

Case Control Study

Thiol/disulphide homeostasis in celiac disease

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Abstract

AIM

To determine dynamic thiol/disulphide homeostasis in celiac disease and to examine the associate with celiac autoantibodies and gluten-free diet.

METHODS

Seventy three patients with celiac disease and 73 healthy volunteers were enrolled in the study. In both groups, thiol/disulphide homeostasis was examined with a new colorimetric method recently developed by Erel and Neselioglu.

RESULTS

In patients with celiac disease, native thiol ($P = 0.027$) and total thiol ($P = 0.031$) levels were lower, while disulphide ($P < 0.001$) level, disulphide/native thiol ($P < 0.001$) and disulphide/total thiol ($P < 0.001$) ratios were higher compared to the control group. In patients who do not comply with a gluten-free diet, disulphide/native thiol ratio was found higher compared to the patients who comply with the diet ($P < 0.001$). In patients with

any autoantibody-positive, disulphide/native thiol ratio was observed higher compared to the patients with autoantibody-negative ($P < 0.05$). It is found that there is a negative correlation between celiac autoantibodies, and native thiol, total thiol levels and native thiol/total thiol ratio, while a positive correlation is observed between disulphide, disulphide/native thiol and disulphide/total thiol levels.

CONCLUSION

This study is first in the literature which found that the patients with celiac disease the dynamic thiol/disulphide balance shifts through disulphide form compared to the control group.

Key words: Anti-gliadin antibodies; Anti-tissue transglutaminase antibody; Gluten-free diet; Oxidative stress; Thiol oxidation

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Core tip: To the best of our knowledge, for the first time in this study, total and native thiol levels in celiac patients were found lower compared to the control group while disulphide level, disulphide/total thiol and disulphide/native thiol ratios were found to be higher. Also, this study is first in which a negative correlation between celiac autoantibodies and native thiol, and total thiol levels and native thiol/total thiol ratio is observed while there is a positive correlation between disulphide level and disulphide/native thiol and disulphide/total thiol ratios.

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INTRODUCTION

Celiac disease (CD), observed in genetically predisposed individuals, is a chronic/autoimmune disease of the small intestine, characterized by symptoms such as mucosal damage induced by gliadin, malabsorption, anemia, diarrhea and growth retardation^[1,2]. While environmental, genetic and immunological factors have a role in etio-pathogenesis of the disease, oxidative stress has also been proved to play a critical role in development of disease^[3,4].

With the development of diagnostic methods, gliadin and related toxic effects of prolamines on small intestine are understood better. Gluten peptides in enterocytes, particularly p31-43 α -gliadin peptides, induce certain signal transduction pathways by accumulating in lysosomes and increase the levels of oxidant radicals^[5]. Based on increased free radicals, a deterioration occurs in the oxidation redox equilibrium^[6]. At the first stage of

oxidative damage in cellular level based upon free radicals, disulphide (-S-S) linkages are formed by thiol groups (-SH) of amino acids such as sulfur containing cysteine and methionine being oxidized as well as the thiol/disulphide balance collapses in favor of disulphide^[7-12]. The resulting disulphide bonds are reduced to thiol groups and thiol reserves increase again. Through these reactions at the cellular level, dynamic thiol/disulphide homeostatic status is maintained^[13]. This dynamic equilibrium is considered to be effective in many cellular processes such as cell death and proliferation, and especially antioxidant balance^[14,15]. Due to these effects, there are certain studies showing that dynamic equilibrium collapses in cardiovascular diseases and cancer, the oxidative stress of which is particularly evident^[16-18].

Dynamic thiol/disulphide homeostasis began to be measured in an easy and repeatable way in 2014 by a new method developed by Erel *et al.*^[19] with high accuracy and sensitivity. In the literature review, we have not found any study examining dynamic thiol/disulphide homeostatic status in celiac patients using this new method.

In this study, we aimed to measure native thiol, total thiol, disulphide, disulphide/native thiol, disulphide/total thiol and native thiol/total thiol levels in celiac patients with a new and fully automated method of analysis and determine dynamic thiol/disulphide homeostasis.

