

Lipid profile, atherogenic indices, and their relationship with epicardial fat thickness and carotid intima–media thickness in celiac disease

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ABSTRACT

OBJECTIVE: In this study, we aimed to investigate the presence of subclinical atherosclerosis by measuring epicardial fat thickness (EFT) and carotid intima–media thickness (cIMT), evaluate low-level inflammation with high-sensitivity C-reactive protein (hsCRP), and evaluate whether there is a relationship among lipid profile, atherogenic indices, and hsCRP with these subclinical atherosclerosis markers in patients with celiac disease (CD).

METHODS: After exclusion and inclusion criteria were applied, 31 patients with CD (24 female, mean age: 39.4±12.3 years) and 32 healthy controls (21 female, mean age: 39.5±4.4 years), totally 63 cases, were recruited. Subclinical atherosclerosis was evaluated with EFT by transthoracic echocardiography and cIMT by ultrasonography. Inflammatory markers including erythrocyte sedimentation rate (ESR), hsCRP, and lipid profile were recorded. Also, atherogenic indices were calculated: Castelli risk index I and II (TG/HDL-c and LDL-c/HDL-c, respectively), atherogenic index of plasma (AIP; logarithm TG/HDL-c), non-HDL-c (TG-HDL-c), and atherogenic coefficient (AC; non-HDL-c/HDL-c).

RESULTS: EFT was significantly higher in the CD group (0.49±0.10 vs. 0.49±0.09; p-value: 0.02). Although cIMT was higher in the patient group, it did not reach statistical significance (0.51±0.08, 0.47±0.08; p-value: 0.10). HDL cholesterol level was found to be significantly lower (42.0±8.8 vs. 50.0±13.7; p-value: 0.01), and the plasma atherogenic index was found to be significantly higher in the patient group (0.98±0.50 vs. 0.62±0.64; p-value: 0.02). hsCRP (3.51±3.18 vs. 1.92±1.40; p-value: 0.02) and ESR (17.2±12.8 with 9.7±3.1; p-value: 0.01) were found to be significantly higher in the CD group. Although there was a significant positive correlation between EFT and hsCRP (r: 0.453; p-value: 0.01), there was a significant negative correlation between cIMT and HDL-cholesterol (−0.339; p-value: 0.05), and a significant positive correlation with the other components of the atherogenic index was found.

CONCLUSION: The risk of atherosclerosis has been increased in patients with CD. Chronic inflammation may be responsible for this increase along with atherogenic indices.

Keywords: Atherogenic dyslipidemia; celiac disease; cIMT; epicardial fat thickness.

Cite this article as: Caliskan Z, Demircioglu K, Sayar S, Kahraman R, Caklili O, Ozcan FB, et al. Lipid profile, atherogenic indices, and their relationship with epicardial fat thickness and carotid intima–media thickness in celiac disease. *North Clin Istanbul* 2019;6(3):242–247.

Received: November 02, 2018 Accepted: January 09, 2019 Online: September 02, 2019

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Atherosclerotic heart disease is the leading cause of morbidity in Western population [1]. Recently due to altering nutritional conditions and dietary habits of developing countries, an increase in cardiovascular mortality has been observed in Turkey as well [1, 2]. A novel study has reported a multifactorial interaction between inflammation and development, and progression and rupture of plaque in atherosclerotic lesions [3]. In this context, it is assumed that atherosclerosis is an immune-inflammatory disease [3, 4]. Also, in most of the patients with acute coronary syndrome, there is an increase in high-sensitivity C-reactive protein (hsCRP), which is a marker of inflammation, and it is reported that hsCRP is a prognostic marker for future cardiovascular events [5]. There is an increase in cardiovascular disease in chronic inflammatory diseases such as ankylosing spondylitis, rheumatoid arthritis, and inflammatory bowel diseases. Subclinical inflammation was held responsible for increase of cardiovascular diseases in these immune-inflammatory conditions, which do not possess conventional cardiovascular risk factors [6–8]. Celiac disease (CD) is an autoimmune disease in which genetically susceptible persons develop antibodies against gluten (gliadin) protein [9]. The disease is characterized with chronic inflammation of proximal segment of small intestine [9]. It also affects other organs and tissues. Some recent studies have reported that CD causes endothelial damage and susceptibility to atherosclerosis [10, 11]. However, in these studies, there are no data to explain the pathogenesis of cardiovascular heart disease risk.

