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Original Article

Increased serum YKL-40 levels in children with sickle cell disease

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ABSTRACT

Background: YKL-40 is a glycoprotein secreted by various cell lines during inflammation and vascular dysfunction. Sickle cell disease (SCD) also involves inflammation and endothelial dysfunction processes. Thus, we aimed to assess the levels of YKL-40 in pediatric SCD patients.

Methods: We evaluated serum levels of YKL-40 in children with steady state SCD and those with vaso-occlusive crisis (VOC) episodes and compared them with healthy subjects.

Results: Overall, 33 children with SCD and 33 healthy controls participated in this study. Serum YKL-40 concentrations of children with steady state SCD were significantly higher than the concentrations found in the healthy controls (median [Q1-Q3]: 71.0 [53.3-133.3] vs. 43.6 [37.9-69.9] ng/mL, p=0.001). Seventeen of the 33 children with SCD (51.5%) had a VOC during the one-year follow-up period. Steady state and VOC episode YKL-40 did not significantly differ in children who were experiencing VOC during the one-year follow-up (77.6 [55.2-126.8] vs. 69.7 [49.3-100.0] ng/mL, p=0.381). During VOC episodes, children with SCD had significantly higher YKL-40 levels than the healthy controls (69.7 [49.3-100.0] vs. 43.6 [37.9-69.9] ng/mL, p=0.005). YKL-40 levels at steady state and during VOC episodes did not show significant correlation (p=0.955).

Conclusions: YKL-40 may have a potential role in the inflammation component of SCD. Circulating YKL-40 levels may be used to monitor chronic inflammation in SCD patients.

Key words: endothelial dysfunction, inflammation, sickle cell disease, YKL-40, chitinase-3-like protein-1, human cartilage glycoprotein 39.

Sickle cell disease (SCD) is an autosomal recessive genetic disease and is one of the most common hemoglobinopathies in the world. The term *SCD* covers mutations in the gene that encodes the beta globin subunit of hemoglobin, leading to a group of diseases (e.g., sickle cell anemia [SCA], hemoglobin SC disease, and hemoglobin S-beta-thalassemia). Substituting glutamic acid with valine at the sixth position of the beta-globin chain leads to the formation of abnormal hemoglobin, known as hemoglobin S (HbS).[1] HbS is the most common abnormal hemoglobin in Türkiye.[2]

The complex pathophysiology of SCD involves HbS polymerization, the sickling of red blood cells, vaso-occlusion, increased blood viscosity, oxidative stress and inflammation, endothelial dysfunction, and ischemia-reperfusion injury. The symptoms mainly occur as a result of

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the abnormal sickling of red blood cells and various subsequent complications.[3] Pain crisis, anemia, infections, acute chest syndrome, delayed growth and development, stroke, and long-term organ damage are common symptoms of SCD.[1,3] Pain crises or vaso-occlusive crises (VOC) are hallmarks of SCD. Polymerization of deoxygenated HbS leads to decreased deformability of red blood cells, and the characteristic "sickle" shape occurs. Rigid sickled red blood cells lead to tissue ischemia by adhering to the vascular endothelium and obstructing the vasculature. Ultimately, severe pain episodes arise due to the ischemic tissue damage and inflammation.[4]

In the pathophysiology of vaso-occlusion, interactions between sickled red blood cells, activated endothelial cells, leukocytes, and platelets play a crucial role. Multicellular aggregation, increased oxidative stress, and a pro-inflammatory environment created by these cells underlie VOCs.[4] Previously, higher neutrophil and platelet counts and high levels of platelet factors 3 and 4, extracellular hemoglobin, and lactate dehydrogenase have been reported during VOCs.[5-8] Chronic hemolysis in SCD induces oxidative stress, and increased oxidative stress triggers inflammatory cytokine release.[9] Furthermore, ischemia-reperfusion injury secondary to microvascular occlusions promotes chronic inflammation in SCD.[10] Both acute and chronic inflammatory responses have been associated with VOCs.[3,4] The inflammatory mediators C-reactive protein (CRP), tumor necrosis factor-alpha (TNF-α), interleukin 6 (IL-6), interleukin 8 (IL-8), transforming growth factor-beta (TGF-β), and interleukin 17 (IL-17) have been shown to be significantly increased in patients with SCD and VOCs when compared to healthy controls.[11,12]

