Increased YKL-40 levels in patients with isolated coronary artery ectasia: an observational study

İzole koroner arter ektazili hastalarda artmış YKL-40 düzeyleri: Gözlemsel bir çalışma

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ABSTRACT

Objective: YKL-40, a new biomarker of localized inflammation, is secreted by macrophages within the atherosclerotic plaques. Coronary artery ectasia (CAE) is a clinical entity with unclear etiopathogenesis. Some studies have revealed that CAE may be a form of atherosclerosis that has more localized and intense inflammatory properties than atherosclerosis. The goal of this study was to investigate YKL-40 and C-reactive protein (CRP) levels in patients with isolated CAE compared to patients with normal coronary arteries (NCA) and coronary artery disease (CAD).

Methods: Our study has an observational and cross-sectional design. Forty-nine patients with isolated CAE (mean age: 60±10 years), 30 age-and gender-matched control participants with NCA (30 patients, mean age: 58±12 years) and 30 patients with CAD (mean age: 61±10 years), were included in the study. The relationship between YKL-40, CRP levels and the presence of CAE was investigated. Univariate and multiple logistic regression analysis were used for analysis of independent variables to predict CAE.

Results: Serum YKL-40 levels were significantly different among study groups (NCA: 110±53 µg/L, CAE: 144±68 and CAD: 180±117, p=0.005). CAD group and CAE group had significantly higher YKL-40 levels than NCA group (p=0.004 and p=0.015, respectively). CRP was not significantly different between three groups. In addition, there were no any statistically significant differences, with respect to age, gender, the presence of hypertension or diabetes mellitus, and the smoking status (p>0.05). Logistic regression analysis revealed only YKL-40 level as the determinant of CAE (OR: 1.010, 95% CI: 1.001-1.019, p=0.027).

Conclusion: YKL-40 levels in patients with isolated CAE compared to patients with NCA were found significantly high and only YKL-40 level was established as the determinant of CAE. We believe that further studies are needed to clarify the possible causative roles of YKL-40 in patients with isolated CAE. *(Anadolu Kardiyol Derg 2013; 13: 465-70)*

Key words: Coronary artery ectasia, YKL-40, C-reactive protein; coronary angiography, systemic inflammation, positive remodeling, regression analysis

ÖZET

Amaç: YKL-40, yeni bir yerel enflamasyon biyobelirteci, aterosklerotik plaklar içerisinde makrofajlar tarafından salınırlar. Koroner arter ektazisi (KAE) etyopatogenezisi kesin olarak ortaya konulmamış klinik bir antitedir. Bazı çalışmalar KAE'nin aterosklerozdan daha yoğun ve lokalize enflamatuvar özelliklere sahip olabileceğini ortaya koydu. Bu çalışmanın amacı eş zamanlı olarak YKL-40 ve C-reaktif protein (CRP) düzeylerini izole KAE'li hastalarda araştırmak ve normal koroner arterli (NKA) veya koroner arter hastalığı (KAH) olan hastalar ile karşılaştırmak.

Yöntemler: Çalışmamız gözlemsel ve kesitsel bir düzene sahiptir. Kırk dokuz izole KAE'lı hasta (ort. yaş: 60±10 yıl) ve 30 yaş ve cinsiyet uyumlu NKA'lı birey (ort. yaş: 58±12 yıl) ve KAH'lı hasta (ort.yaş: 61±10 yıl) çalışmaya dahil edildi. YKL-40, CRP düzeyi ve KAE varlığı arasındaki ilişki araştırıldı. Tek değişkenli ve ardından çoklu lojistik regresyon analizi KAE'yi öngörmede bağımsız değişkenlerin analizinde kullanıldı.

Bulgular: Serum YKL-40 düzeyleri gruplar arasında anlamlı olarak farklıydı (NKA: 110±53 µg/L, KAE: 144±68 ve KAH: 180±117, p=0,005). KAH ve KAE grupları NKA grubuna göre belirgin daha yüksek YKL-40 düzeyine sahiptiler (p=0,004 ve p=0,015, sırasıyla). CRP üç grup arasında anlamlı olarak farklı değildi. Ek olarak, gruplar arasında yaş, cinsiyet, hipertansiyon, diyabet varlığı ve sigara içimi açısından da fark yoktu (p>0,05). Lojistik regresyon analizi yalnızca YKL-40 düzeyini KAE'nin bağımsız belirleyicisi olarak ortaya koydu (OR: 1,010, 95% GA: 1,001-1,019, p=0,027).

