Increased serum YKL-40 level is associated with the presence and severity of metabolic syndrome

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ABSTRACT

Objective: Metabolic syndrome (MS) is defined by a cluster of interdependent physiological, biochemical, and clinical risk factors and linked to a state of chronic inflammation. YKL-40 is known as an inflammatory glycoprotein, which is secreted by various cell lines during inflammation. Thus, we aimed to assess the association of serum YKL-40 levels with the presence and severity of MS.

Methods: In this prospective cross-sectional study, a total of 177 consecutive patients [n=114 MS present and n=63 MS absent] were enrolled. MS was defined according to National Cholesterol Education Program Adult Treatment Panel III (NCEP-ATP III) criteria. Serum YKL-40 and hs-CRP levels were measured for all participants.

Results: Serum YKL-40, hs-CRP and white blood cell count (WBC) were significantly higher in the MS present group (p<0.05). There was a graded relationship between increasing number of MS components and serum YKL-40 level (p<0.05). In addition, serum YKL-40 level was positively correlated with hs-CRP level (r=0.467, p<0.001) and WBC count (r=0.251, p=0.001). In multivariable regression analysis, serum YKL-40 [1.022 (1.011–1.033), p<0.001] and hs-CRP [1.346 (1.111–1.632), p=0.002] were remained as independent predictors for the presence of MS. In the ROC curve analysis, using a cut-off level of 147.0, YKL-40 well predicted the presence of MS with a sensitivity of 73.7% and specificity of 69.8% (AUC: 0.785; 95% CI: 0.718–0.853, p<0.001).

Conclusion: In this study, we demonstrated that serum YKL-40 level was significantly associated with the presence of MS. According to these findings, we concluded that serum YKL-40 may be a novel and useful indicator for MS. *(Anatol J Cardiol 2016; 16: 953-8)*

Keywords: metabolic syndrome, cardiovascular risk factors, hs-CRP, YKL-40, inflammation

Introduction

Metabolic syndrome (MS), an endocrinopathy, is characterized by enhanced insulin resistance which results in glucose intolerance or diabetes mellitus (DM), abdominal obesity, atherogenic dyslipidemia, hypertension, and increased inflammatory condition (1). In the current age, the prevalence of MS is growing because of increased living standards and it has been evidenced that each component of MS was significantly associated with increased risk for development of cardiovascular disease and mortality (2). The exact etiopathogenesis of MS is unclear yet. In recent decades, a significant role of inflammation in the pathophysiology of MS components has been demonstrated (3, 4). The levels of various proinflammatory biomarkers like high-sensitivity C-reactive protein (hs-CRP) and white blood cell (WBC) were increased in MS patients (5, 6). Such an increase in those proinflammatory biomarkers is also linked to higher risk for cardiovascular diseases (7).

YKL-40 is a kind of inflammatory glycoprotein which is produced by activated macrophages, neutrophils, chondrocytes, synovial cells and cancer cells (8–10). The biological role of YKL-40 is still not known in detail. It has been reported that serum YKL-40 levels were elevated in many pathological conditions proceding by inflammation and extracellular remodeling such as infections, asthma, diabetes mellitus, isolated coronary artery ectasia and both peripheral and coronary artery disease (11–15). Furthermore, it has been shown that high YKL-40 levels were significantly associated with cardiovascular and all-cause mortality in both patients with and without coronary artery disease CAD (16, 17).

To the best of our knowledge, no study has been performed to investigate the possible role of serum YKL-40 in adult patients with MS. Therefore, the aim of this study was to investigate the relationship between components/severity of MS and serum YKL-40 level, a novel and reliable indicator of inflammation.

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Methods

Study population

A total of 177 consecutive subjects [n=114 with MS and n=63 without MS] were prospectively recruited between March 2014 and September 2014 from our outpatient clinics of cardiology department. Metabolic syndrome was diagnosed according to the National Cholesterol Education Program Adult Treatment Panel III (NCEP-ATP III) criteria which requires presence of at least three of the following crirteria (1) systolic blood pressure ≥130 mm Hg or diastolic blood pressure ≥85 mm Hg or established treatment of already diagnosed hypertension; (2) fasting plasma glucose (FPG) ≥ 110 mg/dL or already diagnosed type 2 DM; (3) high-density lipoprotein (HDL) cholesterol levels <40 mg/dL in men and <50 mg/dL in women; (4) triglycerides (TG) ≥150 mg/dL or active treatment of dyslipidemia and (5) central obesity [waist circumference (WC) >102 cm for men and >88 cm for women] (18). Among all participants, the number of MS components (severity of MS) was evaluated as the presence of the previously described NCEP-ATP III criteria: DM (1 point), HT (1 point), HDL-cholesterol <40 mg/dL for men or <50 mg/dL for women (1 point), TG ≥150 mg/dL (1 point) and WC >102 or >88 cm (1 point). Scores ranging from 0 to 5 were obtained and increasing scores were correlated the severity of the MS. Baseline clinical demographic characteristics of study groups were reviewed. Height, weight, and WC were measured while fasting and in stand up position. Body mass index (BMI) was calculated by dividing body weight to height squared (kg/m^2). Smoking was defined as current smoking. All of the patients gave informed consent before enrollment. The study was approved by Institutional Ethics Committee.

