.1 ng/mL, \( p = 0.006 \); sırasıyla) düzeyleri kontrol grubuna kıyasla daha yüksek sırtlandığı. Çölyak hastalarında antikor pozitifiği olan hastalarda IMA düğüntü antikor pozitifiği olmayan hastalara kıyasla daha yüksek bulundu. Çölyak hastalarında IMA düzeyi ile anti-gliadin antikor pozitifiğinin birlikte olması, celiak hastalığında daha yüksek olduğunu göstermiştir.
hastalarında yapılan korelasyon analizinde IMA düzeyi ile AGA-IgA \( (r = 0.504, p < 0.001) \), AGA-IgG \( (r = 0.445, p < 0.001) \), Anti-t TGA \( (r = 0.485, p < 0.001) \), Anti-t TGG \( (r = 0.477, p < 0.001) \) ve CRP \( (r = 0.385, p = 0.011) \) düzeyleri arasında pozitif bir korelasyon saptandı.

**Tartışma ve Sonuç:** Kronik inflamasyon ve otoimmüstenin yüksek IMA düzeyleri ile ilişkili olduğu bulundu. İMA’nın çölyak hastalığına, hastalık ciddiyeti ve aktivasyonu için tanı ve takip kriteri olarak kullanılabileceği için, aktif çölyak hastalığında tedavi öncesi ve sonrası İMA düzeylerinin kıyaslanması gerekktedir.

**Anahtar kelimeler:** Gluten enteropatisi; Iksemi modifiye albumin; Oksidatif stres; Otoimmünite.

**Introduction**

Celiac disease is an immune-mediated disease characterized by the hypersensitivity of the gastrointestinal tract to gluten in individuals with genetic susceptibility [1]. The clinical findings may vary depending on environmental, genetic and immune factors. Chronic inflammation, autoimmunity, and oxidative stress are thought to play an important role in the pathogenesis of disease [2, 3]. Although there is a sufficient data about the importance of chronic inflammation and autoimmunity in celiac disease [3], there are still many uncertainties about the relation of oxidative stress with celiac disease.

Oxidative stress occurs when the hemostatic balance between antioxidant defense system collapse on behalf of free radicals [4]. Oxidative stress causes tissue damage by some mechanisms, such as oxidation of molecules in the protein structure and lipid peroxidation [5–10]. The oxidation of molecules in the protein structure occur as a result of the covalent modification of proteins with oxidative stress or reactive oxygen derivatives product. Albumin, being the main protein in human blood and the key to regulating the osmotic pressure of blood is one of these molecules which its structure changes by excessively increasing oxidant radicals.

Albumin is a protein consisting of 585 amino acids. The last amino terminal in albumin structure is the region where transition metals such as cobalt, nickel and copper are connected [11]. The increased hypoxia in ischemic situation, acidosis, and free radical damage, decrease the connection of these transition metals to the N-terminal of albumin [12, 13]. The albumin with this structural changes is called ischemia-modified albumin (IMA). IMA has been used recently as an indirect indicator of oxidative stress and ischemia, due to this formation mechanism [14].

We have not found a study to examine the IMA level in celiac diseases. However, it was determined that IMA level is significantly higher in diseases such as acute myocardial infarction, stable coronary artery disease, cerebrovascular diseases, necrotising enterocolitis, liver cirrhosis, pulmonary embolism, obesity, metabolic syndrome and diabetes mellitus [15–20].

In the course of this study, we expected that IMA levels would be higher in the celiac disease since it is an autoimmune/chronic inflammatory disease. However, in the literature review, we did not find any studies showing the relation of IMA levels between autoimmunity and inflammatory markers. For this reason, we aimed to examine and determine the IMA level in celiac disease and to examine its relation between autoimmunity and chronic inflammation.

**Materials and methods**

**Study population**

This study was conducted in Türkiye Yüksek İhtisas Training and Research Hospital Gastroenterology Clinic and Ankara Numune Training and Research Hospital Internal Medicine Clinic between May and August 2015.

Sixty-five patients with a diagnosis of celiac disease and 65 healthy volunteers without any known chronic disease were included with a total of 130 participants in the study.

