Role of survivin & soluble intercellular adhesion molecule-1 in sickle cell disease

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Abstract:

The prediction of prognosis of an individual with sickle cell anemia could guide therapeutic decision making. Previous studies showed that adhesion molecules contribute to the development of inflammatory vascular complications in some diseases. Other studies showed that survivin and lipoprotein (a) [Lp (a)] enhance the expression of soluble intercellular adhesion molecule-1(s-ICAM-1). Thus, we proposed that survivin, s-ICAM-1 and Lp (a) might affect the risk for complications in patients with sickle cell anemia.

The study consisted of 40 patients with sickle cell trait (SCT) and sickle cell disease (SCD) in addition to 33 controls from Al-Hasa province of Saudi Arabia. All laboratory analyses were measured by the standard methods.

In the SCD group, both serum survivin and Lp (a) were insignificantly higher than in the other two groups. The patient with the highest survivin concentration didn't suffer from hemolytic crisis. Patients with clinical complications had insignificantly lower survivin than patients without complications. Consistent with its need during continued production and survival of red blood cells, survivin expression was positively and significantly correlated with MCV, and reticulocytic count. The levels of Lp (a) and s ICAM-1 were significantly correlated with serum creatinine and ALT suggesting a link with endothelial dysfunction. The correlation between Lp (a), survivin and s ICAM-1 was positive but statistically insignificant.

Conclusion:

Survivin expression may be considered as potentially useful indicator for good prognosis in patients with sickle cell disease.

Key words:

Sickle cell anemia; lipoprotein (a); survivin; intercellular adhesion molecule-1.

Introduction:

Sickle cell disease "SCD" is an autosomal inherited structural disorder of hemoglobin, associated with an amino acid substitution of valine for glutamic acid at the sixth residue of the β chain. This genetic alteration yields an unstable RBC with a shortened survival that under stress (e.g. deoxygenation) becomes sickle-shaped. The life expectancy of affected

individuals has tripled over the last 3 decades, due primarily to early identification through newborn screening programs and decreased death rates from pneumococcal sepsis (Driscoll, 2007).

It has been reported that sickle cells induce endothelial adhesion molecules (Kato *et al*., 2005). Intercellular adhesion molecule-1 (ICAM-1) as well as other adhesion molecules mediate vaso-occlusion in mouse models of SCD (Matsui *et al*., 2001, Belcher *et al*., 2005). Moreover, vaso-occlusion because of hemoglobin S polymerization, and the extent of polymerization itself, may be compounded by adhesion molecule-dependent reticulocyte-monocyte-endothelial interactions in the post capillary venules (Spring *et al*., 2001).

Lipoprotein (a) [Lp (a)] is a particle with an unusual structure consisting of apo (a), which is linked to apo B-100 of an LDL-like particle through disulfide bonds (Takami *et al*., 1998). Elevated levels of Lp (a) are often associated with endothelial dysfunction (Ghorbanihaghjo *et al*., 2008). Therefore, the hypothesis (Takami *et al*., 1998) that LP (a), might induce the expression of adhesion molecules in endothelial cells seems very reasonable.

Survivin is a protein with multiple functions, including an essential role in cytokinesis and a possible role as an inhibitor of apoptosis (Li and Brattain, 2006). Because survivin is generally not expressed in adult tissues, it has been viewed as an excellent target for cancer therapy. On the contrary, recent reports have shown that survivin has an essential role in variety of hematopoietic cells (Gurbuxani *et al*., 2005 and Leung *et al*., 2007). Additionally, extracellular survivin binds to the surface of the majority of granulocytes and a significant part of lymphocytes and monocytes inducing the activation of ∝- chains of β-integrins and their ligand ICAM-1. Therefore, Mera *et al*., (2008) found that both have a possible impact on the development of the inflammatory processes occurring during rheumatoid arthritis.

Some risk factors for the development of complications in an individual with sickle cell anemia are known, but are insufficiently precise to be used for prognostic purposes. The present study was therefore designed to investigate the potential role of survivin, sICAM-1 and Lp (a) in patients with sickle cell anemia and their usefulness in a clinical setting.