Sonuç: İzole KAE'li hastalarda YKL-40 düzeyleri NKA'lı hastalar ile karşılaştırıldığında anlamlı olarak yüksekti ve sadece YKL-40 KAE'nin bağımsız belirleyicisi olarak saptandı. İnanıyoruz ki, daha ileri çalışmalar izole KAE'li hastalarda YKL-40'ın olası nedensel rolünü netleştirmede gereklidir *(Anadolu Kardiyol Derg 2013; 13: 465-70)*

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Anahtar kelimeler: Koroner arter ektazisi, YKL-40, C-reaktif protein,koroner anjiyografi, sistemik enflamasyon, pozitif yeniden şekillenme, regresyon analizi

Introduction

Coronary artery ectasia (CAE) is a clinical entity characterized with localized or diffuse dilatation of the coronary arteries, greater than 1.5 times diameter of adjacent segments. The prevalence of isolated CAE has been reported as 1.2 to 4.9% in various studies (1, 2). Although the etiopathogenesis is not clearly understood; some studies have revealed that CAE may be a form of atherosclerosis that has more localized and intense inflammatory properties than atherosclerosis (3).

YKL-40, also known as chitinase-3-like-1 protein (CHI3L1), is a heparin and chitin binding glycoprotein and a member of the 'mammalian chitinase-like proteins (4, 5). YKL-40, an acute phase protein (6), is secreted by activated macrophages, neutrophils, chondrocytes, vascular smooth muscle cells, and cancer cells (5, 7-11). The molecular processes inducing YKL-40 and precise functions of YKL are still not identified. YKL-40 is closely related to both early and late phases of the atherosclerotic process. YKL-40 promotes maturation of monocytes to macrophages; afterwards YKL-40 gets secreted by macrophages during the late stages of differentiation and eventually by the activated macrophages (12-15).

We hypothesized that YKL-40 may be an important causative factor, related to the burden of localized inflammation in the coronary vessel wall. Since isolated CAE is thought to be a different form of atherosclerosis, YKL-40 may play a pathophysiological role in this entity. To date, no study has been performed to investigate the possible role of YKL-40 in CAE process.

Therefore, the goal of this study was to investigate YKL-40 and C-reactive protein (CRP) levels in patients with isolated CAE compared to patients with angiographically normal coronary arteries and coronary artery disease (CAD).

Methods

Study design

The present study was observational and cross-sectional. The relationship between YKL-40, CRP levels and the presence of CAE was investigated.

Study population

Study population included 109 individuals who underwent coronary angiography with a suspicion of CAD at the outpatient clinic of Rize Education and Research Hospital within 1 year. Forty-nine patients with isolated CAE, without any atherosclerotic lesion with visual assessment (mean age: 60±10 years), 30 age- and gender-matched control participants with normal coronary arteries (NCA) (mean age: 58±12 years) and 30 patients with CAD (mean age: 61±10 years), were included in the study.

Patients with significant organic valvular heart disease, malignancy, collagen vascular disease, chronic kidney and hepatic failure, pulmonary embolism and infectious diseases were excluded from the study.

Informed consent was obtained from all patients prior to the study. The study was performed in accordance with the principles stated in the Declaration of Helsinki and approved by the Local Ethics Committee.

Study protocol

All patients had chest pain or angina equivalent symptoms with either positive treadmill test or myocardial perfusion study. Clinical characteristics, which consisted of multiple descriptors from each patient's history and physical examination, were collected by physicians from the cardiology clinic, of each patient at the time of cardiac catheterization and were stored in the database of coronary angiography laboratory at our institution.

Patients with concomitant CAD were excluded in CAE and NCA group. The control group was selected in a consecutive manner, among the recently catheterized patients, during the study period. The cases with isolated CAE were evaluated by two experienced interventional cardiologists, totally blind to the study.