The celiac group was composed of active and remission patients with polyclinic follow-up, volunteers are older than 18 years of age with diet compliance. The healthy control group was composed of healthy volunteers without any known chronic disease and drug use, who have applied for check up in our hospital. The control group were being included in the study, in the order of application, according to similar age, sex and body mass index (BMI) to the patient group.

Patients with a known documented chronic and inflammatory diseases, acute liver and renal impairment, abnormal proteinuria, thyroid function failure, immunosuppressive drug use and patients without follow-up were not included in the study.

This study was designed in accordance with the declaration of Helsinki and was approved by the local Research Ethics Committee. The written consent of all participants was obtained.
Biochemical parameters

Besides routine blood tests, a blood sample from an antecubital vein was taken from participants in the morning between 08:00 and 10:00 AM after 8 h of fasting in order to determine IMA levels. The blood samples were quickly centrifuged for 10 min at 4000 rpm. The serum samples were stored at −80°C until all blood samples were collected. Then, in all sample laboratory parameters were studied in the same session.

The laboratory parameters without IMA, are the measurements taken from patients when they were included in the study and have been recorded from patients' files. Celiac-specific autoantibodies [anti-gliadin antibodies immunoglobulin A (AGA-IgA), anti-gliadin antibodies immunoglobulin G (AGA-IgG), anti-tissue transglutaminase immunoglobulin A antibodies (Anti-t TGA), anti-tissue transglutaminase immunoglobulin G antibodies (Anti-t TGG)] were examined in the study. The laboratory parameters, AGA-IgA, AGA-IgG, Anti-t TGA and Anti-t TGG were measured by an electroilluminescence immunoassay method using Cobas e 601 (Roche Diagnostics Corp., Indianapolis, IN, USA) analyzer. C-reactive protein (CRP) was measured by an immunoturbidimetric method using Hitachi Modular P800 (Roche Diagnostics Corp., Indianapolis, IN, USA) analyzer. Total protein was measured by colorimetric method and albumin was measured by bromocresol green method using Cobas e 601 (Roche Diagnostics Corp., Indianapolis, IN, USA) analyzer.

IMA measurement

The Ischemia modified albumin levels were measured by a serum ELISA kit (ELABSCIENCE, Human IMA, Cat no: E-EL-H5422). The results were expressed in ng/mL.

Statistical analysis

In this study, “statistical program for social sciences (SPSS) version 15.0 for Windows (IBM Inc., Armonk, NY, USA)” was the software used. The normal distribution of the data was assessed with the Shapiro-Wilk test. Among numerical variables, those with normal distribution were expressed as mean ± standard deviation and those who did not exhibit a normal distribution were shown as a median (IQR). Categorical variables were indicated by a number and percentage. While the student t-test was used for the comparison of two groups of numerical variables with normal distribution and the Mann-Whitney U was used for the comparison of two groups of numerical variables without a normal distribution. Chi-Square and Fisher’s Exact χ² test was used in the comparisons of the categorical data. The correlation was examined among the numerical variables with Pearson vs. Spearman correlation analysis. The effects of the demographic and laboratory findings were refined and the relation between IMA level and antibody level was examined with the partial correlation. A p < 0.05 statistical significance was accepted.

Results

Table 1 summarizes the demographic characteristics and laboratory findings of the study population. It was determined that sex distribution, mean age, and BMI levels were similar with the rates of smoking and alcohol usage between both groups. In celiac patients, alanine aminotransferase (23 IU/L vs. 16 IU/L, p < 0.001; respectively), aspartate aminotransferase (24 IU/L vs. 18 IU/L, p = 0.011; respectively), CRP (4.2 mg/L vs. 1.3 mg/L, p < 0.001; respectively), and IMA (30.8 ng/mL vs. 20.1 ng/mL, p = 0.006; respectively) levels were significantly higher than the control group (Figure 1).