Epicardial fat tissue is an active visceral fat tissue which itself is an endocrine organ. It is well known that epicardial fat tissue thickness (EFT) measured with echocardiography has a significant association with low level of inflammation and subclinical atherosclerosis [12]. Also, carotid intima-media thickness (cIMT) assessed with ultrasound is a marker of early-stage atherosclerotic disease [7].

Atherogenic lipid profile is defined as an increase in serum total cholesterol, low-density lipoprotein cholesterol (LDL-c), and triglycerides (TG), and a decrease in high-density level (HDL-c) cholesterol [13]. Some studies have stated that HDL cholesterol levels are lower in patients with CD compared to healthy controls. Other studies have suggested that Castelli risk index I and II (TG/HDL-c and LDL-c/HDL-c, respectively), plasma atherogenic index (PAI; logarithm TG/HDL-c), non-HDL-c (TG-HDL-c), and atherogenic coefficient (AC; non-HDL-c/HDL-c) indices are more

sensitive in predicting atherosclerotic cardiovascular heart disease risk [13–15].

In this study, we aimed to investigate the presence of subclinical atherosclerosis by measuring EFT and cIMT, evaluate low-level inflammation with hsCRP, and evaluate whether there is a relationship between atherogenic indices and hsCRP with these subclinical atherosclerosis markers in patients with CD.

MATERIALS AND METHODS

Study population

The study was conducted in compliance with Helsinki declaration 1967. Patient consents were obtained from each subject. Inclusion criteria of the study included positive serologic testing for CD (anti-tissue transglutaminase (tTG) or anti-endomysium antibody (EMA)) and confirmation of the diagnosis with endoscopic biopsy (MARSH score) was required. Patients who fulfilled these criteria were advanced to cardiovascular examination and medical history with 12-derivative standard EKG work-up. Patients with angina pectoris were evaluated using a treadmill test and patients with positive test results were excluded. Other exclusion criteria were: active smoking, morbid obesity (body mass index >35 kg/m²), pregnancy, diabetes, another immune or inflammatory diseases besides CD and hypertension (patients under hypertensive treatment or with blood pressure $>140/90$ mmHg). Patients with liver disease, renal disease, cardiovascular, or cerebrovascular disease history (myocardial infarction, transient ischemic attack, or stroke) were also excluded. After exclusion criteria and inclusion criteria were applied, 31 patients with CD (24 female, mean age: 39.4 ± 12.3 years) and 32 healthy controls (21 female, mean age: 39.5 ± 4.4 years), totally 63 cases, were recruited. Age, sex, body mass index (BMI), heart rate, and blood pressure of the patients were recorded. Sedimentation, hsCRP, complete blood count, renal function tests, and immune disease diagnostic tests were evaluated. Blood lipid profile and blood glucose levels of all subjects were assessed after 12-hours fasting. Atherogenic indices were calculated as previously described [15]. Written informed consents were obtained from each subject. The institutional ethics committee approved the study protocol.

Imaging Techniques

Echocardiographic evaluations (EFT measurement)

Echocardiographic evaluation was performed by a clin-

ical data-blind, experienced cardiologist with a 'S5-1 probe Philips EPIQ/G, Bothell, WA' device. EFT was defined as non-echogenic spaces between epicardial layers in two-dimensional imaging. EFT was recorded from parasternal long- and short-axis windows, free wall of right ventricle, end diastolic, and through three cardiac cycles. Maximal measurements from each site were recorded and their mean was calculated.

Ultrasonographic evaluation (carotid intima-media measurement)

cIMT was measured with a high-resolution 7.5 MHz linear ultrasound probe (Hitachi EUB 6500, Osaka, Japan, device compatible). Measurements were performed with two-dimensional ultrasound imaging from internal carotid artery and 10 mm far from carotid artery bifurcation. To minimize the effect of arterial compliance on results, measurements were performed with EKFG monitorization and with peak-R wave match (to correlate with the stage of cardiac cycle) [7, 16]. In every session, measurements were made from three sites. Mean cIMT is defined as the mean of six measurements in two different sessions. To test the repeatability coefficient of EFT and cIMT, measurements of 10 subjects from the control group were repeated. Coefficients were found as 0.920 for EFT and 0.952 for cIMT.