Patients and methods:

Patients

The study population comprised 40 patients with sickle cell disease (SCD), and sickle cell trait (SCT), together with 33 healthy persons as a control group. Classification of subjects enrolled in this study into SCD, SCT was performed by hemoglobin electrophoresis according to Driscoll (2007). Patients and controls were matched for age and gender (P> 0.05). The patients were selected from the health center, King Faisal University (Al-Hasa province, Kingdom of Saudi Arabia) between June and October 2008 based on their medical and /or family history. Data concerning their clinical history were obtained by a specialized clinician. Informed consent was obtained from each patient**.**

Blood samples:

Five mL blood were collected from each patient by venipuncture. Two mL blood were collected in EDTA containing tubes for hemoglobin electrophoresis. The other 3 mL were allowed to clot at room temperature for 30 minutes. Clear sera were obtained by centrifugation (30 min, 2500 rpm). Part of the sera was kept at 4 °C until analysis of serum levels of ALT, blood urea nitrogen (BUN) and creatinine. The other part was stored at – 20 °C for measurement of s ICAM-1, Lp (a) and survivin. Icteric samples were excluded from the study.

Hemoglobin electrophoresis:

The different types of hemoglobins in each blood sample were separated by Helena hemoglobin electrophoresis procedure "Helana laboratories, Texas, USA" using cellulose acetate plate. The patterns were scanned on a scanning densitometer and the relative percent of each band was determined.

Assay procedures:

Human soluble ICAM-1 (s ICAM-1):

According to the manufacturer's instructions, s ICAM-1 level was measured in the serum using enzyme-linked immunosorbent assay kit from DRG (DRG international Inc., USA). The concentrations of s ICAM-1 were determined from the standard curve.

Survivin immunoassay:

Total human survivin concentrations were analyzed by Quantikine human survivin immunoassay (R &D systems, Inc., Minneapolis, USA) according to the manufacturer instructions. Survivin concentration in each sample was calculated from the standard curve.

Lipoprotein (a) ELISA:

Lipoprotein (a) [Lp (a)] was measured by solid phase capture sandwich ELISA assay using a microwell format and reagents from DRG "DRG International., Inc. USA".

Blood chemistry:

The serum levels of Alanine aminotransferase (ALT), bilirubin, blood urea nitrogen and creatinine were measured using Bohehringer Mannheim Reflotron chemistry analyzer (GmbH, Germany).

Statistical analysis:

Data were presented as mean ± SD or % of group. Pearson's chi-square test was used to compare the non-parametric results (table 1). Analysis of variance (ANOVA) was used to detect differences between normal controls, SCT and SCD groups (table 2). Correlation between different variables was performed by Spearman's test (table 3). A *P* value ≤ 0.05 was considered significant. All analyses were performed using the statistical package for the social sciences soft ware, version 10 (SPSS Inc., Chicago, IL, USA).

Table (1)

Clinical features of the sickle cell trait "SCT" and sickle cell disease "SCD" patients from Al-Hasa region using chi-square analysis

Variable	SCT (n= 32)	SCD (n=8)	P value
Gender (M/F)	12/ 20	5/3	>0.05
Immunization	0%	30%	< 0.001
Bone: Pain	46.9%	100%	< 0.001
Osteoarthopathy	37.5%	70%	>0.05
Leg ulcers	0.0%	10%	> 0.05
Chest pain	25%	80%	< 0.001
Pulmonary hypertension	0.0	10%	>0.05
Kidney pain	6.3%	50%	< 0.001
Urinary troubles	3.1%	30%	< 0.01
Brain (Stroke)	0.0%	20%	< 0.01
Liver pain	9.4%	30%	>0.05
Liver: Cholelethiasis	9.4%	40%	< 0.05
Retinopathy	0.0%	10%	>0.05

Values are expressed as % of positive.