Table 1: The demographic characteristics and laboratory findings of study population.

| Variables                     | Control (n=65) | Celiac patients (n=65) | p-Value |
|-------------------------------|---------------|------------------------|---------|
| Gender (female), n (%)        | 40 (61.5)     | 42 (64.6)              | 0.854   |
| Age (years)                   | 40.2 ± 12.6   | 41.7 ± 12.1            | 0.490   |
| BMI (kg/m²)                   | 25.8 ± 3.1    | 26.3 ± 4.2             | 0.441   |
| Smoking, n (%)                |               |                        |         |
| Non-smokers                  | 50 (76.9)     | 55 (84.6)              | 0.658   |
| Smokers                      | 10 (15.4)     | 8 (12.3)               |         |
| Quit smoking                 | 5 (7.7)       | 2 (3.1)                |         |
| Alcohol, n (%)                |               |                        |         |
| Non-using                    | 60 (92.3)     | 58 (89.2)              | 0.409   |
| Using                        | 5 (7.7)       | 3 (4.6)                |         |
| Quit using                   | –             | 4 (6.2)                |         |
| Duration of disease (years)   |               | 6 (6.2)                |         |
| Total protein (g/L)           | 7.9 ± 1.8     | 7.5 ± 1.3              | 0.149   |
| Albumin (g/L)                 | 4.4 ± 0.3     | 4.3 ± 0.6              | 0.232   |
| ALT (IU/L)                    | 16 (12)       | 23 (15.5)              | <0.001* |
| AST (IU/L)                    | 18 (8)        | 24 (11)                | 0.011*  |
| CRP (mg/L)                    | 1.3 (1.8)     | 4.2 (3.8)              | <0.001* |
| IMA (ng/mL)                   | 20.1 (16.2)   | 30.8 (28.9)            | 0.006*  |

BMI, body mass index; ALT, alanine aminotransferase; AST, aspartate aminotransferase; CRP, C-reactive protein; IMA, ischemia modified albumin. *p < 0.05 Statistical significance.
The celiac patients without compliance to gluten had a higher level of IMA than patients with compliance to the gluten diet (35.5 ng/mL vs. 18.9 ng/mL, p = 0.001; respectively). Celiac patients with antibody positivity had a higher IMA level than patients without antibody positivity (Table 2).

A positive correlation was determined between IMA level and AGA-IgA ($r = 0.504$, $p < 0.001$), AGA-IgG ($r = 0.445$, $p < 0.001$), Anti-t TGA ($r = 0.485$, $p < 0.001$) and Anti-t TGG ($r = 0.477$, $p < 0.001$) in the correlation analysis of celiac patients (Figure 2). After the demographic characteristics were adjusted, in the partial correlation analysis; a positive correlation continued between IMA level and AGA-IgA ($r = 0.421$, $p < 0.001$), AGA-IgG ($r = 0.386$, $p < 0.001$), Anti-t TGA ($r = 0.350$, $p < 0.001$) and Anti-t TGG ($r = 0.342$, $p < 0.001$) levels. In the celiac patients, a positive correlation was determined between IMA level and CRP ($r = 0.385$, $p = 0.011$) (Table 3).

**Discussion**

Our study determined a higher IMA level in the celiac patients compared to the control group. In the celiac patients who did not comply with the gluten diet and who were autoantibody-positive, IMA level was determined to be higher than patients who complied with the gluten diet and who were autoantibody-negative. The correlation analysis has shown that celiac antibodies and CRP are associated with IMA. As far as we know, this is the first study that examines the IMA level in celiac patients.

Celiac disease is an autoimmune/chronic inflammatory disease characterized by the body's autoantibody production against gliadin antigen found in gluten [1, 21]. CD+T-helper lymphocytes and T cell-mediated immune response occur as a response after ingestion of gliadin in the body. Both the release of cytokines and the immunogenicity of the gastrointestinal tract disease specific antigen increase with the activation of T cells [22]. These immune responses in B cells proliferate clonally and the autoantibody occur in this immune responses. Tissue damage occurs with the increasing of autoimmunity and chronic inflammation. The Ischemia in villus, atrophy and necrosis occur by the damage done to the tissue in the gastrointestinal tract. Accordingly, a higher IMA level can be determined in the circulation.

Another factor that is effective in the increase of IMA level in celiac disease might be correlated with the increasing of chronic inflammation and autoimmunity due to increased oxidative stress level. It was found that the increase of both inflammation and autoimmunity are associated with oxidative stress levels, increased in studies which were done before [23]. The structural changes can occur in albumin N-terminal region with the increasing of oxidative stress levels. Therefore, IMA level can increase in circulation.

In our study, the IMA level was determined to be higher in celiac patients than the control group. This situation might depend on tissue hypoxia and tissue damage which occurs in the gastrointestinal system in celiac disease. IMA level was determined to be higher in...
Figure 2: Scatterplot of laboratory findings which are associated with IMA in celiac patients; (A) between IMA and AGA-IgA, (B) between IMA and AGA-IgG, (C) between IMA and Anti-t TGA, (D) between IMA and Anti-t TGG, (E) between IMA and CP.

