Original Article

The association between serum YKL-40 levels, mean platelet volume, and c-reactive protein in patients with cellulitis

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Abstract

Background: Lower limb cellulitis is an infectious disease that has serious complications unless it is treated. **Objectives:** In this pilot study, we evaluated whether levels of YKL-40, an acute-phase reactant, and mean platelet volume (MPV), which occurs secondary to inflammation in cellulitis, increase compared to healthy subjects. We also aimed to investigate the association between YKL-40 and MPV in the prognosis of the patients. **Material and Methods:** A total of 55 patients with cellulitis (23 men and 32 women) and a similar age group of 46 healthy individuals (22 men and 24 women) were included in the study. Cellulitis was diagnosed according to guideline. Serum YKL-40 levels, MPV, C-reactive protein (CRP), and other biochemical values of both groups were compared. **Results:** YKL-40 levels (52.2 ± 34.5 ng/mL vs 34.6 ± 18.0 ng/mL, $P = 0.004$), MPV (7.7 ± 1.0 fL vs 6.9 ± 0.7 fL, $P < 0.001$), and CRP (9.5 ± 8.2 mg/dL vs 0.7 ± 0.6 mg/dL, $P < 0.001$) were significantly higher in the patients with cellulitis than the control. The mean recovery time (RT) of the patients was 22.6 ± 6.9 days. We found that YKL-40 (odds ratio [OR] 0.1, confidence interval [Cl] 0.028–0.191, $P = 0.009$) and MPV (OR 2.4, Cl 0.254-4.578, $P = 0.029$) have an independent association with RT. **Conclusion**: YKL-40 and MPV values were correlated with higher CRP in the cellulitis group than in controls. According to these results, increased YKL-40 and MPV levels might be a prognostic factor for cellulitis in patients.

Key words: *Cellulitis, mean platelet volume, YKL-40*

Introduction

YKL-40 (chitinase 3-like 1) is a glycoprotein released by active macrophages, chondrocytes, neutrophils, vascular smooth muscle cells, and some tumour cells.[1-6] It is an acute-phase protein, and its plasma concentration has been shown to increase reversibly in patients by more than 25% following an inflammatory stimulus.[4] High levels of YKL-40 protein have also been found in infections such as pneumonia and sepsis. There appears to be a relationship between the severity of infectious disease and YKL-40 levels, and increased serum YKL-40 levels are observed in several serious pathologies that require pharmacological treatment, mechanical ventilation, and/or haemodialysis for bacteremia.[7-9]

Mean platelet volume (MPV), which reflects the sizes of thrombocytes, is an important marker of thrombocyte function. Compared to small platelets, larger ones have more granules, aggregate more rapidly with collagen, have higher thromboxane A_2 levels, and express increased numbers of glycoprotein I band IIb/IIIa receptors, thus large thrombocytes increase the incidence of occlusive vascular disease.[10-13] Some studies have found that MPV levels are higher in infections such as sepsis and pneumonia.[14,15]

Cellulitis is a clinical diagnosis based on erythema, swelling, and local tenderness of the skin and subcutaneous tissues, which is accompanied by fever and malaise. Group A *Streptococcus* or *Staphylococcus aureus* are responsible for most simple cellulitis cases.[16,17] In this pilot study, we evaluated whether, during the progress of cellulitis, YKL-40 levels, as acute-phase reactants, and MPV levels generated secondarily during the inflammatory process were increased compared to healthy controls. We also aimed to investigate the association between YKL-40 and MPV in the prognosis of the patients.

Material and Methods

Patients

This study was an observational cross-sectional study that was performed in the Infectious Disease Department

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of the Faculty of Medicine of Recep Tayyip Erdogan University between January and June 2013. Fifty-five patients diagnosed with cellulitis (32 females, 23 males) who had applied to the infectious clinic at the hospital were included. A control group of 46 healthy individuals (24 females, 22 males) with no infectious and chronic diseases (diabetes, hypertension, hyperlipidaemia, coronary artery disease, chronic obstructive pulmonary disease, or chronic renal failure) were included. Patients and healthy controls were non-smokers, and did not consume alcohol or use drugs. This study conformed to the Helsinki Declaration and was approved by the Ethics Committee of Ataturk University, School of Medicine, Erzurum, Turkey.