Statistical Analysis

All analyses were performed with SPSS 9.0 (SPSS for Windows 9.0, Chicago, IL). Variables were expressed as mean±standard deviation. Student's t-test was used for comparison of two groups. Pearson correlation analysis was used to test the relationship between EFT and cIMT. Multivariate linear regression model was used to test independent predictors of EFT.

RESULTS

Clinical Characteristics of the Study Population

Clinical features and laboratory results of the patient and control groups are summarized in Table 1. Age, gender, BMI, systolic and diastolic blood pressures, heart rate, fasting blood glucose, serum urea nitrogen, and creatinine levels were similar between groups. There was no significant difference between groups in terms of lipid panel, which includes total cholesterol, triglycerides, LDL cholesterol, non-HDL cholesterol, Castelli risk index I, II, and atherogenic coefficient,

TABLE 1. Demographic and biochemical characteristics of patients with celiac disease and control subjects

	Celiac disease (n=31)	Control group (n=32)	p
Age (years)	39.4±12.3	39.5±4.4	0.84
Gender female/male (n/n)	24/7	21/11	0.30
Body mass index (kg/m ²)	24.8±4.2	24.7±4.3	0.97
Systolic BP (mmHg)	119.7±9.1	118.7±8.7	0.64
Diastolic BP (mmHg)	75.5±5.2	77.0±5.7	0.26
Heart rate (beat/minute)	72.9±3.7	74.1±10.9	0.54
Fasting plasma glucose (mg/dl)	93.1±6.7	90.9±6.0	0.18
BUN (mg/dl)	19.9±7.1	18.3±4.9	0.30
Creatinine (mg/dl)	0.67±0.19	0.64±0.14	0.44
Total cholesterol (mg/dl)	180.4±24.6	186.4±31.2	0.40
Triglycerides (mg/dl)	119.1±44.8	108.4±51.1	0.14
HDL cholesterol (mg/dl)	42.7±8.8	50.0±13.7	0.01
LDL cholesterol (mg/dl)	113.0±20.9	115.7±27.3	0.65
Non-HDL cholesterol (mg/dl)	76.3±49.5	50.8±57.5	0.06
Castelli risk index I	3.00±1.54	2.26±1.54	0.06
Castelli risk index II	2.76±0.83	2.46±0.86	0.17
Atherogenic index of plasma	0.98±0.50	0.62±0.64	0.02
Atherogenic coefficient	1.20±1.22	1.27±1.54	0.85
Hemoglobin (mg/dl)	13.1±1.1	14.0±1.1	0.22
hsCRP (mg/l)	3.51±3.18	1.92±1.40	0.02
ESR (mm/h)	17.2±12.8	9.7±3.1	0.01
Disease duration (years)	5.1±5.4	n/a	n/a
EFT (cm)	0.49±0.10	0.43±0.09	0.02
cIMT (cm)	0.51±0.08	0.47±0.08	0.10*

*Non-parametric test (Mann-Whitney U). BP: Blood pressure; BUN: Blood urea nitrogen; HDL: High-density lipoprotein; LDL: Low-density lipoprotein; hsCRP: High-sensitivity C-reactive protein; ESR: Erythrocyte sedimentation rate; EFT: Epicardial fat thickness; cIMT: Carotid intima-media thickness; atherogenic coefficient: non-HDL-c/HDL-c; atherogenic index of plasma: log TG/HDL-c; Castelli risk index I: TC/HDL-c; Castelli risk index II: LDLc/HDL-c; non-HDL-c: TC-HDL-c.

whereas HDL cholesterol was found to be significantly lower (42.7±8.8 vs. 50.0±13.7; p-value: 0.01) and plasma atherogenic index was significantly found to be higher (0.98±0.50 vs. 0.62±0.64; p-value: 0.02) in the patient group. hsCRP (3.51±3.18 vs. 1.92±1.40; p-value: 0.02) and ESR (17.2±12.8 with 9.7±3.1; p-value: 0.01) were found to be significantly higher in the CD group and EFT was significantly higher in the CD group (0.49±0.10 vs. 0.43±0.09; p-value: 0.02). Although cIMT was higher in the patient group, it did not reach statistically significant levels (0.51±0.08 vs. 0.47±0.08; p-value: 0.10).