Table 3: The relation of entire population and IMA in patients group with the other parameters.

| Variables      | All population | Celiac patients |
|----------------|----------------|-----------------|
|                | IMA            | IMA             |
|                | r   | p-Value | r    | p-Value |
| Age            | −0.048 | 0.604 | −0.076 | 0.502 |
| BMI            | −0.027 | 0.907 | 0.101 | 0.307 |
| Total protein  | 0.201 | 0.124 | 0.308 | 0.028* |
| Albumin        | 0.209 | 0.108 | 0.288 | 0.085 |
| ALT            | 0.158 | 0.305 | 0.307 | 0.027* |
| AST            | 0.173 | 0.358 | 0.340 | 0.019* |
| CRP            | 0.275 | 0.076 | 0.385 | 0.011* |
| AGA-IgA        | –    | –    | 0.504 | <0.001* |
| AGA-IgG        | –    | –    | 0.445 | <0.001* |
| Anti-t TGA     | –    | –    | 0.485 | <0.001* |
| Anti-t TG      | –    | –    | 0.477 | <0.001* |
| AGA-IgAb       | –    | –    | 0.421 | <0.001* |
| AGA-IgGb       | –    | –    | 0.386 | <0.001* |
| Anti-t TGAb    | –    | –    | 0.350 | <0.001* |
| Anti-t TGGb    | –    | –    | 0.342 | <0.001* |

IMA, ischemia modified albumin; BMI, body mass index; ALT, alanine aminotransferase; AST, aspartate aminotransferase; CRP, C-reactive protein; AGA-IgA, anti gliadin antibodies IgA; AGA-IgG, anti gliadin antibodies IgG; Anti-t TGA, anti-tissue transglutaminase IgA antibodies; Anti-t TGG, anti-tissue transglutaminase IgA antibodies. *p < 0.05 Statistical significance. \(^{a}\)Demographic and laboratory parameters adjusted.
analysis done by us. Also, a positive correlation was determined between IMA level with CRP (chronic inflammation indicator) and celiac autoantibodies in doing correlation analysis.

In the literature, there are studies supporting the results of our research. Leitemperguer et al. [28] has determined that IMA level was higher in the control group with rheumatoid arthritis which is an autoimmune/chronic inflammatory disease. Similarly, it was found that IMA level was higher in the control group with the Behçet's disease [29]. IMA level was higher than normal in autoimmune/chronic inflammation disease when all results were considered together. In these diseases, the reasons why IMA level was high might be related to 1) proinflammatory cytokines, which are synthesized based on chronic inflammation, increase the reactive oxygen types and these reactive oxygen types further increase the IMA level which causes structural change in albumin. The determination of high IMA level in Behçet disease has been explained with this mechanism [29].  2) The increase in disease-specific antigens' immunogenecity results from the increased chronic inflammation and the increase in autoantibody level and tissue damage. In our study, the relation between inflammatory markers/autoantibodies and IMA level supports our hypothesis. In the study of Roy et al. [30], conducted with patients with subclinical hypothyroidism, determination of a positive correlation between IMA and CRP also supports our results.

The determination of high IMA levels in symptomatic patients with diet-incompliance leads us to think that IMA can be an effective diagnosis and follow-up marker for disease severity and activation in celiac disease.

The main limitation of this study is based on its being cross-sectional, the inflammatory markers and IMA levels have not been determined after activation and remissions in the clinical follow-up of celiac patients.

As a result, we determined that the IMA levels in the celiac patients were higher than the IMA levels of the control group. The IMA level in the celiac patients with diet-incompliance and autoantibody positive was determined higher compared to the patients with diet-compliance and autoantibody negative. These results show that the level of IMA in celiac patients was determined to be high because it is correlated with both pathological changes of intestinal structure and increasing of inflammation-autoimmunity. In order to use IMA as a diagnosis and follow-up marker for disease severity and activation in celiac disease, IMA levels must be compared before and after treatment of active celiac disease. A prospective randomized controlled study is required for this.

Conflict of interest statement: The authors declare there are no conflicts of interest.

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