YKL-40 (chitinase-3-like protein-1, human cartilage glycoprotein 39) is a mammalian glycoprotein related in sequence to family 18 of bacterial and fungal chitinases. However, it does not exhibit enzymatic activities. While YKL-40 is expressed in various cell types, its exact biological function is currently unknown. Increased levels of YKL-40 have been linked to inflammation, tissue remodeling, angiogenesis, and cancer.[13,14] Previous studies have investigated the role of YKL-40 in various cardiovascular, gastrointestinal, endocrinological, immunological, musculoskeletal, neurological, respiratory, urinary, and infectious diseases and found contradictory results. YKL-40 has been found to be an important proinflammatory protein in certain diseases. However, in some other diseases, it has not been found to be significantly different from healthy individuals.[15] YKL-40 is identified to be a potential biomarker of inflammation and vascular dysfunction.[16] SCD and VOCs also are also characterized by inflammation and endothelial dysfunction. A meeting abstract reported higher serum YKL-40 and cytokine levels in children with SCD in comparison with their healthy counterparts, and weak correlations between serum YKL-40 levels and salivary cytokine levels.[17] To the best of our knowledge, original research comparing serum YKL-40 levels between pediatric SCD patients and healthy children has not previously been published. The primary objective of this study was to evaluate serum levels of YKL-40 in children with steady state SCD and those with VOC episodes and compare them with healthy subjects. The secondary objective was to investigate correlations between YKL-40 and the inflammatory biomarkers CRP, IL-6, and TNF-α in children with SCD.

Materials and Methods

Study design and study sample

This comparative cross-sectional study was conducted at Mersin University Hospital and investigated the inflammatory biomarkers of children with SCD. Children with SCD and age- and sex-matched healthy controls were the subjects. Children with SCD followed in the Pediatric Hematology department and healthy children admitted to the well-child outpatient clinic were included in the study. Inclusion criteria for the patient group were as follows:

having been diagnosed with SCD based on hemoglobin electrophoresis and genetic testing; age 2 to 17 years; and having consent from his/her parents or legal guardians to participate in the study. For the patient group, exclusion criteria were the presence of VOC at last one month prior to the study, chronic simple or blood exchange transfusions, drug use except hydroxyurea, sickle hepatopathy, renal dysfunction, hypertension, endocrine disorder, overweight and obesity, serious infections and inflammatory diseases, and smoking. Inclusion criteria for the control group were as follows: being healthy and age 2-17 years; having normal weight; not smoking; having no medical or family history of congenital hematologic disease, blood disorder, chronic systemic disease, genetic disorder or malignancy; and having consent from his/her parents or legal guardians to participate in the study. Child assent and parent informed consent were obtained for participation. This study was approved by Mersin University Clinical Research Ethics Committee (2016-04-14/108).

Data collection

All children with SCA (n=23) and hemoglobin S-beta-thalassemia (n=10) who were admitted to the Pediatric Hematology clinic between May 1, 2016 and May 1, 2017 and fulfilled the appropriate criteria constituted the study sample. For each SCD patient, an age- and gender-matched healthy child with normal growth and development was also included in the study. In total, data were collected from 33 children with SCD and 33 healthy children.

Baseline evaluations and one-year follow-ups were conducted for the patients. Laboratory data were collected from 33 patients with steady state SCD and from 33 healthy controls at the baseline evaluation. In 17 patients who had VOCs during the one-year follow-up period, a second evaluation was performed, and laboratory data were recollected at the VOC episode. Serum samples of the SCD and control groups were obtained on the day of admission to the hospital.