Table (2)

Comparison of laboratory characteristics of the three studied groups

Variable	Controls (n= 33)	SCT (n= 32)	SCD (n= 8)	P value
MCV	82.9 ± 7.1	76.6 ± 8.2 a	81.6 ± 10.1	<0.001
Reticulocytic count (%)	1.6 ± 0.6	1.87 ± 0.6	8.1 ±3 a,b	<0.001
Total hemoglobin (g/dL)	13.8 ±1.9	12.8 ± 1.3 a	10.4 ± 1.5 a,b	<0.001
Hemoglobin S (%)	0.0	37.9 ± 3.4 a	73.1 ± 5.1 a,b	<0.001
Hemoglobin F (%)	0.0	0.0	24.3 ±5.4 a,b	<0.001
Hemoglobin A (%)	97.3 ± 0.3	59.1 ±3.4 a	0.0 a,b	<0.001
Hemoglobin A2 (%)	2.6 ± 0.3	2.9 ± 0.4 a	2.6 ± 0.37 b	<0.001
ALT (U/L)	15.4 ± 15.4	12.6 ±16.3	12 ± 6	> 0.05
Creatinine (mg/ dL)	0.8 ± 0.2	0.59 ± 0.12 a	0.6 ±0.14 a	<0.001
Blood urea nitrogen (mg/ dL)	31.6 ±11.9	24 ± 4.2 a	20.9 ± 1.29 a	<0.001
Lp a (mg/dL)	14.9 ± 8.4	15.4 ± 7.8	16.1 ± 5.7	> 0.05
Survivin (pg/mL)	4.7 ± 3.7	4.09 ± 7.95	6.6 ± 7.8	> 0.05
sICAM-1 (ng/mL)	342.7 ± 57.4	356.5 ± 34	346.2 ± 41.5	> 0.05

Values are expressed as mean ± SD

P was calculated using one way analysis of variance (ANOVA) t or X^2 test as appropriate.

[a]Significant difference from the control group.

[b]Significant difference from the SCT group.

Table (3)

Correlation analysis between serum Lp (a), survivin, soluble intercellular adhesion molecule-1(sICAM-1) and some variables in the three studied groups

		Age	Hb-A2	MCV	Retic. count	ALT	Creatinine
Lp (a)	Controls	0.7	0.8	0.5	0.7	0.1	0.9
	SCT	0.7	0.6	0.8	0.6	0.2	0.6
	SCD	0.3	0.05[a]	0.01[a]	0.3	0.05[a]	0.05[a]
Survivin							
	Controls	0.4	0.26	0.68	0.57	0.9	0.2
	SCT	0.2	0.19	0.6	0.03[a]	0.5	0.7
	SCD	0.4	0.002[a]	0.01[a]	0.15	0.3	0.04[a]
ICAM-1							
	Controls	0.02[a]	0.9	0.6	0.12	0.8	0.9
	SCT	0.5	0.03[a]	0.9	0.4	0.05[a]	0.7
	SCD	0.7	0.26	0.7	0.4	0.3	0.5

a = P<0.05

Results:

The study included 73 subjects divided into three groups. Based on hemoglobin electrophoresis, 8 patients with fetal hemoglobin (Hb F) and sickle cell hemoglobin (Hb S) were included in the SCD group, whereas 32 patients with Hb S and absent Hb F were included in the SCT group (figure 1). The third group included 33 healthy subjects as controls. The subjects in this study were from both sexes and their ages were matched ($p>0.05$).