TABLE 2. Correlations between EFT and cIMT and other study variables

	EFT		cIMT	
	r	p	r	p
Age (years)	-0.096	0.61	0.016	0.93
Systolic BP (mmHg)	-0.189	0.31	-0.242	0.19
Diastolic BP (mmHg)	-0.111	0.55	-0.108	0.56
hsCRP (mg/dl)	0.453	0.01	-0.068	0.71
HDL- cholesterol (mg/dl)	0.179	0.33	-0.339	0.05
LDL- cholesterol (mg/dl)	-0.124	0.50	0.362	0.04
Triglyceride (mg/dl)	-0.119	0.52	0.506	0.004
Triglyceride/HDL-c ratio	-0.082	0.66	0.473	0.007
LDL-c/HDL-c ratio	-0.162	0.38	0.444	0.01
Log Triglyceride/HDL-c ratio	-0.082	0.66	0.473	0.007
Non-HDL-c (mg/dl)	-0.097	0.60	0.504	0.004
Non-HD-c/LDL-c ratio	0.117	0.53	0.187	0.31

EFT: Epicardial fat thickness; cIMT: Carotid intima-media thickness; BP: Blood pressure; hsCRP: High-sensitivity C-reactive protein; HDL-c: High-density lipoprotein cholesterol; LDL-c: Low-density lipoprotein cholesterol; ESR: Erythrocyte sedimentation rate; atherogenic coefficient: non-HDL-c/HDL-c; atherogenic index of plasma: log TG/HDL-c; Castelli risk index I: TC/HDL-c; Castelli risk index II: LDL-c/HDL-c; non-HDL-c: total cholesterol-HDL-c.

Correlation Analysis Between cIMT and EFT and Other Variables

While there was a significant positive correlation between EFT and hsCRP ($r: 0.453$; p -value: 0.01), no relation was found between EFT and other variables. On the other hand, there was a negative correlation between cIMT and HDL-cholesterol (-0.339 ; p -value: 0.05) and a positive correlation with the other components of the atherogenic indices (Table 2).

Multiple regression analysis was performed to determine the independent predictors of the increase in EFT. When EFT was taken as an independent variable and for diagnosis of CD, hsCRP, BMI, triglycerides, LDL, and HDL-cholesterol values were considered as dependent variables, and the presence of CD was determined as an independent predictor for the increase in EFT ($\beta: 0.060$; $p=0.03$; Table 3).

DISCUSSION

This study showed that in patients with CD and without coronary heart disease risk factors, (i) EFT has increased statistically; however, although cIMT has shown

TABLE 3. Multivariate predictors of increased EFT in the study population

	B	SE (B)	p
Intercept	0.310	0.157	0.001
Celiac disease	0.060	0.028	0.03
HsCRP (mg/dl)	0.014	0.001	0.17
Body mass index (kg/m ²)	0.001	0.004	0.25
Triglyceride (mg/dl)	0.001	0.001	0.41
LDL-c (mg/dl)	0.001	0.001	0.66
HDL-c(mg/dl)	0.002	0.001	0.24

hsCRP: High-sensitivity C-reactive protein; LDL-c: Low-density lipoprotein cholesterol; HDL-c: High-density lipoprotein cholesterol.

an increase, it is not statistically significant, (ii) there is an increase in atherogenic indices of patients with CD including lipid parameters, ESR, and hsCRP compared to controls, and (iii) there is a close relationship between subclinical atherosclerosis markers, such as EFT and cIMT, and inflammatory markers.

It has been reported that in immune diseases, the atherosclerotic process progresses [6–8, 11]. Among coronary risk factors, chronic systemic inflammation itself can be the main culprit [11]. A recent study by Baena-Díez JM et al. has reported that in immuno-inflammatory diseases, the risk of cardiovascular events increases significantly [17]. Yarur et al. observed that the risk of ischemic heart disease increases in inflammatory bowel diseases [18]. CD is a chronic autoimmune enteropathy, which is induced by gluten containing diet in genetically susceptible persons [9, 11]. The proximal segment of small intestine is the primary target organ [9]. Nevertheless, the autoimmune nature of CD has targeted other organ systems including the cardiovascular system [10, 11, 19]. Gluten enteropathy is characterized with villus atrophy, crypt hyperplasia, and increased lymphocyte infiltration [19]. The intestinal epithelial layer is infiltrated by CD 8+ T cells intensely and triggers enterocyte apoptosis in epithelial tissues [19, 20]. Exposure to gluten-containing foods activates CD8 T lymphocytes in peripheral circulation and clusterization in intestinal tissues [21]. For gliadin protein to be recognized by CD 8+ lymphocytes, it has to be presented by epithelial tissues. In this process, CD8+ T lymphocytes secrete interferon (IFN) gamma [22]. Also, intestinal microbiota contributes to activation of CD8+ T cells [23]. It has been proved that IFN gamma increases intestinal per-

meability and plays an important role in the inflammatory process by increasing gluten peptide translocation [24]. This inflammatory process is responsible for pathogenesis of the disease and it can also be related to the atherosclerotic process.