MATERIALS AND METHODS

Study population

This study was conducted in Turkey Yuksek Ihtisas Training and Research Hospital Gastroenterology Clinic and Ankara Numune Training and Research Hospital Internal Medicine Clinic between January and June 2015.

The study included a total of 146 participants including 73 celiac patients and 73 healthy volunteers. Celiac group is composed of first 73 celiac patients, over the age of 18, who admitted to the polyclinic for routine control. Patients that were diagnosed with CD *via* endoscopic biopsy and subject to regular follow-up in our clinic were included in the patient group in order of their applications. The healthy control group consisted of healthy volunteers, who have applied to our hospital for a check-up, without a chronic disease and drug use and those with similar demographic characteristics to the patient group.

Patients with known diabetes mellitus, kidney failure, malignancy, liver disease, thyroid disease, rheumatic disease, cardiovascular and cerebrovascular disease; smoking, alcohol consumption, vitamin supplements and unfollowed patients were excluded from the study.

In our clinic, the diagnosis of celiac disease in routine is made endoscopically with 2nd part duodenal biopsy and anti-gliadin antibody IgA-G or anti-tissue transglutaminase IgA-D positivity. Crypt hyperplasia, villus atrophy and submucosal lymphocytic infiltration is considered significant in the biopsy.

We created two subgroups (GCD: Patients non-

compliant with gluten free diet, GFD: Patients compliant with gluten free diet) to understand the effect of diet in oxidative stress in CD. Poor compliance to diet is defined as taking any kind of gluten containing materials. Patients' compliance to gluten diet is obtained from patient files and applied questionnaires. Patients that are compliant to gluten free diet from the beginning and for at least 5 years are included in GFD group.

Body mass index (BMI) was calculated by dividing body dry weight to the square of tall stature in meters (BMI = kg/m²).

The study was conducted in accordance with the Declaration of Helsinki 2013 Brasil version and was approved by the Local Ethics Research Committee. All subjects provided written informed consent prior to participation in the study.

Biochemical parameters

For thiol/disulphide hemostasis tests, venous blood samples were drawn from patient and control groups after overnight fasting. Blood samples were swiftly centrifuged at 4000 rpm for 10 min, then plasma and serum samples were separated and stored at -80 °C. Then all parameters were studied in the same session and in the same serum sample.

Laboratory parameters other than thiol/disulphide hemostasis parameters of the participants were their routine parameters at the time they were included in the study and those were recorded from patient files.

Thiol/disulphide homeostasis

Thiol/disulphide levels were measured by a newly developed, fully-automated and colorimetric method by Erel and Neselioglu^[19]. When disulphide levels were divided to native thiol and total thiol levels: Disulphide/native thiol and disulphide/total thiol ratios were obtained. When native thiol level was divided to total thiol level, native thiol/total thiol ratio was obtained as a result.

Statistical analysis

Statistical Package for Social Sciences (SPSS) for Windows 20 (IBM SPSS Inc., Chicago, United States) program was employed for statistical assessments. Kolmogorov-Smirnov test was utilized to determine the distribution of data. Continuous variables with normal distribution were expressed as mean ± SD, and continuous variables without normal distribution were expressed as median (min-max). Categorical variables were presented in numbers and percentage. Continuous variables were compared to independent sample *t*-test or Mann-Whitney *U* test where necessary. The relationship between the numeric parameters was analyzed by Pearson and Spearman correlation analysis. In the examination of the relation between thiol/disulphide homeostasis parameters and celiac antibodies, the effects of demographic and clinical factors were adjusted by partial correlation. A *P* < 0.05 was considered significant for statistical

analyses.

RESULTS

The demographic characteristics and laboratory findings of all groups are summarized in Table 1. The study population consisted of a total of 146 patients, including 73 celiac patients (female/male: 58/15; age: 44.1 ± 13 years, BMI: 24.5 ± 4.7 kg/m²) and 73 controls (female/male: 55/18; age: 43.7 ± 13.6 years, BMI: 24.9 ± 4.7 kg/m²). There were no significant difference between two groups in terms of sex, age and BMI levels (*P* > 0.05). The median disease duration of followed celiac patients was determined as 6 years (min: 1 years, max: 25 years).

