

# Plasma YKL-40 levels correlate with the severity of coronary atherosclerosis assessed with the SYNTAX score

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## KEY WORDS

atherosclerosis, biomarker, coronary artery disease

## ABSTRACT

**INTRODUCTION** YKL-40 is a protein released locally by inflammatory cells. Thus, it may constitute a biomarker of inflammatory conditions, such as atherosclerosis.

**OBJECTIVES** The aim of the study was to determine YKL-40 levels in patients with ischemic heart disease and to analyze the correlation of this biomarker with the severity of coronary atherosclerosis.

**PATIENTS AND METHODS** The study included 158 patients: 52 with stable ischemic heart disease and 67 with acute coronary syndrome: ST-segment elevation myocardial infarction (STEMI;  $n = 47$ ) or non-ST-segment elevation myocardial infarction (NSTEMI;  $n = 20$ ). The control group included 39 individuals without abnormalities in coronary vessels. We evaluated plasma YKL-40 levels and their correlation with the severity of coronary atherosclerosis assessed with the SYNTAX score.

**RESULTS** Patients with myocardial infarction had higher plasma YKL-40 levels than those with stable ischemic disease (median [range], 235.3 [161.6–366.1] ng/ml vs 61.2 [53.1–83.1] ng/ml;  $P < 0.001$ ) or controls (median [range], 235.3 [161.6–366.1] ng/ml vs 55.7 [51.2–75.2] ng/ml;  $P < 0.001$ ). No differences were found in YKL-40 concentrations between STEMI and NSTEMI patients (median [range], 263 [150.3–363.7] ng/ml and 214.9 [163.4–367.6] ng/ml, respectively;  $P = 0.7$ ). The SYNTAX score in patients with ischemic heart disease correlated positively with YKL-40 concentrations ( $R = 0.34$ ;  $P < 0.001$ ).

**CONCLUSIONS** YKL-40 can be considered a potential biomarker of coronary atherosclerosis severity.

**INTRODUCTION** Although biomarkers might be helpful in the stratification of cardiovascular risk, nowadays they are primarily used for research purposes. The only biomarkers that were listed in the 2012 European guidelines on cardiovascular disease prevention in clinical practice were C-reactive protein (CRP), fibrinogen, homocysteine, and lipoprotein-associated phospholipase A2.<sup>1</sup> However, the role of these parameters was questioned in the updated guidelines from 2016.<sup>2</sup> This stimulated research, including genetic studies, on other biochemical parameters that are easy to determine and that could provide guidance on the management of ischemic heart disease.<sup>3</sup>

One of the currently investigated candidate biomarkers is YKL-40, a protein released by macrophages and neutrophils. YKL-40 is a growth

factor for smooth muscle cells, vascular endothelial cells, and fibroblasts.<sup>4,5</sup> Moreover, it is involved in adhesion and migration of smooth muscle cells and vascular endothelial cells, acting as a chemotactic factor.<sup>6,7</sup> Unlike CRP, which is synthesized primarily in the liver, YKL-40 is produced locally by inflammatory cells. Hence, this protein can be considered a biomarker of both acute inflammatory response and chronic inflammation associated with various conditions, such as diabetes mellitus and obesity. Previous studies demonstrated that YKL-40 concentrations correlated positively with insulin resistance.<sup>8–11</sup> Since inflammation has been implicated in the pathogenesis of atherosclerosis, YKL-40 is also considered a potential biomarker and prognostic factor in cardiovascular diseases.

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The aim of this study was to measure plasma YKL-40 concentrations in patients with ischemic heart disease and to evaluate if this parameter correlates with the severity of coronary atherosclerosis assessed with the SYNTAX score.

**PATIENTS AND METHODS** This single-center cross-sectional study was conducted in the years from 2013 to 2016 at the Department of Cardiology of Wrocław Medical University (Wrocław, Poland).

Study participants were recruited from among patients referred for diagnostic coronary angiography due to stable ischemic heart disease, acute coronary syndrome, or other indications such as valvular disease, arrhythmia, or cardiomyopathy. Patients with a history of percutaneous coronary intervention or surgical revascularization, stage 4 or 5 kidney disease, cancer, or active inflammation were excluded from the study. Depending on coronary angiography results, patients were considered for percutaneous or surgical revascularization, or for conservative treatment. The study group included patients in whom coronary angiography revealed ischemic heart disease (either stable disease or acute coronary syndrome), whereas the control group comprised patients without coronary artery abnormalities. Prior to coronary angiography, a 5-ml sample of venous blood was collected from a peripheral vein of each patient. The samples were centrifuged at 1200 g for 15 minutes at room temperature and stored in EDTA tubes at a temperature of  $-50^{\circ}\text{C}$  until analysis. Plasma YKL-40 concentrations were determined once, using the MicroVue YKL-40 immunoenzymatic assay (Quidel, San Diego, United States, California). The levels were measured with an automatic gamma scintillation counter, 2470 Wizard (PerkinElmer, Waltham, United States, Massachusetts). The minimum and maximum detection limits of the YKL-40 assay are 5.4 ng/ml and 300 ng/ml (prior to sample dilution), respectively. Other laboratory parameters were measured by automatic analyzers (Sysmex, Kobe, Japan).