Laboratory measurements

Serum YKL-40, IL-6, TNF-α, and CRP levels, as well as complete blood count values in venous blood samples, were obtained. YKL-40, IL-6, and TNF-α concentrations were determined by an enzyme-linked immunosorbent assay (ELISA). The measurements were carried out using the YKL-40 human ELISA kit (201-12-2034 SunredBio), IL-6 ELISA kit (KAP 1261 Diasource) and TNF-α-ELISA kit (KAP 1751 Diasource). The manufacturer's protocols for each ELISA kit were followed. The DSXTM Four-Plate Automated ELISA Processing System MikroELISA device was utilized for analysis. For each sample, the concentrations of YKL-40, IL-6, and TNF-α were determined by calculating them from the curves and equations obtained from plotting the optical density values corresponding to the known concentrations of standards provided in each analysis kit. IL-6 and TNF-α levels were only measured in the patient group. CRP levels were analyzed using the immunoturbidimetric method and a CRP value less than 5 mg/L was considered normal.

Statistical analysis

Statistical Package for the Social Sciences version 21.0 (IBM SPSS Corp.; Armonk, NY, USA) was used for statistical analysis. The Shapiro-Wilk test and histograms were used to test for normality. For continuous variables, mean ± standard deviation or median (with first and third quartiles, Q1-Q3) values are provided; for categorical variables, numbers (n) and percentages (%) are provided as descriptive statistics. The two independent groups (patient and healthy control groups) were compared with the Student t-test or Mann-Whitney U test, and the two dependent groups (steady state and VOC episode groups) were compared with the Wilcoxon test. The three independent groups (steady state, VOC episode, and healthy control groups) were compared with the Kruskal-Wallis test. Relationships between continuous variables were examined with the Spearman correlation coefficient. Categorical variables were compared with the chi-square test. The statistical significance level was set at $p<0.05$.

Results

Overall, 33 children with SCD and 33 healthy controls participated in this study. The mean age of the children with SCD was 12.4 ± 3.7 years, and the mean age of the healthy controls was 11.7 ± 4.2 years (p=0.460) Twenty of the children with SCD (60.6%) and 21 of the healthy controls (63.6%) were male (p=0.800). All children with SCD were using hydroxyurea.

Serum YKL-40 concentrations of children with steady state SCD were significantly higher than the concentrations found in the healthy controls (71.0 [53.3-133.3] vs. 43.6 [37.9-69.9] ng/mL, p=0.001). CRP concentrations in the serum of children with steady state SCD was significantly increased compared to the healthy controls (p=0.001). White blood cell (WBC) count did not differ between the children with steady state SCD and the healthy controls (p=0.380, Table I).

Seventeen children with SCD (51.5%) had a VOC during the one-year follow-up period. The median duration between the baseline evaluation at steady state and the second evaluation at VOC episode was 5.8 ± 2.7 months (min-max: 1.5-10 months). Steady state and VOC episode YKL-40, CRP, IL-6, and TNF-α levels did not significantly differ in children with SCD who were experiencing VOC during the one-year follow-up (p>0.05). WBC count significantly increased during VOC compared with the WBC count in steady state SCD (14.30 [10.27-19.83] vs. 10.50 [8.70-13.37] x10^3/μL, p=0.017). During VOC episodes, children with SCD had significantly higher YKL-40 and CRP levels than the healthy controls (p=0.005 and p<0.001, respectively). Table II shows a comparison of inflammatory biomarkers at steady state SCD and VOC episodes, as well as a comparison of VOC episode biomarker levels with healthy controls.

When grouped according to the occurrence of VOCs during the one-year follow-up, there were no significant differences in the steady-state concentrations of YKL-40, CRP, IL-6, TNF-α, or in the steady-state WBC counts between children with SCD who experienced VOCs and those who did not (p > 0.05). There was no significant difference in baseline WBC counts among children with SCD who experienced VOCs during the one-year follow-up, those who did not experience VOCs, and healthy controls (Table III).