Exclusion criteria were as following: documented coronary artery disease, any type cardiomyopathy, decompensated heart failure, significant valvular heart disease, peripheral vascular disease, acute or chronic kidney and/or liver disease, evidence of acute or chronic infection or inflammation, chronic obstructive lung disease, asthma, autoimmune disease, anemia, hematologic disease and any malignant disease.

Laboratory analysis

Blood samples for biochemiacal tests were collected after 12-h fasting. Centrifusion at a speed of 1600 bpm/min for 15 min were applied to blood samples immediately, and serum specimens for YKL-40 and hs-CRP measurements were separated and stored at −70°C before analysis. Serum YKL-40 concentration was measured by using ELISA kit provided from Quantikine R&D systems, Minneapolis, USA (Catalog Number DC3L10) according to the manufacturer's instructions and serum hs-CRP levels were determined using the immunoturbidimetric method. Other laboratory parameters were determined by standard methods.

Statistical analysis

Whether the parameters normally distributed or not was assessed with Kolmogorov-Smirnov test. Normally distributed vari-

ables were represented as mean±standard deviation and if not represented by the median and interquartile range. Categorical data were represented as number and percentage values. Student's t-test was used for comparison of parametric variables. Mann–Whitney U test was used for comparison of nonparametric variables. We performed chi-square (χ^2) test to compare the categorical variables. Pearson and Spearman rank tests were used to disclose the correlation between YKL-40, hs-CRP and severity (components) of MS. Model characteristics of discrimination and calibration were studied by receiver-operating characteristic (ROC) curves and Hosmer-Lemeshow goodness-of-fit tests. The ROC curve analysis was also used for determination of optimal cut-off value of YKL-40 for the prediction of the presence of MS. The independent predictors for the presence of MS were analyzed by using logistic regression analysis. Possible confounding factors were tested in univariable regression analysis and confounders with a p value of <0.25 were tested in multivariable logistic regression analysis. A probability value of less than 0.05 was considered the minimum level of statistical significance. In all statistical analysis SPSS 20.0 Statistical Package Program for Windows (SPSS Inc., Chicago, IL, USA) was used.

Results

Baseline clinical characteristics of the study groups were demonstrated in Table 1. Patients in the MS present group were more likely to be diabetes mellitus, hypertension and higher use of drugs including renin-angiotensin system (RAS) blocker, diuretic, calcium channel blocker, β-blocker, statin and oral antidia-

Table 1. Baseline clinical characteristics of the study population (n=177)

Parameters	MS absent (n=63)	MS present (n=114)	#P
Age, years	55.2±8.9	57.2±8.7	0.139*
Female gender, n (%)	47 (74.6)	86 (75.4)	0.902
Hypertension, n (%)	12 (19.0)	100 (87.7)	<0.001
Diabetes mellitus, n (%)	7 (11.1)	88 (77.2)	<0.001
Smoking, n (%)	5 (7.9)	17 (14.9)	0.178
WC, cm	88.8±12.1	108.1±11.2	<0.001*
BMI, kg/m^2	25.8±5.7	33.9±6.2	<0.001*
Medications, n (%)			
RAS blocker	12 (19.0)	77 (67.5)	<0.001
Diuretic	5 (7.8)	38 (33.3)	<0.001
CCC	4 (6.3)	26 (22.8)	0.005
β-blocker	4 (6.3)	20 (17.5)	0.037
ASA	5 (7.9)	22 (19.3)	0.044
Statin	3 (4.8)	21 (18.4)	0.011
Oral antidiabetic	3 (4.8)	62 (54.4)	<0.001

Data are given as mean±SD or %. ASA - acetylsalicylic acid; BMI - body mass index; CCC - calcium channel blocker; MS - metabolic syndrome; RAS - renin-angiotensin system; WC - waist circumference; #Chi-square test; *Student t test

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Table 2. Laboratory parameters of the study population