Diagnosis of Cellulitis

Cellulitis was diagnosed by an infection specialist according to physical examination findings and laboratory results as follows:[16,18] (1) oedema, rash, tenderness, and warming of the skin in the lower extremities; (2) elevated white blood cell count (WBC), erythrocyte sedimentation rate (ESR), and C-reactive protein (CRP) levels (however, normal values in these tests did not automatically exclude the diagnosis of cellulitis); (3) cultivation of the infecting agent from aspirate or biopsy material; and (4) exclusion of the presence of deep vein thrombosis (DVT) using superficial ultrasonography (USG) and Doppler USG.

Diagnosis of DVT

DVT was defined by a radiology specialist, using Doppler USG (10 mHz direct ultrasound probe, Toshiba Xario, Tokyo, Japan), as a decrease in the calibration of femoral and popliteal veins and was visualized as an intraluminal isoechoic thrombus reflux with poor recanalization (a symptom of DVT).[19]

Recovery time (RT) for cellulitis

The recovery criteria of cellulitis was determined according to the guidelines[17,20] as follows: (1) improvement of clinical symptoms, (2) a complete recovery of oedema, rash, tenderness, and warming of the skin and soft tissues. We estimated recovery time according to guidelines.

Laboratory measurements

Serum samples were stored at −30°C. Serum fasting glucose, blood urea nitrogen, creatinine, aspartate aminotransferase, alanine aminotransferase, and other biochemical tests were performed using photometric assays and the Abbott Architect C16000 analyser (Abbott Diagnostics, Illinois, USA). CRP tests were performed via the nephelometric method of the Coulter Image 800 device (Beckman, California, USA). Haematological tests for MPV, WBC, platelets, and haemoglobin (Hb) were performed using the Abbott Cell DynRuby analyser (Abbott Diagnostics, Illinois, USA).

Measurement of YKL-40

Serum levels of human YKL-40 were quantified using commercially available enzyme-linked immunosorbent assay (ELISA) kits (East Biopharm, Hangzhou, China). The intra-assay and inter-assay coefficients of variation (CV) were <10% and <12%, respectively. The sensitivity was calculated to be 0.52 ng/mL.

Evaluation of blood culture

Blood cultures were detected by automated BACT-ALERT (France) system, and were performed by oxacillin and cefoxitin disk diffusion test (30 mg, Oxoid, England) and Kirby-Bauer disc diffusion method proposed by CLSI.

Statistical analyses

Independent sample *t*-test was used to apply normal distribution parameters and Mann-Whitney U test used to apply non-normal distribution parameters. Nested analysis of variance (ANOVA) test followed by Bonferroni test was used to apply gender subgroup analyses. Pearson's correlation test and Stepwise multivariate (MVA) logistic regression analyses were used to apply RT, YKL-40, and MPV and other parameters.

Results

Laboratory values in studied groups

The mean age of cellulitis patients and control subjects was 61.8 ± 14.2 years and 61.5 ± 7.5 years, respectively. In the cellulitis group, YKL-40 levels were 52.2 ± 34.5 ng/mL, MPV was 7.7 ± 1.0 fL, platelets were 270 ± 101 × 10^9/L, WBC was 11.8 ± 3.3 × 10^9/L, CRP was 9.5 ± 8.2 mg/dL, and ESR was 38 ± 25 mm/h. The mean recovery time (RT) of the patients with cellulitis was 22.6 ± 6.9 days. Blood cultures were positive in 27 patients with cellulitis. Coagulase-negative Staphylococci were detected in 15 of them, 6 patients had *Staphylococcus aureus*, and 6 patients had a positive culture for Group A Streptococcus.