Steady state YKL-40 levels were moderately correlated with steady state CRP levels in children with SCD (rho=0.40, p=0.022). There was no significant correlation between steady state YKL-40 levels and steady state IL-6, TNF-α, or WBC values (p>0.05). VOC episode biomarker levels did not show significant correlations (p>0.05). Steady state YKL-40 levels and VOC episode YKL-40 levels did not show significant correlation (rho= -0.015, n=17, p=0.955). In healthy subjects, YKL-40 levels, CRP levels, and WBC counts did not show significant correlations (p>0.05).

Discussion

This study showed that serum YKL-40 and CRP levels increased in children and adolescents with steady state SCD and with VOC episodes, and steady state YKL-40 was correlated with

Table I. Comparison of YKL-40, CRP, and WBC values between patients with steady state SCD and healthy controls.

Biomarkers	Steady state SCD (n=33)	Healthy controls (n=33)	**p**
YKL-40, ng/mL	71.00 (53.3-133.3)	43.60 (37.9-69.9)	0.001
CRP, mg/L	4.32 (2.71-10.24)	0.98 (0.40-3.65)	0.001
WBC, x10^3/μL	12.00 (9.20-15.00)	10.62 (8.65-13.44)	0.380

Mann-Whitney U test, data are presented as median and interquartile range (Q1-Q3).
CRP, C-reactive protein; SCD, sickle cell disease; WBC, white blood cell.

steady state CRP, while steady state and VOC episode YKL-40 levels did not significantly differ.

The expression pattern of YKL-40 points to its potential involvement in sterile inflammation and endothelial dysfunction, even though its precise function is still unknown.[18] A comprehensive review indicated that YKL-40 can be considered a marker for systemic inflammatory and autoimmune disorder diagnosis, prognosis, and disease activity.[13] Higher serum concentrations of YKL-40 are known to be associated with severe forms of

Table II. Comparison of inflammatory biomarkers at steady state and VOC episode, and comparison of VOC episode biomarker levels with healthy controls.

Biomarkers	Steady state (n=17)	VOC episode (n=17)	p*	Healthy controls (n=33)	p**
YKL-40, ng/mL	77.56	69.74	0.381	43.60	0.005
	(55.22-126.76)	(49.31-100.02)		(37.9-69.9)	
CRP, mg/L	7.10	6.57	0.149	0.98	<0.001
	(3.91-13.15)	(3.25-25.0)		(0.40-3.65)	
WBC, x10^3/μL	10.50	14.30	0.017	10.62	0.053
	(8.70-13.37)	(10.27-19.83)		(8.65-13.44)	
IL-6, pg/mL	6.57	35.27	0.266	-	-
	(4.02-26.22)	(10.77-174.15)			
TNF-α, pg/mL	21.05	15.25	0.831	-	-
	(15.27-42.42)	(11.07-37.42)			

*Wilcoxon test, data are presented as median and interquartile range (Q1-Q3), comparison of steady state and VOC episode biomarker levels in patient group experiencing VOC during the one-year follow-up.
**Mann-Whitney U test, data are median and interquartile range (IQR 25-75%), comparison of patients' vaso-occlusive crisis episode biomarker levels with healthy controls' biomarker levels.
CRP, C-reactive protein; IL-6, interleukin-6; TNF-α, tumor necrosis factor alpha; VOC, vaso-occlusive crisis; WBC, white blood cell.

Table III. Comparison of inflammatory biomarkers between patients experiencing vaso-occlusive crisis and those who were not during the one-year follow-up, and healthy controls.