The severity of coronary atherosclerosis was assessed on the basis of coronary angiography results, using the SYNTAX score calculator available online (<http://www.syntaxscore.com>). The SYNTAX score was calculated by 3 independent physicians (certified and experienced interventional cardiologists) and averaged. SYNTAX score assessors were blinded to YKL-40 concentrations.

In addition, all patients underwent echocardiography to assess left ventricular ejection fraction. Echocardiography was performed before coronary angiography in patients with stable ischemic heart disease and controls, and after coronary angiography (before discharge) in those with myocardial infarction.

The study protocol was approved by the local ethics committee at Wrocław Medical University (decision no. KB-483/2013; October 17, 2013).

**Statistical analysis** Statistical analysis was performed with Statistica 12 package (StatSoft, Tulsa, United States, Oklahoma). Normal distribution of the study variables was verified with the Shapiro–Wilk test. Depending on the result, the significance of between-group differences in quantitative variables was assessed with the Mann–Whitney test, Kruskal–Wallis analysis of variance (ANOVA), *t* test, or univariate ANOVA. The significance of relationships between qualitative variables was verified with the  $\chi^2$  test, with Yates correction for continuity whenever the assumption on minimum expected frequencies was not satisfied. Associations between the pairs of variables were analyzed based on Pearson linear correlation coefficients (*r*) for normally distributed variables or based on Spearman rank correlation coefficients (*R*) for the variables with distributions other than normal. Study variables were presented as means, medians, and SDs. The threshold of statistical significance for all tests was set at a *P* level of less than 0.05.

**RESULTS** The study included 158 participants: 52 patients with stable ischemic heart disease, 67 patients with acute coronary syndrome (47 patients with ST-segment elevation myocardial infarction [STEMI] and 20 patients with non-ST-segment elevation myocardial infarction [NSTEMI]), and 39 controls without coronary artery abnormalities. The clinical characteristics of participants are presented in **TABLE 1**.

Patients with myocardial infarction had higher plasma YKL-40 levels than those with stable ischemic disease (median [range], 235.3 [161.6–366.1] ng/ml vs 61.2 [53.1–83.1] ng/ml;  $P < 0.001$ ) or controls (median [range], 235.3 [161.6–366.1] ng/ml vs 55.7 [51.2–75.2] ng/ml;  $P < 0.001$ ). No differences were found in YKL-40 concentrations between STEMI and NSTEMI patients (median [range], 263 [150.3–363.7] ng/ml vs 214.9 [163.4–367.6] ng/ml;  $P = 0.7$ ).

In patients with ischemic heart disease, the SYNTAX score correlated positively with YKL-40 concentrations ( $R = 0.34$ ;  $P < 0.001$ ) (**FIGURE 1**). The correlation tended to be stronger in women ( $R = 0.53$ ;  $P < 0.001$ ) than in men ( $r = 0.21$ ;  $P = 0.04$ ).

A negative correlation was found between the YKL-40 concentration and left ventricular ejection fraction in the whole study group ( $R = -0.35$ ;  $P < 0.001$ ). Moreover, plasma YKL-40 levels correlated positively with leukocyte count ( $R = 0.29$ ;  $P < 0.001$ ) and patient age ( $R = 0.18$ ;  $P < 0.05$ ).

**DISCUSSION** This study demonstrated that plasma YKL-40 concentrations in patients with myocardial infarction were significantly higher than in individuals with stable ischemic heart disease and those without coronary artery abnormalities. This observation is consistent with the results of previous studies conducted in smaller groups of patients.<sup>12,13</sup> However, some authors showed that the concentration of YKL-40 was also higher in