The mean total protein levels in celiac patients were determined similar to the control group (*P* > 0.05). In celiac patients, mean albumin (4.4 ± 0.3 g/L vs 4.1 ± 0.3 g/L, respectively; *P* = 0.002), median alanine aminotransferase (23 IU/L vs 20 IU/L, *P* = 0.035), aspartate aminotransferase (20 IU/L, etc., 17 IU/L, respectively; *P* = 0.002) and c-reactive protein (3.5 mg/L vs 1.2 mg/L, respectively, *P* = 0.008) levels were higher, compared to the control group.

Mean native thiol (322.7 ± 39.7 mmol/L vs 339.6 ± 51.3 mmol/L, respectively, *P* = 0.027) and total thiol levels (343.7 ± 41.9 mmol/L vs 360.4 ± 50.3 mmol/L, *P* = 0.031) were determined lower in celiac patients, compared to the control group, while native thiol/total thiol ratio did not differ significantly between the groups (*P* > 0.05). Mean disulphide level (13.0 ± 3.7 mmol/L vs 10.2 ± 3.9 mmol/L, respectively; *P* < 0.001), disulphide/native thiol (3.8% ± 1.2% vs 2.8% ± 1.1%, respectively, *P* < 0.001) and disulphide/total thiol ratio (4.1% ± 1.4% vs 2.9% ± 1.1%, respectively, *P* < 0.001) were determined higher in celiac patients compared to the control group.

According to dietary compliance and antibody positivity in the celiac group, the distribution of native thiol, total disulphide and disulphide/native thiol ratios were shown in detail in Table 2. According to this; in patients with dietary compliance, mean native thiol was higher (327.9 ± 35.6 mmol/L vs 310.6 ± 46.8 mmol/L, *P* = 0.013), mean disulphide (12.0 ± 3.3 mmol/L vs 13.8 ± 3.2 mmol/L, respectively; *P* = 0.034) level and disulphide/native thiol ratio (3.5% ± 1.7% vs 5.2% ± 1.4%, respectively, *P* < 0.001) were much lower compared to patients without dietary compliance. As for antibody positive patients, native thiol level was determined low, disulphide level and disulphide/native thiol ratio were determined higher.

The correlation analysis of native thiol, total thiol, disulphide, disulphide/native thiol, disulphide/total thiol and native thiol/total thiol with demographic and clinical findings is shown in Table 3 in detail. Celiac autoantibodies displayed a negative correlation with native thiol, total thiol and native thiol/total thiol levels and a positive correlation with disulphide, disulphide/native thiol and disulphide/total thiol ratio. The relation

Table 1 Demographic characteristics and laboratory findings of study population

Variables	Celiac (n = 73)	Control (n = 73)	P value
Gender (male), n (%)	15 (20.5)	18 (24.7)	0.553
Age (yr)	44.1 ± 13	43.7 ± 13.6	0.866
BMI (kg/m ²)	24.5 ± 4.7	24.9 ± 4.7	0.867
Smoking, n (%)			
Non-smokers	49 (67.1)	50 (68.5)	
Smokers	18 (24.7)	17 (23.3)	0.981
Quit smoking	6 (8.2)	6 (8.2)	
Alcohol, n (%)	2 (2.7)	-	-
Duration of disease (yr)	6 (1-25)	-	-
Total protein (g/L)	7.4 ± 0.6	7.4 ± 0.5	0.964
Albumin (g/L)	4.4 ± 0.3	4.1 ± 0.3	0.002 ^a
ALT (IU/L)	23 (8)	20 (7)	0.035 ^a
AST (IU/L)	20 (12)	17 (9)	0.002 ^a
CRP (mg/L)	3.5 (8.4)	1.2 (2)	0.008 ^a
Native thiol (μmol/L)	322.7 ± 39.7	339.6 ± 51.3	0.027 ^a
Total thiol (μmol/L)	343.7 ± 41.9	360.4 ± 50.3	0.031 ^a
Disulphide (μmol/L)	13.0 ± 3.7	10.2 ± 3.9	< 0.001 ^a
Disulphide/native thiol (%)	3.8 ± 1.2	2.8 ± 1.1	< 0.001 ^a
Disulphide/total thiol (%)	4.1 ± 1.4	2.9 ± 1.1	< 0.001 ^a
Native thiol/total thiol (%)	93.8 ± 2.6	94.3 ± 5.7	0.553

^aP < 0.05. BMI: Body mass index; ALT: Alanine aminotransferase; AST: Aspartate aminotransferase; CRP: C-reactive protein.