Routine laboratory measurements

Blood samples were drawn by venipuncture to measure routine blood chemistry parameters after fasting for at least 8 hours before coronary angiography. Fasting blood glucose, serum creatinine, total cholesterol, high-density lipoprotein (HDL) cholesterol, low-density lipoprotein (LDL) cholesterol, and triglyceride levels were recorded. Glucose, creatinine, and lipid profile were determined by standard methods. Serum CRP was analyzed using a nephelometric technique (Beckman Coulter Immage 800; Fullerton, CA, USA; normal range: 0-0.8 mg/dL).

YKL-40 measurement

Blood samples were centrifuged immediately, and serum specimens for YKL-40 were frozen at -20°C before analysis. Serum YKL-40 concentration was measured with enzyme immunoassay (EIA) method using the commercially available test MicroVue YKL-40 (Quidel, San Diego, CA, USA) according to the manufacturer's instructions. The range of the assay was 33-467 µg/L.

Coronary angiography

Coronary angiography was performed by a standard Judkin`s technique using the Allura Xper FD10 (Philips, Amsterdam, Netherlands) and 6-French right and left coronary catheters without the use of nitroglycerin. Coronary angiograms were recorded in right and left oblique planes using cranial and caudal angulations, with a rate of 30 frames/s. During coronary angiography, iopromide (Ultravist 370, Schering AG, Berlin, Germany) was used as the contrast agent in all patients and control participants.

Isolated CAE was defined as the localized or diffuse non-obstructive lesions of the epicardial coronary arteries with luminal dilatation exceeding 1.5 times of normal adjacent segment, without any atherosclerotic lesions through visual assessment (1, 2). When there was no identifiable adjacent normal segment, the mean diameter of the corresponding coronary segment in the control group served as the normal values.

Statistical analysis

The SPSS statistical software (SPSS for windows, version 15.0, Inc., Chicago, IL, USA) was used for all statistical calculations. Continuous variables are given as mean ± SD; categorical variables were defined as percentages. Data were tested for normal distribution using the Kolmogorov-Smirnov test. Mean values were compared by ANOVA followed by the Tukey HSD test among different groups. Logistic regression with stepwise method was used for multivariate analysis of independent variables. Presence of CAE was dependent variable; YKL-40 and other all were independent variables in our study. After exclusion of irrelevant variables from model, the regression with enter method were performed. Statistical significance was defined as $p<0.05$. All tests of significance were two-tailed.

Results

Clinical characteristics of the study population

The clinical characteristics of the study population are detailed in Table 1. There were no any statistically significant differences, between the three groups with respect to age, gender, the presence of hypertension or diabetes mellitus, and the smoking status ($p>0.05$).

YKL-40 and CRP concentrations in study groups

Serum YKL-40 levels were significantly different among study groups (NCA: 110±53 µg/L, CAE: 144±68 and CAD: 180±117, $p=0.005$). CAD group and CAE group had significantly higher YKL-40 concentrations than NCA group ($p=0.004$ and $p=0.015$, respectively) (Fig. 1). However, the difference between CAD and CAE groups was not statistically significant.

Serum CRP level was not significantly different between three groups. CRP had a limited correlation with YKL-40 ($r=0.239$, $p=0.016$).

Independent determinants of CAE

Logistic regression analysis revealed only YKL-40 level as the determinant of CAE (OR: 1.010, 95% CI: 1.001-1.019, $p=0.027$) (Table 2).

Table 1. Baseline characteristics of the study population

Variables	NCA (n=30)	Isolated CAE (n=49)	CAD (n=30)	*F	*p
Age, years	58±12	60±10	61±10	0.831	0.439
Gender, male, %	63	69	57	-	0.516
BMI, kg/m^2	29±4	32±7	30±5	2.458	0.091
Hypertension, %	43	63	60	-	0.216
Diabetes mellitus, %	11	22	27	-	0.298
Smoking, %	43	44	47	-	0.954
Hyperlipidemia, %	43	59	73	-	0.063
Family history of CAD, %	36	22	33	-	0.394
Glucose, mg/dL	109±34	108±36	112±31	0.155	0.857
Creatinine, mg/dL	0.79±0.11	0.89±0.21	0.90±0.29	2.158	0.121
Total cholesterol, mg/dL	190±32	187±41	203±43	1.622	0.203
LDL, mg/dL	118±27	116±31	131±39	2.051	0.134
HDL, mg/dL	43±10	41±13	43±11	0.692	0.503
Triglyceride, mg/dL	142±108	153±94	144±46	0.145	0.865
CRP, mg/dL	0.53±0.39	0.67±0.83	0.58±0.64	0.408	0.666
YKL-40, µg/L	110±53	144±68**	180±117***	5.494	0.005
Leukocytes, mm^{-3}	7529±1806	7149±1894	7466±2378	0.388	0.679
Neutrophils, mm^{-3}	4465±1367	4149±1490	4125±1785	0.478	0.622
Lymphocytes, mm^{-3}	2344±748	2251±1310	2484±803	0.437	0.647
Monocytes, mm^{-3}	530±175	525±215	619±250	1.969	0.145