**TABLE 1** Characteristics of the study groups

Parameter	Stable ischemic heart disease (n = 52)	Acute coronary syndrome (n = 67)	Control group (n = 39)	P value
Sex, male/female, n	36/16	44/23	19/20	0.1
Age, y, mean (SD)	67.0 (9.6)	65.9 (12.5)	63.3 (9.2)	0.3
Arterial hypertension, n (%)	45 (86.5)	55 (82.0)	35 (89.7)	0.5
Type 2 diabetes, n (%)	20 (38.4)	19 (28.3)	7 (17.9)	0.1
Atrial fibrillation, n (%)	12 (23.0)	4 (5.9)	6 (15.3)	<0.05 <sup>a,b</sup>
Valvular disease, n (%)	5 (9.6)	19 (28.3)	5 (12.8)	<0.05 <sup>c,d</sup>
Heart failure, n (%)	2 (3.8)	3 (4.4)	1 (2.5)	0.9
Obesity, n (%)	8 (15.3)	7 (10.4)	5 (12.8)	0.8
Smoking, n (%)	6 (11.5)	14 (20.8)	6 (15.3)	0.3
Statin use, n (%)	42 (80.7)	25 (37.3)	22 (55)	<0.05 <sup>a,b</sup>
LVEF, %, median (IQR)	62.5 (52.5–66.5)	56 (50–60)	65 (65–70)	<0.001 <sup>a,b,c</sup>
eGFR, ml/min/1.73 m <sup>2</sup> , mean (SD)	78.8 (20.6)	77.8 (25.4)	76.4 (18.8)	0.9
Hemoglobin, g/dl, mean (SD)	13.7 (1.3)	13.7 (2.0)	13.9 (1.4)	0.8
White blood cell count, G/l, median (IQR)	7.0 (6.3–7.0)	9.9 (8.4–12.5)	6.7 (4.3–11.8)	<0.001 <sup>c,d</sup>
Platelet count, G/l, median (IQR)	215.5 (185.0–247.0)	253 (118–432)	232 (143–344)	0.1
Total cholesterol, mg/dl, median (IQR)	177 (153–212)	210.5 (128–344)	218.5 (123–309)	<0.01 <sup>a,b</sup>
LDL-C, mg/dl, median (IQR)	99.5 (80.5–144.5)	137 (111–161)	142 (62–210)	<0.01 <sup>a,b</sup>
HDL-C, mg/dl, median (IQR)	44 (38–55)	48 (42–60)	51 (33–82)	0.1
Triglycerides, mg/dl, median (IQR)	124 (92–159)	99 (60–144)	144 (92–188)	<0.01 <sup>c,d</sup>
YKL-40, ng/ml, median (IQR)	61.2 (53.1–83.1)	235.3 (161.6–366.1)	55.7 (51.2–75.2)	<0.001 <sup>c,d</sup>
SYNTAX score, median (IQR)	18.0 (10.5–32.7)	20 (10–26)	–	<0.001 <sup>b,c</sup>

A P value of less than 0.05 is considered significant.

- a** Stable ischemic heart disease vs acute coronary syndrome
- b** Stable ischemic heart disease vs control group
- c** Acute coronary syndrome vs control group
- d** Acute coronary syndrome vs stable ischemic heart disease

SI conversion factors: to convert LDL-C and HDL-C to mmol/l, multiply by 0.0259; triglycerides to mmol/l, by 0.0113.

Abbreviations: eGFR, estimated glomerular filtration rate; HDL-C, high-density lipoprotein cholesterol; IQR, interquartile range; LDL-C, low-density lipoprotein cholesterol; LVEF, left ventricular ejection fraction

patients with stable ischemic heart disease than in healthy controls,<sup>14–16</sup> which was not observed in our study. This discrepancy might result from the fact that our control group included individuals without significant coronary artery abnormalities and not without any cardiac disorders. Like other authors, we did not observe significant differences in YKL-40 concentrations in patients with various types of myocardial infarction (STEMI or NSTEMI).<sup>12</sup>

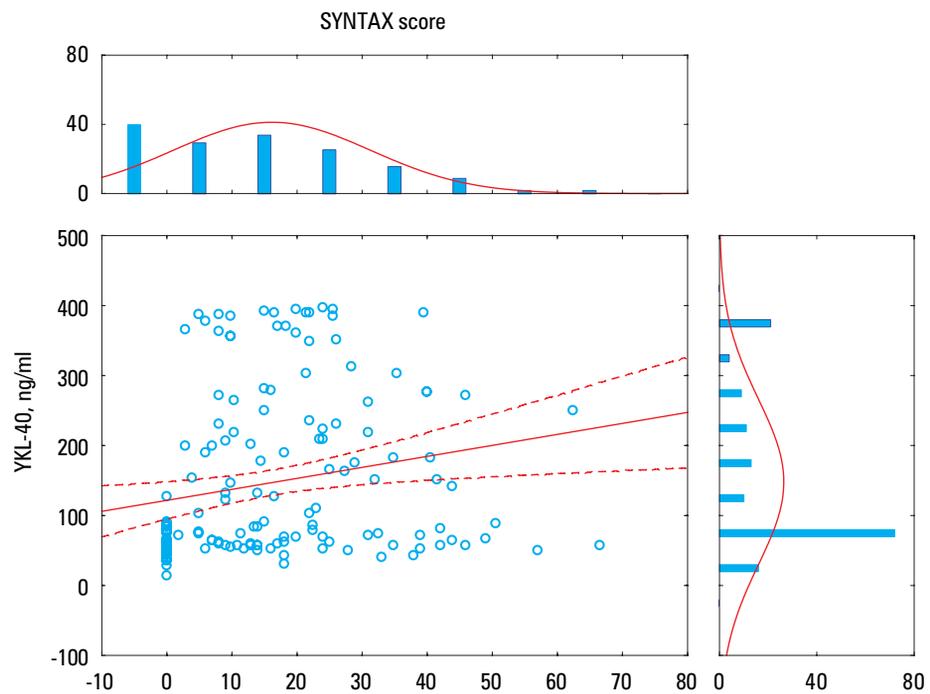
Plasma YKL-40 concentrations in our participants correlated negatively with left ventricular systolic function expressed by left ventricular ejection fraction. This observation is partially consistent with the results by Hadegaard et al<sup>17</sup> who found an inverse relationship between plasma YKL-40 levels in acute myocardial infarction and improvement in left ventricular systolic function at 6 months after STEMI.