Table 2 Dietary compliance of native thiol, disulphide and disulphide/native thiol and its distribution regarding antibody positivity

Variables	Native thiol (μmol/L)	P value	Disulphide (μmol/L)	P value	Disulphide/native thiol (μmol/L)	P value
Diet						
GCD (n = 22)	310.6 ± 46.8	0.013 ^a	13.8 ± 3.2	0.034 ^a	5.2 ± 1.4	< 0.001 ^a
GFD (n = 51)	327.9 ± 35.6		12.0 ± 3.3		3.5 ± 1.7	
AGA-IgA						
(-) (n = 33)	310.5 ± 39.5	0.015 ^a	14.1 ± 3.7	0.020 ^a	4.7 ± 1.9	0.005 ^a
(+) (n = 40)	333.8 ± 40.1		12.0 ± 3.8		3.6 ± 1.4	
AGA-IgG						
(-) (n = 47)	308.5 ± 36.8	0.027 ^a	13.9 ± 3.1	0.001 ^a	4.6 ± 1.7	< 0.001 ^a
(+) (n = 26)	330.5 ± 45.2		11.1 ± 3.9		3.0 ± 1.1	
Anti-t TGA						
(-) (n = 29)	315.5 ± 38.2	0.001 ^a	13.9 ± 3.9	0.019 ^a	4.5 ± 1.9	0.007 ^a
(+) (n = 44)	346.2 ± 40.5		11.7 ± 3.8		3.4 ± 1.5	
Anti-t TGG						
(-) (n = 61)	318.1 ± 37.6	0.002 ^a	13.5 ± 3.9	0.009 ^a		0.035 ^a
(+) (n = 12)	345.3 ± 51.5		10.3 ± 3.0			

^aP < 0.05. GCD: Gluten-containing diet; GFD: Gluten-free diet; 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.

between thiol/disulphide homeostasis parameters and celiac autoantibodies were observed to continue even when the effects of demographic and clinical findings were removed.

C-reactive protein level displayed a negative correlation with native thiol, total thiol and native thiol/total thiol levels, and a positive correlation between disulphide, disulphide/native thiol, disulphide/total thiol levels.

DISCUSSION

To our knowledge, for the first time in this study, total and native thiol levels in celiac patients were

determined lower compared to the control group while disulphide level, disulphide/total thiol and disulphide/native thiol ratios were found to be higher. Also this is the first study to determine a negative correlation of celiac autoantibodies with native thiol and total thiol levels with native thiol/total thiol ratio, and a positive correlation of disulphide level with disulphide/native thiol and disulphide/total thiol ratios.

Celiac disease is a disease characterized by the inflammatory response created by intestinal mucosa based upon gliadin peptides taken with gluten containing food and consequently mucosal inflammation, crypt hyperplasia and villus atrophy^[20]. The most important factor in etiopathogenesis of the disease is considered

Table 3 Findings related to thiol/disulphide hemostasis parameters in celiac patient group

