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Assessment of Newly Diagnosed Celiac Disease Presented at Different Ages and its Relation to Nitrosative Stress and Lipid Peroxidation

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Abstract

Background and objectives: The clinical presentations of celiac disease (CD) are remarkably various age dependent. Free radicals overproduction may implicate in pathogenesis of CD or its complications. This study aimed to assess newly diagnosed CD from the following points of view: clinical presentation, cardiac involvement and free radicals overproduction taking in consideration the age of diagnosis.

Methods: This study designed as a cross sectional in cohort patients with newly diagnosed celiac disease. Patients presented with diarrhea responded to the gluten free diet and positive serological tests of CD were admitted in the study. Left ventricular function was assessed by measuring the ejection fraction (%) and the free radicals were assessed by measuring the serum NO and peroxynitrite (ONOO) as well as malondialdehyde (MDA), a biomarker of lipid peroxidation.

Results: One hundred eighty two newly diagnosed CD patients (73males and 109 females) were studied. There were no significant differences in intestinal and extra intestinal clinical manifestations at any age ranged between 4 and 65 years. Ejection fraction of patients at any age of clinical presentation was within normal range of corresponding healthy subjects. Also the hematological indices and biochemical tests did not show significant variation regarding the age. Significant high serum MDA, NO and ONOO levels compared with healthy subjects' levels were observed.

Interpretations and conclusions: There are no significant differences between child and adult CD regarding the clinical presentations, biochemical findings, cardiac assessment and overproduction of reactive oxygen and nitrogen. Nitrosative stress syndrome is associated with celiac disease at any age.

Keywords: Celiac disease; Age; Nitrogen species

Introduction

The clinical presentations of celiac disease (CD) are remarkably various and age dependent [1]. The classic presentations of CD are failure to thrive, malnutrition, diarrhea, abdominal pain and distension within the first couple of years of life. Many patients presented at a later age with subtle symptoms or gastrointestinal symptoms which included; abdominal pain, diarrhea or constipation, bloating, and excessive gas. Extra-intestinal manifestations included; arthritis, dermatitis herpetiformis skin lesion, dental enamel hypoplasia, recurrent aphthous stomatitis, anxiety, depression, migraine, hypotonia etc. [2,3]. Celiac disease has been associated with osteoporosis, decreased fertility, miscarriage, type 1 diabetes, autoimmune thyroiditis, intestinal adenocarcinoma and non-Hodgkin's lymphoma [4-7]. Few studies reported the association between CD and cardiovascular diseases. Ludvigsson et al. reported 13 out of 187 patients with myocarditis were positive for anti-tissue-transglutaminase antibodies (IgA t-TG) and nine of them were positive for anti-endomysial antibodies (AEAs). Positive association between CD and later cardiovascular diseases in Swedish population observed [8]. Others found that Swedish adults CD, compared with controls, were less likely to have had a diagnosis of hypertension or hypercholesterolemia but slightly more likely to have had atrial fibrillation [9]. On the other hand nitric oxide (NO) which is involved in the inflammatory process and endothelium dysfunction may be implicated in pathogenesis of CD or its complications. Increased luminal NO concentrations in the small intestine have previously been reported in patients with untreated CD [10]. In one study from Sweden, rectal NO production increased after gluten challenge in patients with celiac disease and correlated with mucosal myeloperoxidase [11]. An increase of markers of oxidative damage of lipids (thiobarbituric acid-reactive substances and lipid hydroperoxides) and proteins (carbonyl groups) have been demonstrated in plasma, in circulating cells and in intestinal cells of patients with CD [12-14]. The rational of this study is to look for the role of age on the clinical presentation including the subclinical cardiac involvement, and the status of the free radicals. Therefore, this study is aimed to assess the newly diagnosed celiac disease in patients presented at different age groups taking in consideration the left ventricle function by determining the ejection fraction (%) and the vascular endothelium function by determining the circulated nitrogen species.

Materials and Methods

This study was done in Diyala Teaching Hospital in Diyala in cooperation with Department of Biochemistry, College of Science at Baghdad University in Baghdad, Iraq from January to December 2011. The study approved by an institutional review committee and informed consent obtained from each patient prior to admit in the study. The study designed as a cross sectional in the patients with newly diagnosed celiac disease as well as in the healthy subjects (the control group).