Recent studies have pronounced the relationship between atherosclerosis and inflammation more strongly. EFT and cIMT have been designed as non-invasive, easily repeatable and applicable, cost-efficient methods to assess atherosclerosis. This is the first study to evaluate cardiovascular risk assessment with EFT in patients with CD. Along with its mechanic-shield effect, epicardial fat tissue has paracrine and metabolic features, which play a role in the development of atherosclerosis [25, 26]. This tissue is the production site for various proinflammatory cytokines including interleukin 6, TNF alpha, and leptin. This tissue is adjacent to coronary arteries and this neighborhood can initiate a paracrine inflammatory effect to enhance the development of atherosclerosis. Also secretion of inflammatory cytokines can also cause a systemic inflammatory effect [25, 26]. In this study, although we have not assessed inflammatory mediators such as interleukin 6 and TNF alpha, the close relationship between hsCRP and EFT supports our hypothesis, which underlines the role of inflammation in atherosclerosis.

In our study, another important finding was the statistically insignificant increase of cIMT in patients compared to controls, decrease in HDL cholesterol, and increase in TG/HDL cholesterol levels, which can be expressed as an atherogenic index. A close relationship between cIMT and atherogenic indices was observed. Ciacci et al. reported hypercholesterolemia in newly diagnosed gluten-unrestricted patients, but this has not been proven with other studies (probably due to recruitment of more subclinical patients with CD) [27, 28]. On the contrary, it has been proposed that low HDL cholesterol can be a manifestation of CD [29]. In our study, HDL cholesterol levels were significantly lower in patient cohort, compatible with the current literature. These changes can be attributed to malabsorption of lipids and/or decrease in Apo A1 secretion [27–29].

cIMT and EFT are important subclinical markers of atherosclerosis and represent early-stage cardiovascular disease [7, 12, 16]. HDL cholesterol has a strong antioxidant capacity as well as an ability to transfer cholesterol molecules to tissues for degradation [30]. Oxidative modification of LDL cholesterol has a key role in pathogenesis of atherosclerosis. Oxidized LDL can initiate the

atherosclerotic process and speed disease progression [31]. Along with low HDL cholesterol levels, the oxidative stress caused by CD causes imbalance between oxidants and anti-oxidants, thus causing lipid membrane oxidation. This situation can also cause direct toxic effects on endothelial and smooth muscle cells [32]. In this context, some studies have reported that gliadin protein can have particles which can trigger oxidative stress as well as proinflammatory cytokine release [32, 33]. It has been observed that some gliadin peptides can accumulate in lysosomes [31–33] and increase free radical levels [34, 35]. Another cause for increased atherosclerosis risk in CD can be oxidative modification of LDL cholesterol by gliadin peptides.

Conclusions

This study shows that CD causes predisposition to subclinical atherosclerosis by increasing EFT and cIMT. The fact that there is a close relationship between the increase in ET and cIMT suggests that in these patients, inflammation of the disease may have a role in the atherosclerotic process.

Along with conventional lipid panels, evaluation of atherosclerotic index can help identify atherosclerosis risk.

Ethics Committee Approval: The Ethics Committee of Istanbul Medeniyet University provided the ethics committee approval for this study (Date: 12.09.2018 Number: 2018/0343).

Conflict of Interest: Each and every author does not have any personal or financial relationships that have any potential to inappropriately influence (bias) his or her actions or manuscript.

Financial Disclosure: No financial or other potential conflicts of interest exist (includes involvement with any organization with a direct financial, intellectual, or other interest in the subject of the manuscript) regarding the manuscript. In addition, there are no any grants and sources of financial support related to the topic or topics of the manuscript.

Authorship Contributions: Concept – ZC, MC; Design – ZC, MC, SS; Supervision – HLD; Materials – KD, RK; Data collection and/or processing – FBO, OK, OFB; Analysis and/or interpretation – OK, OC, HLD; Writing – OC, MC; Critical review – HLD, RK.

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