Variables	Native thiol		Total thiol		Disulphide		Disulphide/total thiol		Disulphide/native thiol		Native thiol/total thiol	
	<i>r</i>	<i>P</i> value	<i>r</i>	<i>P</i> value	<i>r</i>	<i>P</i> value	<i>r</i>	<i>P</i> value	<i>r</i>	<i>P</i> value	<i>r</i>	<i>P</i> value
Age	0.261	0.026 ^a	0.262	0.025 ^a	-0.041	0.729	-0.132	0.264	-0.122	0.302	0.021	0.861
BMI	0.19	0.107	0.187	0.114	-0.033	0.783	-0.096	0.421	-0.113	0.34	0.045	0.702
Total protein	-0.032	0.786	0.005	0.97	0.059	0.618	0.032	0.787	0.086	0.472	-0.156	0.187
Albumin	0.009	0.937	0.025	0.835	-0.037	0.754	-0.065	0.582	-0.040	0.735	-0.071	0.548
AST	0.051	0.666	0.046	0.702	-0.03	0.801	-0.057	0.631	-0.031	0.796	0.033	0.781
ALT	-0.091	0.444	-0.116	0.329	-0.063	0.598	-0.012	0.919	0.002	0.985	0.094	0.427
CRP	-0.327	0.018 ^a	-0.304	0.038 ^a	0.369	0.015 ^a	0.287	0.043 ^a	0.332	0.029 ^a	-0.244	0.038 ^a
AGA-IgA	-0.325	0.009 ^a	-0.266	0.035 ^a	0.384	0.024 ^a	0.324	0.010 ^a	0.325	0.009 ^a	-0.266	0.035 ^a
AGA-IgG	-0.332	0.008 ^a	-0.271	0.022 ^a	0.298	0.010 ^a	0.297	0.011 ^a	0.253	0.031 ^a	-0.279	0.017 ^a
Anti-t TGA	-0.342	0.007 ^a	-0.28	0.017 ^a	0.305	0.009 ^a	0.311	0.004 ^a	0.280	0.035 ^a	-0.294	0.028 ^a
Anti-t TGG	-0.35	0.00 ^a	-0.316	0.004 ^a	0.315	0.007 ^a	0.34	0.001 ^a	0.302	0.014 ^a	-0.304	0.019 ^a
AGA-IgA ¹	-0.313	0.006 ^a	-0.301	0.026 ^a	0.334	0.004 ^a	0.353	< 0.001 ^a	0.315	0.011 ^a	-0.319	0.013 ^a
AGA-IgG ¹	-0.335	0.004 ^a	-0.324	0.005 ^a	0.309	0.018 ^a	0.366	0.023 ^a	0.349	0.033 ^a	-0.288	0.045 ^a
Anti-t TGA ¹	-0.261	0.043 ^a	-0.243	0.035 ^a	0.376	0.036 ^a	0.322	0.011 ^a	0.335	0.009 ^a	-0.273	0.038 ^a
Anti-t TGG ¹	-0.333	0.032 ^a	-0.282	0.037 ^a	0.294	0.031 ^a	0.305	0.026 ^a	0.336	0.036 ^a	-0.314	0.013 ^a

^a*P* < 0.05. ¹Demographic characteristics and laboratory parameters are adjusted. 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.

to be environmental factors such as gliadin and the autoimmune response against them. Although the role of oxidative stress in the etiopathogenesis of the disease is unknown, in studies conducted with different cell models, intracellular oxidative imbalance occurs as a result of gliadin exposure and oxidant radicals are formed as a result of lipid peroxidation^[21]. These oxidant radicals have been shown to form -S-S bonds by oxidizing -SH groups found in the side chain of sulfur containing amino acids and consequently increase oxidized metabolites in the cell^[22]. In this case thiol/disulphide equilibrium, which is balanced under physiological conditions, is weakened and disrupted in favor of disulphide form. As a result of all these reactions, cell morphology, membrane permeability and vital cellular activities such as apoptosis and cell proliferation are disrupted^[1,5].

There are certain studies in the literature investigating thiol and disulphide amounts in low molecular thiol compounds that constitute a small portion of total body thiol pool such as cysteine, glutathione (GSH) and oxidized glutathione thiol^[23,24]. Until 2014, any colorimetric method that measures total thiol and disulphide amount in the body had not yet been developed. But Erel *et al*^[19] developed a fully-automated method in 2014, by which total thiol, native thiol and disulphide amounts can be measured easily and repetitively with high sensitivity and specificity.