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The criteria of inclusion were chronic diarrhea which responded to the gluten free diet and positive serological testing included anti-transglutaminase (IgG, and IgA) and endomysial antibodies as serological hallmarks of florid celiac disease [15]. Jejunum biopsy carried on in doubtful cases. The criteria of exclusion included syndromes mimicking celiac disease: autoimmune enteropathy, radiation enteritis, bacterial overgrowth, common variable immunodeficiency syndrome, amyloidosis, Whipple's disease, hypogammaglobulinemia, acquired immune deficiency syndrome, inflammatory bowel disease, exocrine pancreatitis/insufficiency, hyperthyroid disease, tropical sprue, giardiasis, post-infectious diarrhea, intestinal lymphoma, protein intolerance and tuberculosis. A total number of 182 patients (73male and 109 female) allocated consecutively from consultant clinic and who fulfilled the above criteria was enrolled in this study. They were sub-grouped into three groups according to their age: 4-10, 10.1-20, 20.1-30 and ≥ 30.

Medical history, physical examination and anthropometric measurements done to each patient enrolled in the study. Laboratory investigations included serological tests (anti-transglutaminase (IgG, and IgA) and endomysial antibodies), hematological indices; hemoglobin level (Hb), mean corpuscular volume (MCV), mean corpuscular hemoglobin (MCH), mean corpuscular hemoglobin concentration (MCHC), white blood cell and platelet count, serum albumin, fasting serum glucose and renal function tests (serum creatinine and blood urea). Left ventricular function was assessed by measuring the ejection fraction (%) using B-mode echocardiography. Venous blood samples were obtained from patients and healthy subjects (n=20) which served as the control group. The sera separated by centrifugation and kept at -20°C for further analysis to determine the serum level of malondialdehyde, nitric oxide and peroxynitrite. Serum malondialdehyde was determined using a modified procedure prescribed by [16]. In brief, two volumes of cold trichloroacetic *acid* (10% w/v) were added to one volume of serum, centrifuged 10 minutes to precipitate protein. An equal volumes of supernatant and thiobarbituric acid (0.67% w/ v) were mixed, incubated in boiling water bath for 30 minutes. The absorbance recorded at 532 nm using UV-visible spectrophotometer. The concentration of malondialdehyde was calculated using the extinction coefficient 1.56×10^5 M^{-1}.cm and is expressed as μmol/L. Serum peroxynitrite was determined using the procedure of [17] as described by [18]. This method is based on peroxynitrite-mediated nitration of phenol, resulting in nitrophenol formation. The procedure conducted in a dark room and as follows: A measured volume of serum (50 μL) was placed in a test tube and 5 mM phenol in 50 mM sodium phosphate buffer (150 mM NaCl, 50 mM $Na_2HPO_4.2H_2O$, pH 7.4) was added to a final volume of 3 mL and mixed well. After 2 hours incubation at 37°C, 25 μL of 0.1 M NaOH was added and mixed. The absorbance of the sample at 412 nm was then immediately recorded spectrophotometrically. The yield of nitrophenol was calculated from extinction coefficient= 4400 M^{-1}. cm. Serum nitric oxide was estimated by the use of Greiss reaction as described by others [19]. Briefly 500 μL of serum was added to 50 μL HCl (6.5M) and 50 μL sulfunalic acid (37.5 mM). After incubation for 10 min, 50 μL naphthylethylenediamine dihydrochloride (12.5mM) was added and incubated for further 30 min, centrifuged for 10 min at 1000g. The absorbance at 540 nm was immediately recorded. The concentration of nitric oxide (μmol) in serum was calculated from the best fit line equation of the standard curve using lithium nitrate, a nitric oxide donor, as standard.

Statistical Analysis

The results were expressed as absolute number, percent, mean ± SD. The data were analyzed using Student's "t" test (one paired, two tailed) and simple correlation test taking the $p \leq 0.05$ as lowest limit of significance.

Results

A total number of 182 patients (73 male and 109 female) were involved in the study. The patients were sub-grouped according to their ages into 4 groups (Table 1). The body mass index of patients aged more than 30 years indicated that those patients were overweight. The most common frequent symptoms and signs were abdominal distention, abdominal pain, flatus and diarrhea in all age groups. Extra-intestinal manifestations included signs of iron deficiency anemia (koilonychias), nutritional deficiency (angular stomatitis), dermatological changes (skin lesions, alopecia), menstrual disturbances (11%) and male infertility (9.6%) (Table 1) were also observed. Diabetes mellitus and Sjogren's syndrome were associated in 3.3% (6 out of 182) and 4.9% (9 out of 182) respectively (Table 1). High systolic (≥ 140 mmHg) and diastolic (≥ 90 mmHg) blood pressures were observed in 11.5 and 17% respectively. Hematological indices revealed abnormal low MCHC levels and within normal range of mean white cell count of whatever (Table 2). Biochemical tests including the mean level of serum albumin, fasting glucose, creatinine and blood nitrogen urea were within normal values. Ejection fraction (%) was within normal value in all celiac patients. Serum malondialdehyde level, a biomarker of lipid peroxidation process, was significantly higher in CD patients than corresponding level of healthy subjects (Table 3). Reactive nitrogen species including serum nitric oxide and peroxynitrite were significantly higher than corresponding values of healthy subjects (Table 3). These mean values tended to increase with the age increased.