In the control group, YKL-40 levels were 34.6 ± 18.0 ng/mL, MPV was 6.9 ± 0.7 fL, platelets were 262 ± 69 × 10^9/L, WBC was 7.3 ± 2.5 × 10^9/L, CRP was 0.7 ± 0.6 mg/dL, and ESR was 16 ± 14 mm/h. YKL-40 levels ($P = 0.004$), MPV ($P < 0.001$), WBC ($P < 0.001$), CRP ($P < 0.001$), and ESR ($P < 0.001$) were significantly higher in patients with cellulitis compared to controls. The demographic characteristics and the biochemical parameters of the patients are shown in Table 1.

Relationships of RT, YKL-40, and MPV with clinical and laboratory variables

Pearson correlation analyses showed a positive correlation between RT and YKL-40 (r = 0.480, $P < 0.001$),

MPV (r = 0.329, P = 0.004), ESR (r = 0.490, P < 0.001), and CRP (r = 0.436, P < 0.001). There was a positive correlation between YKL-40 and WBC (r = 0.333, P = 0.002), MPV (r = 0.468, P < 0.001), CRP (r = 0.481, P < 0.001), and ESR (r = 0.296, P = 0.007). There was also a positive correlation between MPV and CRP (r = 0.251, P = 0.024), and ESR (r = 0.296, P = 0.007).

Factors associated with YKL-40 levels

Stepwise MVA analyses were performed in which YKL-40 was used as the dependent variable and YKL-40, MPV, CRP, ESR, WBC, platelet counts, Hb, glucose, BUN, creatinine, AST, ALT, age, and gender were used as independent variables [Table 2]. We found that YKL-40 (odds ratio [OR] 0.1, confidence interval [Cl] 0.028-0.191, P = 0.009) and MPV (OR 2.4, Cl 0.254-4.578, P = 0.029) have an independent association with RT.

Subgroup analysis of YKL-40 levels and MPV

The test population was divided into the following subgroups: Cellulitis males (CEM), control males (COM), cellulitis females (CEF), and control females (COF). YKL-40 values were significantly higher in the CEM (P = 0.031) and CEF (P = 0.012) groups than the COF group. The MPV values were significantly higher in the CEM (P = 0.012) and CEF (P < 0.001) groups than the COM group. The MPV values were significantly higher in the CEF (P = 0.024) group than the COF group. The results are shown in Table 3.

Table 1: The main characteristics and laboratory parameters for the two groups

	Mean±SD		*P* value
	Cellulitis *n*=55	Control *n*=46	
Age (years)	61.8±14.2	61.5±7.5	0.921
Gender (M/F)	23/32	22/24	0.748
YKL-40 (ng/mL)	52.2±34.5	34.6±18.0	0.004
MPV (fL)	7.7±1.0	6.9±0.7	0.001
CRP (mg/dL)	9.5±8.2	0.7±0.6	0.001
WBC (x10^9/L)	11.8±3.3	7.3±2.5	0.001
Platelet (x10^9/L)	270±101	262±69	0.222
Hb (g/dL)	12.6±2.0	13.2±2.0	0.220
FPG (mg/dL)	107±37	105±32	0.363
BUN (mg/dL)	39±19	36±10	0.438
Creatinin (mg/dL)	0.9±0.3	0.9±0.2	0.905
AST (IU/L)	26±15	23±9	0.340
ALT (IU/L)	26±19	22±15	0.296
ESR (mm/h)	38±25	16±14	0.001
LDH (mg/dL)	276±76	195±37	0.001
Tbil (mg/dL)	1.0±0.5	0.8±0.3	0.055
Ibil (mg/dL)	0.5±0.3	0.3±0.1	0.011

M: Male, F: Female, MPV: Mean platelet volume, WBC: White blood cells, FPG: Fasting plasma glucose, BUN: Blood urea nitrogen, ESR: Erythrocyte sedimentation rate, LDH: Lactate dehydrogenase, Tbil: Total bilirubin, Ibil: Indirect bilirubin