We have not found any study in the literature examining dynamic thiol/disulphide balance in celiac disease. However, there are studies conducted with low molecular weight thiol compounds. Stojiljković *et al*^[25] have shown that in intestinal tissues of celiac patients in the pediatric age group, GSH level that constitutes a big part of intracellular thiol content decreases and lipid hydroperoxide level which is an oxidant substance that plays a role in cell membrane damage increases. These results have indicated that GDH redox cycle is disrupted in celiac patients. In a

study conducted with asymptomatic celiac patients by Odetti *et al*^[6] oxidant radicals derived from protein (carboxyl groups) and lipids (thiobarbituric acid-reactive substances) were determined high.

In our study, total and native thiol levels in celiac patients were determined lower compared to the control group; disulphide level, disulphide/total thiol and disulphide/native thiol ratios were found to be higher and eventually dynamic equilibrium was observed to shift to disulphide form. This case may be due to high levels of oxidant radicals in celiac disease. Our hypothesis is supported by the two studies mentioned above, in which the level of oxidant radicals increase in celiac patients. The increase in the level of oxidant radicals in celiac disease may be due to two cases. Firstly, the disease being a chronic inflammatory disease and secondly, being an autoimmune disease. Previously many studies have indicated that oxidant radicals increase in inflammatory/autoimmune diseases and accordingly oxidative stress level increases^[26-28].

For instance, Nanda *et al*^[29] have determined that in autoantibody positive hypothyroidis patients, levels of oxidant radicals are higher compared to those with autoantibody negative and observed a positive correlation between autoantibodies and oxidant radicals. Determining a positive correlation of C-reactive protein and celiac autoantibodies with disulphide/native thiol level and determining the disulphide form significantly high in autoantibody positive celiac patients strongly supports our thesis.

Another reason for determining low thiol reserve in celiac patients compared to the control group may be due to lack of thiol-containing food intake based upon deteriorated intestinal mucosa. However determining disulphide form and albumin level higher in celiac group compared to the control group indicates that this abnormal

thiol/disulphide equilibrium in celiac patients is not due to lack of oral intake but rather to oxidative stress.

In our study, disulphide/native thiol ratio was determined higher in patients who do not comply with gluten diet compared to those who comply with the diet. We think that this case could be associated with inflammation. Because previous studies have indicated that inflammation is higher in patients who do not comply with gluten diet than those who comply with diet^[30,31]. Another reason may be due to the significant increase in oxidative stress based upon gliadin toxicity in patients who do not comply with gluten diet^[21].

The main limitation of our study is its cross-sectional design and that repetitive measurements have not been done in the patient group. The other limitation is that the information whether participants in the control group have taken thiol containing nutrients or not, is only limited to anamnesis.

For the first time in this study, thiol/disulphide balance was shown to shift towards disulphide form in celiac patients, compared to the control group. Also this is the first study to examine the effects of celiac autoantibodies and gluten-free diet on dynamic thiol/disulphide equilibrium. According to all these results, disrupted thiol/disulphide equilibrium in celiac patients was thought to be associated with autoimmunity and inflammation. In order these results to be clarified, further studies are required to examine the association between thiol/disulphide homeostasis parameters and proinflammatory cytokines that play an active role in celiac disease.

COMMENTS

Background

Celiac disease (CD), observed in genetically predisposed individuals, is a chronic/autoimmune disease of the small intestine, characterized by symptoms such as mucosal damage induced by gliadin, malabsorption, anemia, diarrhea and growth retardation.

Research frontiers

Dynamic thiol/disulphide homeostasis began to be measured in an easy and repeatable way in 2014 by a new method developed by Erel and his colleagues with high accuracy and sensitivity.

Innovations and breakthroughs

The authors to measure native thiol, total thiol, disulphide, disulphide/native thiol, disulphide/total thiol and native thiol/total thiol levels in celiac patients with a new and fully automated method of analysis and determine dynamic thiol/disulphide homeostasis.

Applications

Disrupted thiol/disulphide equilibrium in celiac patients was thought to be associated with autoimmunity and inflammation. In order these results to be clarified, further studies are required to examine the association between thiol/disulphide homeostasis parameters and proinflammatory cytokines that play an active role in CD.

Peer-review

In the present paper, entitled "Thiol/disulphide homeostasis in celiac disease", Kaplan *et al* measured thiol/disulphide homeostasis, an indirect evaluation for oxidative stress, in patients with CD.

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