Data are presented as mean±SD and percentage

*ANOVA followed by the posthoc Tukey HSD test and Chi-square test

Posthoc Tukey HSD test - **- p=0.015, ***-p=0.004

BMI - body mass index, CAD - coronary artery disease, CAE - coronary artery ectasia, CRP - C - reactive protein, HDL - high - density lipoprotein, LDL - low-density lipoprotein, NCA - normal coronary arteries

Table 2. The independent relationship of YKL-40 with coronary artery ectasia

N=79 (NCA+CAE)	CAE (Dependent variable)	*p
Variables	OR (95 CI)	
YKL-40, µg/L	1.010 (1.001-1.019)	0.027
Age, years	1.024 (0.969-1.082)	0.396
Gender, male	1.713 (0.435-6.745)	0.441
BMI, kg/m^2	1.087 (0.974-1.214)	0.136
Constant	0.006	0.079
Nagelkerke R Square	0.170	

*Logistic regression with stepwise method was used for multivariate analysis of independent variables including age, gender, BMI, HT, DM, smoking, family history of CAD, T.Chol, LDL, HDL, triglyceride, fasting plasma glucose, creatinine, CRP and leukocytes. After exclusion of irrelevant variables from model, the regression with enter method were performed and then obtained results are presented.

BMI - body mass index, CAD - coronary artery disease, CAE - coronary artery ectasia, CRP - C - reactive protein, DM - diabetes mellitus, HDL - high - density lipoprotein, HT - hypertension, LDL - low-density lipoprotein, NCA - normal coronary arteries, T. Chol - total cholesterol

Discussion

In the present study, we found significantly higher YKL-40 levels in patients with isolated CAE compared to patients with angiographically normal coronary arteries. YKL-40 concentrations were not different in patients with CAE and CAD.

Many different biomarkers were proposed to predict cardiovascular mortality and morbidity in vascular events. Systemic inflammation is one of these markers (16, 17). However, markers of systemic inflammation, particularly CRP, are influenced by many other factors, which include the general inflammatory response as well as atherosclerosis-related reaction. Therefore, systemic inflammation, a non-specific marker for atherosclerosis, does not indicate specific local inflammation at the tissue level, in a vascular event.

YKL-40, a poor prognostic sign in patients with heart failure, is also associated with the prognosis and extent of vascular involvement in patients with stable coronary artery disease (CAD) (18-20). In addition, increased levels of YKL 40 related to endothelial dysfunction, recurrent atrial fibrillation and cerebrovascular events (21-23).

There is still controversy regarding the mechanisms and reasons in the pathogenesis of CAE. The frequent coexistence of CAE with CAD and the histopathological findings resembling those of atherosclerosis have allowed to the conclusion that atherosclerosis may play a role in the pathogenesis, and CAE is a variant of atherosclerosis related to positive remodeling described as the enlargement of the area within the external elastic membrane. However, there are several unknown aspects, such as why some patients with CAD have CAE while most of the patients have not and why CAE is related to other pathological entities such as collagenosis, connective tissue diseases, and vasculitis. To date, YKL-40 as a pathophysiological mediator of CAE has not been identified. Therefore, the biological function of YKL-40 in CAE is unknown.