Parameters	MS absent (n=63)	MS present (n=114)	#P
Hemoglobin, g/dL	14.0±1.1	13.7±1.1	0.187
Platelet, 10^3/mm^3	251±61	267±70	0.139
WBC, 10^3/mm^3	7.2±1.4	7.8±1.6	0.009
Creatinine, mg/dL	0.72±0.15	0.75±0.17	0.330
Uric acid, mg/dL	4.4±1.3	4.7±1.4	0.145
Total cholesterol, mg/dL	180±40	202±46	0.002
HDL-cholesterol, mg/dL	53.7±12.4	43.9±9.1	<0.001
LDL-cholesterol, mg/dL	104.2±36.5	121.6±39.5	0.004
Triglyceride, mg/dL[a]	108 (78–148)	192 (148–250)	<0.001*
hs-CRP, mg/L[a]	0.6 (0.3–1.4)	2.9 (1.1–6.5)	<0.001*
YKL-40, ng/mL	129.2±34.6	174.1±43.0	<0.001

Data are given as mean±SD or %. HDL - high density lipoprotein; hs-CRP - high-sensitivity C-reactive protein; LDL - low density lipoprotein; MS - metabolic syndrome; WBC - white blood cell. [a]Median (interquartile range). #Student t test; *Mann–Whitney U test

Table 3. Pearson and Spearman correlation analysis of total metabolic syndrome score with potential continuous variables

Variables	R	#P
Platelet	0.176	0.019
Uric acid	0.199	0.008
LDL-cholesterol	0.249	0.001
White blood cell	0.208	0.006
hs-CRP	0.533	<0.001*
YKL-40	0.571	<0.001

r - correlation coefficient; hs-CRP - high-sensitivity C-reactive protein; LDL - low-density lipoprotein; #Pearson rank test; *Spearman rank test

betic when compared to the MS absent group (p<0.05). WC, BMI, serum total cholesterol, LDL-cholesterol and triglyceride levels were significantly higher, whereas serum HDL-cholesterol was significantly lower in the MS present group (p<0.05). Furthermore, serum YKL-40 (174.1±43.0 vs. 129.2±34.6 ng/mL, p<0.001), hs-CRP [2.9 (1.1–6.5) vs. 0.6 (0.3–1.4) mg/L, p<0.001] and WBC count (7.8±1.6 vs. 7.2±1.4 x 10^3/mm^3, p=0.009) were also significantly higher in the MS present group (Table 2). Additionally, there was a graded relationship between increasing number of MS components (severity of MS) and serum YKL-40 level (116.6±30, 133.4±36, 139.2±34, 150.4±39, 176.6±40, 195.8±39 ng/mL, respectively).

In correlation analysis, total number of MS components (severity of MS) showed a significantly positive correlation with

platelet count, serum uric acid, LDL-cholesterol, WBC, hs-CRP and YKL-40 levels (Table 3). Also, serum YKL-40 level was positively correlated with hs-CRP level (r=0.467, p<0.001) and WBC count (r=0.251, p=0.001) as illustrated in Figure 1.