Discussion

We found that the levels of YKL-40, MPV, CRP, ESR, and WBC were significantly higher in patients with cellulitis than in healthy controls. According to MVA analysis YKL-40, MPV, and ESR levels were found to be strongly predictive markers for RT. Similarly, there was a positive correlation between RT and serum YKL-40, ESR, CRP, and MPV. Also, MPV and YKL-40 levels are strongly correlated with CRP; therefore, MPV and YKL-40 levels may be good marker and prognostic factor for patients with cellulitis. Both gender with cellulitis, we observed increased levels of WBC, CRP, and YKL-40 compared to controls, but the rate of increase of this parameters in women was more prominent than in men. This might indicate that women respond to infection by increasing acute-phase reactant levels. MPV levels of both sex were significantly higher than the control group. In addition, in both sexes, YKL-40

Table 2: Multivariate (stepwise) logistic regression analysis of factors related to recovery time in cellulitis

Dependent	Independent	OR (95% Cl)	*P* values
Recovery time	ESR	0.2 (0.056-0.257)	0.003
	YKL-40	0.1 (0.028-0.191)	0.009
	MPV	2.4 (0.254-4.578)	0.029
	Age		N.S.
	Hb		N.S
	WBC		N.S
	Plt		N.S
	AST		N.S
	ALT		N.S
	Glucose		N.S
	BUN		N.S
	Creatinine		N.S
	CRP		N.S

ESR: Erythrocyte sedimentation rate, MPV: Mean platelet volume, WBC: White blood cell counts, Plt: Platelets, BUN: Blood urea nitrogen, CRP: C-reactive protein, OR: Odds ratio, CI: Confidence interval

Table 3: Subgroup analysis of gender groups by ANOVA

	Male in cellulitis	Female in cellulitis	Male in control	Female in control
YKL-40 (ng/mL)	50.8±34.6	53.2±34.9	42.2±23.4	28.1±7.9*,¶
MPV (fL)	7.5±1.1	7.7±0.8	6.7±0.4^{α,β}	7.0±0.8^{π}
CRP (mg/dL)	7.4±6.1	11.0±9.3	0.9±0.9$^{¥,β}$	0.5±0.3$^{#,β}$
WBC (x10^9/L)	12.1±3.2	11.6±3.4	8.6±3.0$^{┼,&}$	6.1±1.1^{w,β}

MPV: Mean platelet volume, CRP: C-reactive protein, WBC: White blood cells, ANOVA: Analysis of variance. ^{w}P<0.001, $^{┼}P$=0.002, $^{#}P$=0.003, $^{¥}P$=0.008, ^{α}P=0.012, $^{*}P$=0.031 vs. male in cellulitis. ^{β}P<0.001, $^{&}P$=0.004, $^{¶}P$=0.012, ^{π}P=0.024 vs. female in cellulitis

and MPV levels are increase as secondary to the infection. We speculated that because there is a strong correlation between RT with YKL-40, and MPV, these markers could be used to determine disease severity and estimate the treatment response.

Serum levels of acute-phase reactants,[21] such as CRP, and cytokines including tumour necrosis factor (TNF)-α and interleukin (IL)-6 increase in patients with cellulitis secondary to dense infection. TNF-α and IL-6 play a role in the regulation of acute-phase proteins.[22] Because YKL-40 is an acute-phase reactant, an increase in released TNF-α and IL-6 could increase YKL-40.[23] Moreover, serum YKL-40 levels were found as decreased in patients whom treated with TNF-α blockers.[23] In a previous study, increased YKL-40 levels were found to be correlated with increased TNF-α and IL-6 levels during endotoxemia.[8] Increased serum YKL-40 levels have also been reported in patients with sepsis,[24] and YKL-40 has been determined to be a good predictor of inflammation in these patients. In another study, significantly increased serum YKL-40 levels were observed in response to streptococcus infection.[7] In the present study, serum YKL-40 levels were found to be higher in patients with cellulitis and to be correlated with serum CRP levels, which is in agreement with other published studies. These results suggest that YKL-40 levels may be a good predictor of disease prognosis.