Discussion

The results of this study demonstrate that there are no significant differences in the clinical presentation, hematological indices and biochemical testing in respect to the age-onset of CD. Both nitrosative stress and lipid peroxidation processes are activated in CD at any age of CD onset.

The cardiovascular risk factors in this study are: high BMI and hypertension in patients aged ≥ 31 years while the ejection fraction is stable and within normal value in all studied groups. The association between CD and heart diseases is not clearly established [20-22]. Several reports indicated a higher CD prevalence among patients with idiopathic dilated cardiomyopathy and myocarditis [23,24]. The ejection fraction, in CD patients with cardiac involvement, may be so low that required cardiac transplantation as mentioned by Chicco et al. who demonstrated that patients treated with gluten free diet with worst left ventricular ejection fraction managed by cardiac transplantation [25]. The findings of this study do not demonstrate clinical or echocardiographic evidence that indicate cardiac disease. In one case report, chronic hypocalcaemia due to CD causes irreversible heart failure and abnormal ECG findings as a result of dilated cardiomyopathy [26]. This study does not demonstrate clinical evidence of myocarditis or dilated cardiomyopathy, therefore, the ejection fraction is within normal percent. This observation is not due to the effect of gluten free diet because these results obtained from newly diagnosed CD.

In this study, the elevated serum biomarkers of nitrosative stress found in this study are in agreement with other studies that which report significant increase of urinary nitrates and postulated the role of nitrogen species as a pathogenetic feature of CD. Children with symptomatic, untreated CD and with screening-detected CD have increased levels of NO oxidation products in their urine [27]. Median

	(n=52)	(n=59)	(n=27)	(n=44)
Age group (year)	4-10	10.1-20	20.1-30	> 30
Age (year)	7.16 ± 1.73	14.18 ± 2.63	24.45 ± 2.96	42.66 ± 8.17
Gender (M:F)	24:28	19:40	15:12	15:29
Height (m)	1.017 ± 0.11	1.34 ± 0.17	1.58 ± 0.12	1.50 ± 0.14
Weight (kg)	17.81 ± 2.98	35.03 ± 11.14	57.37 ± 10.43	55.3 ± 7.47
BMI (kg/m^2)	17.45 ± 3.2	19.2 ± 2.82	22.87 ± 3.03	25.08 ± 5.79
Gastrointestinal signs and symptoms				
Oral ulceration	3(5.8)	1(1.7)	0(0)	4(9.1)
Vomiting	10(19.2)	11(18.6)	4(14.8)	3(6.8)
Dyspepsia	6(11.5)	4(6.8)	1(3.7)	6(13.6)
Diarrhea	8(15.4)	8(13.6)	8(29.6)	8(18.2)
Constipation	3(5.8)	15(25.4)	4(14.8)	1(2.3)
Abdomen distension	18(34.6)	8(13.6)	8(29.6)	14(31.8)
Abdomen pain	20(38.5)	16(27.1)	11(40.7)	14(31.8)
Flatus	25(48.1)	13(22)	15(55.6)	30(68.2)
Extraintestinal manifestations				
Fatigue	18(34.6)	7(11.9)	6(22.2)	8(18.2)
Skin lesions	1(1.9)	2(3.4)	2(7.4)	4(9.1)
Koilonychia	3(5.8)	0(0)	3(11.1)	1(2.3)
Hair loss	2(3.8)	12(20.3)	2(7.4)	7(15.9)
Angular stomatitis	2(3.8)	3(5.1)	1(3.7)	0(0)
Teeth loss	4(7.7)	5(8.5)	3(11.1)	3(6.8)
Joints pain	3(5.8)	7(11.9)	1(3.7)	2(4.5)
Menstrual disturbances	0(0)	5(8.5)	3(11.1)	4(9.1)
Infertility Associated diseases	0(0)	3(5.1)	2(7.4)	2(4.5)
Diabetes mellitus	1(1.9)	2(3.4)	1(3.7)	2(4.5)
Sjogren's syndrome	1(1.9)	3(5.1)	2(7.4)	3((6.8)
Systolic blood pressure (≥ 140 mmHg)	6(11.5)	4(6.8)	3(11.1)	8(18.2)
Diastolic blood pressure(≥90 mm Hg)	6(11.5)	9(15.3)	4(14.8)	12(27.3)
Ejection fraction (%)	60.6 ± 7.3	67.5 ± 5.03	63.74 ± 5.18	62.16 ± 5.18

The results are expressed as number (%) and as mean ± SD.