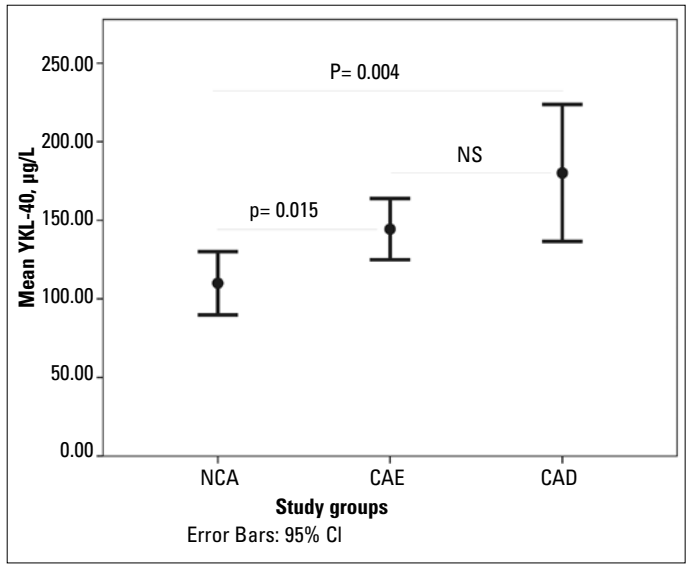

Figure 1. YKL-40 levels among coronary artery ectasia, normal coronary arteries and coronary artery disease groups

CAD - coronary artery disease, CAE - coronary artery ectasia, NCA - normal coronary arteries, NS - not significant
ANOVA with posthoc Tukey HSD test

In our study, the source of elevated serum levels of YKL-40 may probably be activated inflammatory cells within the coronary vessel wall. YKL-40, in order to protect the cells from apoptosis, may participate in proliferation and differentiation of cells, as a cellular survival factor (24). At the cellular level, YKL-40 may be induced to repair local damage and changes in the microenvironment. Increased serum YKL-40 levels may possibly represent the extent of specific local inflammation at the tissue level in the coronary arterial wall, and also the requirement for reparative mechanisms or even an over-expression of compensatory mechanisms in some patients. Another potential mechanism is that undefined systemic vascular wall abnormality may activate macrophages and in this way induce local specific inflammation and other vessel changes.

Local inflammation caused by infiltrating macrophages in the vessel wall plays a crucial role in the development of atherosclerosis (25) and CAE (26). YKL-40, after inducing the maturation of monocytes to macrophages, is secreted by macrophages during the late stages of differentiation and eventually by the activated macrophages (5, 12-15). Clinical studies revealed elevated YKL-40 levels particularly in diseases characterized with inflammation, extra-cellular remodeling and ongoing fibrosis (11). YKL-40 is also an adhesion and migration factor for vascular cells and is secreted by differentiated vascular smooth muscle cells (27-29).

Although the histopathological examinations of ectatic vessels have revealed similar findings as seen in atherosclerosis (30) it is not known exactly why connective tissue disorders (31, 32), infections (33), and Kawasaki (34) disease are related with CAE (35, 36). Studies on CAE etiology have all focused on vascular endothelium and the biological properties of the arterial wall. However the exact mechanism of abnormal luminal dilatation in CAE is still unknown. The histological examination of the ectatic

segments revealed diffuse atherosclerotic alterations and disruption of the vascular media layer (37).

In our study, CRP was not related to CAE. In this aspect, the known relation between CAD and CRP is different and the possible role of CRP on CAD appears to be invalid for CAE. Even though coronary ectasia has been related to inflammatory process, a recent study, comparing CAE patients with CAD and normal coronary angiograms also found similar CRP levels. In addition, former studies demonstrated conflicting results (38, 39) on CRP levels in patients with CAE (40).

Study limitations

This study was carried out in a relatively limited number of patients. In the current study, the patients did not undergo IVUS (intravascular ultrasonography) to detect whether there was a positive atherosclerotic remodeling in ectatic arteries. Hence, the coexistence of non-obstructive CAD (<40%) in patients with "isolated" CAE cannot be established absolutely. Nevertheless, in clinical practice, isolated CAE patients do not undergo IVUS routinely and coronary artery ectasia is usually diagnosed with visual assessment of coronary angiography. Other inflammatory cytokines except CRP might be searched to clarify possible causative mediators. Furthermore, circulating YKL-40 may not fully reflect the activity of YKL-40 at the tissue level.

Conclusion

In conclusion, to the best of our knowledge, this is the first study displaying increased serum YKL-40 levels without increased systemic inflammatory response in patients with isolated CAE. Although we cannot conclude the underlying pathologic process of CAE, we believe that these findings may be pivotal for further studies searching the specific roles of YKL-40 signaling on ectatic process in coronary vasculature.

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