Moreover, we observed a significant positive correlation between YKL-40 concentrations and peripheral leukocyte count, which suggests that

YKL-40 levels may reflect the severity of inflammation. This finding is consistent with the results of previous studies, which demonstrated that YKL-40 may be an inflammatory biomarker, either in acute conditions, such as pneumonia and meningitis,<sup>18,19</sup> or in chronic inflammatory diseases associated with elevated proinflammatory activity, such as diabetes mellitus and chronic obstructive pulmonary disease.<sup>8,20</sup> Rathke and Vestergaard<sup>21</sup> identified YKL-40 as a proinflammatory factor involved in the pathogenesis of atherosclerosis.

While the concentration of YKL-40 was previously reported to correlate positively with the presence of arterial hypertension,<sup>22–24</sup> we did not observe such a relationship in our study. This discrepancy may be explained by the fact that more than 85% of our patients (135 of 158) presented with arterial hypertension. Several previous studies documented a link between YKL-40 concentrations and other comorbidities such as diabetes mellitus, atrial fibrillation, heart failure, and alimentary obesity.<sup>8,10,11,25–31</sup> However,

**FIGURE 1** Correlation between YKL-40 concentrations and SYNTAX score in patients with ischemic heart disease



we did not observe this relationship in our study, probably because the number of patients with these conditions was too small.

We observed a positive correlation between plasma YKL-40 concentrations and patient age, which is in line with previous findings.<sup>32</sup>

Our study showed a positive correlation between YKL-40 concentrations and the severity of coronary atherosclerosis assessed with the SYNTAX score. To the best of our knowledge, none of the previous studies used this calculator to evaluate the association between the YKL-40 level and the severity of atherosclerosis. Nevertheless, the YKL-40 concentration was previously shown to correlate with other biomarkers of atherosclerosis severity, such as the number of involved coronary vessels,<sup>14</sup> degree of coronary artery stenosis, coronary artery calcium score determined by computed tomography angiography in patients with diabetes mellitus,<sup>33</sup> or coronary atherosclerosis index values in patients with sleep apnea syndrome.<sup>16</sup> However, it should be emphasized that according to more recent guidelines on cardiovascular disease management, the SYNTAX score is a more appropriate tool to determine the severity of coronary atherosclerosis.<sup>34-37</sup>

A primary limitation of this study was the small size of the subgroups with various comorbidities and risk factors. This might explain the discrepancies between our findings and previous results in terms of the nonsignificant difference in plasma YKL-40 concentrations between controls and patients with stable ischemic heart disease, as well as the lack of significant associations between YKL-40 concentrations and the presence of arterial hypertension, type 2 diabetes, atrial fibrillation, heart failure, and obesity. Moreover, it should be emphasized that in contrast to other biomarkers (eg, CRP

synthesized primarily in the liver), YKL-40 is released locally by inflammatory cells; however, we measured its concentration in peripheral blood, which also might have affected the results. Nevertheless, the measurement of YKL-40 concentrations in plasma seems justified given the practical application of this biomarker.

To summarize, this study demonstrated that patients with STEMI and NSTEMI presented with significantly higher concentrations of YKL-40 than individuals with stable ischemic heart disease and those with no evidence of coronary abnormalities. The type of myocardial infarction had no effect on YKL-40 levels. Plasma YKL-40 levels correlated with the severity of coronary atherosclerosis assessed with the SYNTAX score, with the severity of inflammation expressed by plasma leukocyte count, and with left ventricular systolic function expressed by left ventricular ejection fraction.

**CONTRIBUTION STATEMENT** KS and MN-K conceived the concept for the study and designed the research. KS, WK, MP, and BK conducted the study. KS, WK, DB, MP, AM, and MN-K analyzed the results and drafted the manuscript.

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