In order to determine independent predictors for the presence of MS, univariable and multivariable logistic regression analysis were performed (Table 4). Univariate regression analysis showed that age, hemoglobin, platelet, uric acid, LDL-cholesterol, WBC, hs-CRP and YKL-40 levels were possible confounding factors for the presence of MS. In multivariable regression analysis, serum YKL-40 [odds ratio (OR): 1.022; 95% confidence interval (CI): 1.011–1.033, p<0.001] and hs-CRP [OR: 1.346; 95% CI: 1.111–1.632, p=0.002] remained as independent predictors for the presence of MS. In the ROC curve analysis, using a cut-off level of 147.0, serum YKL-40 predicted the presence of MS with a sensitivity of 73.7% and specificity of 69.8% [area under curve (AUC): 0.785; 95% confidence interval (CI): 0.718–0.853, p<0.001] (Fig. 2). Moreover, YKL-40 indicated good calibrations for the presence of MS (Hosmer–Lemeshow test: Chi-square (χ^2)=7.937; p value=0.440).
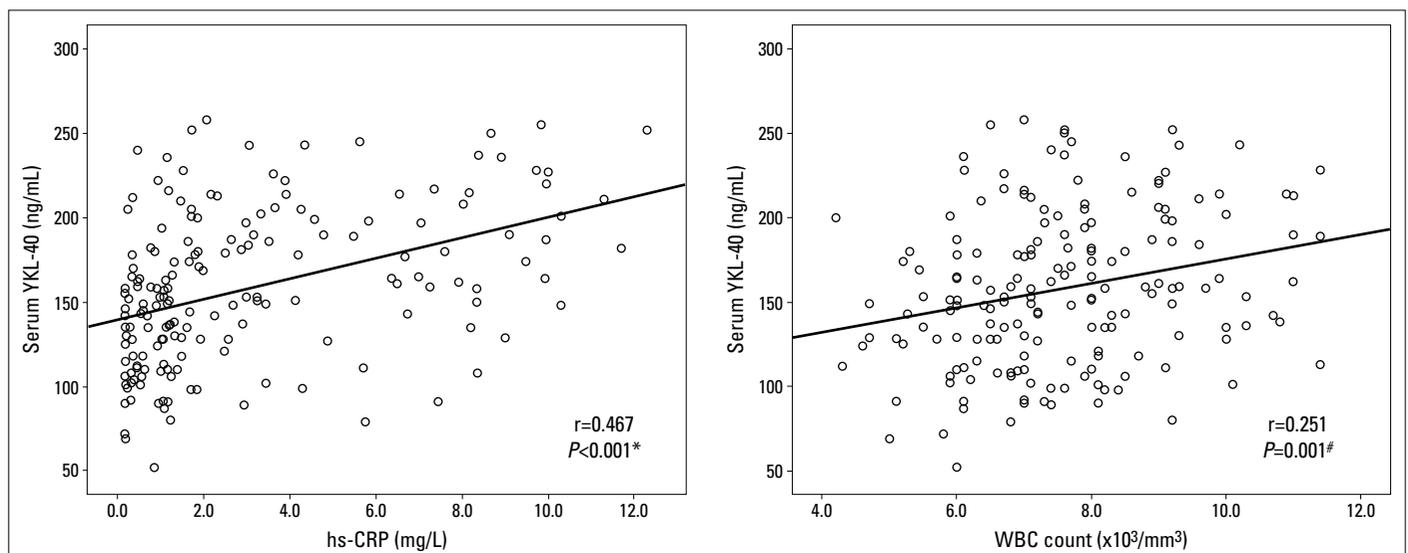

Figure 1. Correlation analysis showing the association of serum YKL-40 level with hs-CRP level and WBC count. (*Spearman rank test, #Pearson rank test)

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Table 4. Univariable and multivariable logistic regression analysis representing the independent predictors of metabolic syndrome

Variables	Univariable		Multivariable	
	OR (95% CI)	P	OR (95% CI)	P
Age	1.027 (0.991–1.064)	0.140	1.018 (0.977–1.062)	0.388
Hemoglobin	0.831 (0.631–1.094)	0.187	0.940 (0.666–1.328)	0.727
Platelet	1.004 (0.999–1.008)	0.141	1.001 (0.995–1.007)	0.672
Uric acid	1.183 (0.943–1.484)	0.146	1.039 (0.774–1.394)	0.800
LDL-cholesterol	1.013 (1.004–1.022)	0.006	1.007 (0.997–1.018)	0.173
White blood cell	1.318 (1.067–1.629)	0.013	1.161 (0.899–1.499)	0.253
hs-CRP	1.566 (1.285–1.907)	<0.001	1.346 (1.111–1.632)	0.002
YKL-40	1.029 (1.019–1.039)	<0.001	1.022 (1.011–1.033)	<0.001

CI-confidence interval; hs-CRP-high-sensitivity C-reactive protein, LDL-low-density lipoprotein; OR-odds ratio
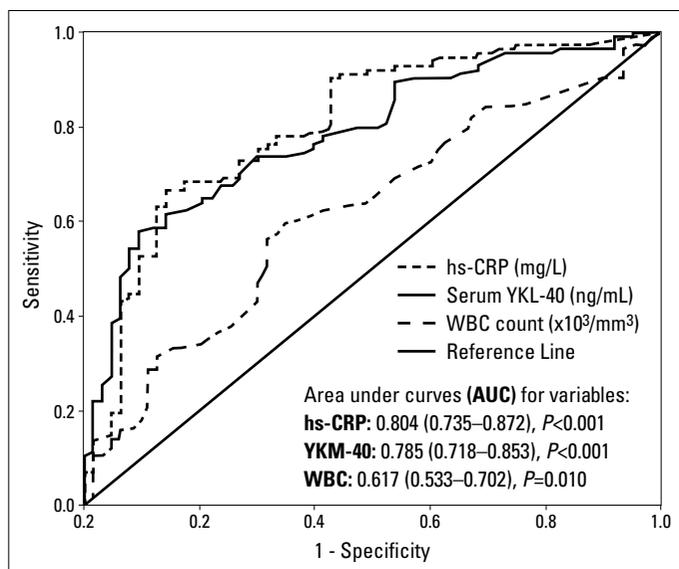

Figure 2. Comparison of receiver-operating characteristic (ROC) curves of serum YKL-40, hs-CRP and WBC for predicting the presence of MS. (ROC curve analysis)

Discussion

The major findings of our study were as follows: (i) To the best of our knowledge, the present study is the first clinical study showing a graded relationship between increasing number of MS components and serum YKL-40 level; (ii) We also demonstrated a positive correlation between YKL-40 level and other systemic inflammatory markers including hs-CRP and WBC count; (iii) Furthermore, for the first time, YKL-40 was found as an independent predictor for the presence of MS.