Baseline bio-markers	SCD without VOC (n=16)	SCD with VOC (n=17)	p*	Healthy controls (n=33)	p**
YKL-40, ng/mL	65.00	77.56	0.692	43.60	0.003
	(51.2-135.2)[a]	(55.22-126.76)[a]		(37.9-69.9)[b]	
CRP, mg/L	2.85	7.10	0.061	0.98	0.001
	(1.25-8.32)[a]	(3.91-13.15)[a]		(0.40-3.65)[b]	
WBC, x10^3/μL	14.25	10.50	0.072	10.62	0.175
	(9.95-16.50)	(8.70-13.37)		(8.65-13.44)	
IL-6, pg/mL	10.94	6.57	0.746	-	-
	(3.72-187.56)	(4.02-26.22)			
TNF-α, pg/mL	37.45	21.05	0.296	-	-
	(15.73-159.06)	(15.27-42.42)			

*Mann-Whitney U test, data are presented as median and interquartile range (Q1-Q3), comparison of SCD patients course with and without VOC.
**Kruskal-Wallis test, data are presented as median and interquartile range (Q1-Q3), comparison of the three groups; different letters represent significant differences at $p < 0.05$ probability level.
CRP, C-reactive protein; IL-6, interleukin-6; SCD, sickle cell disease; TNF-α, tumor necrosis factor alpha; VOC, vaso-occlusive crisis; WBC, white blood cell.

inflammatory diseases and cardiovascular inflammatory conditions.[15,19-21] Higher levels of YKL-40 were expected in patients with beta-thalassemia major. However, the level of YKL-40 was found to be within the normal range in patients between the ages of 15–69 and only a slight correlation was found with the liver status.[22] Previous studies have explained their findings with the involvement of YKL-40 in the inhibition of vascular endothelial cell apoptosis, inducing the loss of endothelial barrier function and endothelial-mesenchymal transition.[15,19] Endothelial dysfunction and inflammation have also been demonstrated in children with SCD and are present in both VOCs and in steady state SCD.[23] Therefore, YKL-40 is also likely to be elevated in children with SCD. For the first time in the literature, the current study demonstrates increased serum YKL-40 levels in children with SCD both in VOCs and in steady state compared to healthy controls.

The main inflammatory events in SCD involve increases in leukocyte numbers and their activation, expression of adhesion molecules in leukocytes, proinflammatory cytokines, neutrophilic extracellular traps, secretory phospholipase A2 enzyme, placental growth factor, and leukotriene E4, as well as decreases in anti-inflammatory cytokines.[24] The inflammatory state in SCD involves the production and secretion of numerous pro-inflammatory mediators. The cytokines TNF-α, IL-1-alpha, IL-6, IL-17, interferon-gamma, platelet-derived CD40 ligand and herpesvirus entry mediator ligand (TNSF14), IL-1-beta and IL-18; and the chemokines IL-8, monocyte chemoattractant protein-1, regulated on activation, normal T cell expressed and secreted (RANTES), platelet factor 4, macrophage inflammatory protein 1-alpha, eotaxin-1 and fractalkine; the growth factors granulocyte-macrophage colony-stimulating factor, macrophage colony-stimulating factor, TGF-β and pro-angiogenic molecules; and the acute phase proteins CRP and pentraxin-3 are reported to be elevated in SCD patients when compared to controls.[25,26] Our findings add to the existing literature on elevated YKL-40 in both steady-state SCD and VOCs. Our findings also support the existing literature on upregulated acute phase protein CRP both in steady state SCD and in VOCs.

IL-6 is an activated cytokine that is significantly increased in the peripheral blood of patients with SCD. IL-6 has been found to be increased in steady state SCD and further increased during vaso-occlusion.[27,28] We also demonstrated an increase in serum IL-6 levels during VOC compared with steady state SCD, although it was statistically insignificant. Expression of TNF-α was reported to be normal or increased in both steady state SCD and VOC episodes.[28] We found consistently statistically similar TNF-α levels in steady state SCD and VOC episodes. Due to a limited research budget, we did not measure IL-6 and TNF-α concentrations in the healthy control group.