Table 1: Characteristics and the clinical presentations of celiac disease patients.

	(n=52)	(n=59)	(n=27)	(n=44)
Age group (year)	4-10	10.1-20	21-30	> 30
Hematological indices				
Hemoglobin (g/dl)	11.54 ± 1.81	11.6 ± 1.67	11.87 ± 2.35	11.82 ± 1.58
MCV (µm^3)	83.01 ± 6.42	82.86 ± 8.84	83.15 ± 9.07	84.2 ± 5.35
MCH (pg)	28.86 ± 3.54	29.27 ± 3.43	28.41 ± 4.5	30.07 ± 3.36
MCHC (g/dl)	23.07 ± 5.67*	23.57 ± 5.80*	23.33 ± 6.73*	24.95 ± 5.58*
White cell count (per mm^3)	7820 ± 2141	8031 ± 1954	8837 ± 2633	8064 ± 2393
Blood platelet count(per mm^3)	259103 ± 76972	239114 ± 73166	258214 ± 67447	240489 ± 83885
Blood urea (mmol)	5.18 ± 1.31	5.27 ± 1.27	5.43 ± 1.29	5.11 ± 0.95
Serum creatinine (µmol)	87.14 ± 16.45	88.16 ± 16.97	94.41 ± 17.58	90.68 ± 15.47
Fasting serum glucose (mmol)	5.54 ± 1.21	5.61 ± 1.75	5.03 ± 1.32	5.35 ± 1.96
Serum albumin (g/L)	43.78 ± 7.38	36.30 ± 7.0	39.51 ± 7.38	39.59 ± 7.60

The results are expressed as mean ± SD. * significantly differed from reference value. The reference values are: hemoglobin (female 11.5-15.5 g/dl, male 14-18 g/dl), MCV 76-98 µm, MCH 27-35pg, MCHC31-35 pg/dl, White cell count 4000-10000 cells per mm^3, Blood platelet count 150000-400000 per mm^3, Blood urea 2.5-6.6 mmol/L, serum creatinine 55-120 µmol, Fasting serum glucose 3.6-5.8 mmol, Albumin 36-47 g/L.

Table 2: Laboratory investigations.

urine NO level was doubled and significantly higher after 4 weeks of oral gluten challenge and it positively correlated with endomysium antibodies [28]. Children with CD on a gluten-free diet for 1 year displayed a reduction in urinary nitrite/nitrate [29]. Previous studies did not measure or assess the peroxynitrite free radical as this study and our findings document the role of nitrative stress syndrome in this disease. Significant higher level of MDA reported in this study is in agreement with other studies which, carried out in CD children, confirmed that CD is associated with oxidative damage [12,13,27]. There is evidence that gluten ingestion induced an increased oxidative stress due to overproduction of free radicals: reactive oxygen and nitrogen species [30]. This study adds further information about overproduction of free radicals in adult CD. We can conclude that the clinical presentation, biochemical findings, cardiac assessment and overproduction of reactive oxygen and nitrogen species follow the same pattern at any age onset of newly diagnosed CD. The significant

	Healthy subjects	Celiac disease patients			
Number	20	(n=52)	(n=59)	(n=27)	(n=44)
Age group (year)	22-40	4-10	10.1-20	20.1-30	≥ 30
Serum malondialdehyde (µmol)	0.564 ± 0.217	2.05 ± 0.86*	2.18 ± 0.14*	2.22 ± 0.82*	2.15 ± 0.92*
Serum nitric oxide (µmol)	74.92 ± 24.08	118.5 ± 0.62*	130.0 ± 22.5*	142.0 ± 24.3*	146.5 ± 21.0*
Serum peroxynitrite (µmol)	1.903 ± 0.66	9.7 ± 1.96*	9.93 ± 4.0*	10.34 ± 3.4*	11.20 ± 4.2*

The results are expressed as mean ± SD. * p<0.001 compared with healthy subjects

Table 3: Assessment of reactive nitrogen species and lipid peroxidation in celiac disease patients.

high levels of reactive oxygen and nitrogen species are observed in newly diagnosed celiac disease.

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