As a cluster of atherothrombotic risk factors, MS is significantly associated with an increased risk for development of DM, stroke, cardiovascular disease, cardiovascular and/or all-cause mortality (19–21). All the constituents of MS were shown to be associated with systemic and vascular inflammation (22, 23). Thus, MS is thought to be a state of chronic low grade inflamma-

tion (24, 25). In their study, Oda et al. (5) showed that hs-CRP level, a marker of low-grade systemic inflammation, was significantly higher in patients with MS and hs-CRP was an independent risk factor for MS. Moreover, Dallmeier et al. (4) demonstrated that MS was associated with multiple inflammatory biomarkers and they also concluded that the association between inflammation and MS was largely accounted by MS components (3). Similarly, our study also showed significantly higher hs-CRP levels in patients with MS. However, because of other possible strong predictors for the presence of MS like YKL-40, hs-CRP did not reach statistical significance to predict the presence of MS.

YKL-40, a new inflammatory marker with an established role in cell proliferation, differentiation, and regulation of extracellular tissue remodeling (9, 26). Because of its close association with both acute and chronic inflammatory status, recently YKL-40 was shown to be related with insulin resistance, endothelial dysfunction, CAD, peripheral arterial disease and carotid atherosclerosis (14, 27, 28). Recent studies also reported that increased serum YKL-40 levels have been associated with heart failure, acute myocardial infarction, the presence and extent of CAD (29–31). Moreover, YKL-40 anticipated cardiovascular mortality in patients with or without cardiac problems as well as overall mortality (17, 32). Nielsen et al. (33) showed that YKL-40 levels were also increased in patients with both type 1 and type 2 DM. Similary, in a recent study, Hempen et al. (34) showed that serum YKL-40 level was associated with degree of obesity and YKL-40 level decreased after weight loss. They concluded that expansion of the visceral adipose tissue may contribute to an increased inflammation within the tissue. In their study, Mygind et al. (35) have investigated the influence of statin treatment on serum YKL-40 and hs-CRP in patients with stable CAD. They demonstrated that serum YKL-40 and hs-CRP levels were significantly lower in statin treated group as compared to non-statin treated group. The findings of this study indicated that serum YKL-40 could be a biomarker for the pleiotropic effects of statins, and with the ability to monitor treatment efficiency, the atherosclerotic burden and the risk of future cardiovascular events and death in patients with stable CAD (35). Our study results are in consistent with the previous study findings. We demonstrated for the first time a graded relation between serum YKL-40 level and total number of MS components (severity of MS). In multivariable regression analysis, serum YKL-40 level was found as a significant and independent predictor for the presence of MS.

Study limitations

Our study results should be interpreted in the light of some limitations. First, the present study is not a multicenter study with a relatively limited patient number which restricts the generalizability of our results. Second, it was a cross-sectional study with no prospective follow-up data, thus we could not conclude on the temporal relationships of YKL-40 and MS. Third, in addition to hs-CRP and WBC count, other proinflammatory cytokines

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might be measured to clarify possible causative and associated mediators of inflammation in development of MS. Fourth, we tried but could not be sure to have fully excluded patients with infectious diseases (especially subclinic or atypical infection). Fifth, MS was diagnosed only according to the NCEP-ATP III (2001) criteria and other diagnostic criteria of MS proposed by the World Health Organization (WHO) or the International Diabetes Foundation (IDF) was not used.

Conclusion

The present study is the first clinical study that was demonstrated that serum YKL-40 level was significantly higher in patients with MS and serum YKL-40 was an independent predictor for the presence of MS in our study population. According to our findings, serum YKL-40 might be a useful biomarker of MS. Increased serum YKL-40 level can also be a sign of ongoing inflammation in patients with MS. Further large-scale prospective studies are needed to elucidate and confirm the mechanistic and prognostic role of serum YKL-40 in MS.

Conflict of interest: None declared.

Peer-review: Externally peer-reviewed.

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