Previous studies investigating predictor biomarkers of VOC provide evidence of the association between high-adhesive phenotypes and the occurrence of VOCs. Higher adhesion biomarkers during steady state SCD were found to predict the frequent occurrence of VOCs.[29,30] Steady state TNF-α, IL-6, and WBC levels, taken together, were found to discriminate between low and high VOC risk groups in children with SCD.[31] A previous study of risk prediction modeing for VOCs in children with SCD reported that YKL-40 failed to distinguish the patients with VOC and those with steady-state disease, and patients with a high risk of VOC could not be detected via YKL-40.[31] Aforementioned feasibility study evaluated YKL-40 to predict VOC risk[31], the current study, on the other hand, evaluated YKL-40 levels in children with SCD in comparison with healthy controls. While the current study did not aim to assess the predictive value of inflammatory biomarkers during steady-state SCD and VOC, a comparison of children experiencing VOC and those who were not during the one-year

follow-up revealed a non-significant difference in steady state YKL-40, CRP, WBC, IL-6, and TNF-α levels. This finding may contribute to research in the prediction of VOCs among individuals with SCD.

Rees and Gibson reviewed more than 100 different blood and urine biomarkers described in SCD and concluded that these biomarkers are mostly closely intercorrelated.[32] Our findings add to the existing literature on a positive correlation between serum YKL-40 and CRP in steady-state SCD.

Chronic transfusions and sickle organopathies may alter biomarker profiles of SCD patients, and altered biomarkers of hemolysis, anemia, and hypoxemia, as well as damage to specific organs, may alter biomarkers of inflammation.[32] For this reason, we did not include children with SCD receiving chronic simple or blood exchange transfusions, with sickle hepatopathy or nephropathy, or with other potential inflammatory conditions. Hydroxyurea is linked to decreased inflammatory cytokines in children with SCD.[33] Therefore, the use of hydroxyurea by all of our patients contributed to ensuring group homogeneity.

This study has several limitations. First, various patient factors and environmental factors (eg, hypoxia, dehydration, stress, low humidity, exposure to cold or weather changes) may trigger and exacerbate VOCs, and inflammatory profiles may vary depending on the triggers.[34,35] However, we did not assess the potential trigger(s) of VOC in our patients. Second, some genotypes are associated with the severity of SCD and VOC[36], but we did not consider the inflammation-related gene polymorphisms or SCD haplotypes of our patients. Third, VOC has previously been suggested to consist of sequential phases and inflammatory markers that increase from the beginning of a pain event and become significant in the severe, constant pain phase.[37] We cannot know for certain that we took blood samples from all patients in the same phase of VOC, but we can say that serum samples were obtained from patients with severe, debilitating pain within 24 hours of hospital admission.

In conclusion, serum YKL-40 and CRP levels in children and adolescents with SCD were higher both in steady state SCD and during VOCs, and steady state YKL-40 was correlated with steady state CRP. Our findings suggest a potential role of YKL-40 in the inflammation component of SCD. Circulating YKL-40 levels may be used to monitor chronic inflammation in SCD patients. Further studies utilizing serial measurements are warranted to clarify the peak timing and decline dynamics of YKL-40, and to determine whether it may serve as an earlier indicator of VOCs or demonstrate superiority over other serologic inflammatory markers.

Ethical approval

The study was approved by Mersin University Clinical Research Ethics Committee (date: 14.04.2016, number: 2016-108).

Author contribution

The authors confirm contribution to the paper as follows: Study conception and design: VA, SÜ, ÖT, BT, ŞBF, FK; data collection: VA, ŞBF, FK; analysis and interpretation of results: ÖT, BT; draft manuscript preparation: VA, SÜ, ÖT. All authors reviewed the results and approved the final version of the manuscript.

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Conflict of interest

The authors declare that there is no conflict of interest.

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