TNF-α and IL-6 are related to oxidative stress and stimulate megakaryopoiesis.[10,11] These cytokines enhance oxidative stress, which contributes to platelet activation. Platelet activation leads to the release of immature and activated thrombocytes from bone marrow to peripheral blood, thus increasing MPV levels. A previous study revealed a strong correlation between CRP and MPV.[25] Increased CRP levels suggest that TNF-α and IL-6 levels could also increase, thereby explaining the increased MPV levels. A relationship between higher levels of MPV and diseases such as myocardial infarction, venous thromboembolism, and stroke has been reported.[26-28] MPV is a good indicator of youth and the presence of large thrombocytes in peripheral blood. Increased large thrombocytes in peripheral blood can increase the levels of aggregate substances released by them, and thus occlusive arterial or venous diseases could easily occur. In bacterial septicaemia cases with no thrombocytopenia, MPV levels have been reported to decrease after treatment.[28] Another study reported that MPV levels were increased in patients with pneumonia.[15] Finding a correlation between CRP and MPV might prove that MPV could be used as a prognostic factor in patients with cellulitis.

Previous study reported that YKL-40 levels were higher in males than in females.[29] In experimental study showed that YKL-40 was significantly downregulated by estrogen supplementation in the ocular posterior segment of ovariectomised mice.[30] Also, YKL-40 levels in our study were higher in males than females of control groups. However, in the study, elevated of YKL-40 levels during cellulitis were found to be higher in females than in males. In current study, MPV level was found to be higher in females than in males in control group, but no statistically significant. Similarly, other researchers have found no statistically significant differences in MPV between women and men.[31,32] Also, MPV level was found to be higher in females than in males in cellulitis group, but no statistically significant. CRP level was found to be higher in males than in females of control group, but no statistically significant. However, in the study, elevated of CRP levels during cellulitis were found to be higher in females than in males. Several studies have reported higher CRP levels in women than in men.[33,34] We hypothesize that elevated levels of inflammatory markers during cellulitis, particularly CRP, related an increased YKL-40 and MPV levels and severe of cellulitis. Current study showed that increased YKL-40 level and elevated CRP concentrations were more strongly associated in women than men. However, the current study found that increased YKL-40 and MPV levels may be predicted severe of cellulitis for 2 genders.

Blood cultures were positive in 27 patients. The cellulitis infection of the patients was localized to skin and soft tissues. So as there was no bacteremia, the cultures of the rest of the patients were negative. In addition, CRP response does not detected in some infections or its level is not correlated with the infection severity. CRP levels may increase due to noninfectious reasons and may mislead the clinician about the course of infection. In such patients other acute phase reactants are used such as procalcitonin and resistin.[35] According to MVA our study has shown that YKL-40 and MPV may be independent predictors for RT. However, there was no strong correlation between CRP and RT. In MVA, YKL-40, and MPV had a strong correlation with ESR. However, as ESR may be rapidly affected from some conditions like anemia and its level lately increases and lately returns to normal during an infection the search continues for better and inexpensive markers that can predict the severity of an infection. Serum levels of YKL-40 in the rats made endotoxemic was increased after 2 h of endotoxin injection and had a peak level in 24. Hour and its level were still high in 36th h.[8] As a result YKL-40 and MPV may be new markers to confirm the diagnosis and predict the prognosis in patients with cellulitis.

Study Limitations

Firstly, this study was a pilot study and thus the sample size did not allow any generalizations. Secondly, the relatively higher cost of YKL-40 than CRP was the main handicap. Thirdly, YKL-40 and MPV can increase also in other inflammatory conditions as same as CRP.

Finally, YKL-40 is eliminated by the kidneys so in the presence of renal failure its values may be changeable.

Conclusion

YKL-40 and MPV levels were higher and correlated with CRP in patients with cellulitis. CRP is a marker of systemic inflammation, is also increased in cellulitis infection. According to these results, increased YKL-40 and MPV levels might be a prognostic factor for cellulitis.

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