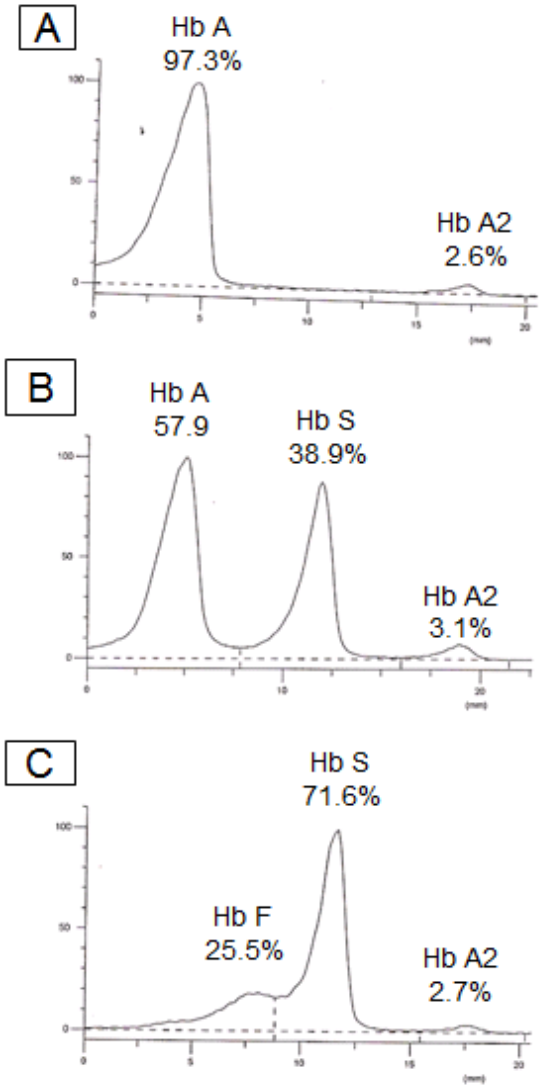

Figure (1): Electrophoretic pattern of hemoglobin fractions in: a) normal controls, b) SCT & c) SCD.

The general characteristics of the study population

The clinical manifestations of the sickle cell trait (SCT) and sickle cell disease (SCD) patients are shown in table 1.

Comparison of laboratory findings in the three groups

In table (2), the mean corpuscular volume (MCV) differed significantly between the SCT and control groups. Whereas, the reticulocytic count increased, the total hemoglobin decreased in patients with SCD than in the other two groups ($P<0.001$). Serum ALT didn't significantly differ between the three groups. Surprisingly, patients with SCD or SCT have lower serum creatinine and blood urea nitrogen (BUN) than the control subjects.

Concerning serum survivin, its median value and upper limit in the control group were 4.8 pg/ml and 14.8 pg/ml, respectively (data not tabulated). In this study, one patient had higher survivin concentrations than 14.8 pg/ml. The results of his laboratory analyses were 26.4 pg/ml for serum survivin, Hb S 71.7 % and Hb F 25.6%.

Although statistically insignificant, both serum survivin and Lp (a) were higher in the SCD than SCT or the control group (table 2). Moreover, there was no statistically significant difference in serum sICAM-1 between the three groups.

Correlations between the different studied parameters

In table 3, serum Lp (a) and survivin were significantly correlated with hemoglobin A2, MCV and serum creatinine in SCD group. Serum survivin was positively and significantly correlated with the reticulocytic count in the SCT group. Serum s ICAM-1 was significantly correlated with age in the control group and with hemoglobin-A2 in the SCT group.

Correlations between serum survivin, s ICAM-1 and the different clinical complications of sickle cell anemia:

Comparison of serum survivin in SCD patients with or without clinical complications (table 4) showed that its levels were decreased non-significantly in the presence of any complication than in its absence ($P> 0.05$). In the SCT group, the reverse pattern was detected. Regarding sICAM-1, the same pattern was detected only in relation to kidney and liver pains in the SCT group (data not shown).

Examining the association between the examined parameters showed positive association between Lp (a) and survivin ($r=0.05$, $P\leq 0.05$) as well as between Lp (a) and s ICAM-1 ($r= 0.51$, $P> 0.05$) in the SCD group.

Table (4)

Serum survivin concentrations in relation to the different symptoms in patients with sickle cell disease (SCD) and sickle cell trait (SCT)

Symptom	SCD		P	SCT		P
Osteomyelits	Negative	11.5 ± 12	0.4	Negative	2.79 ± 3.5	0.3
	Positive	4.4 ± 4.3		Positive	6.2 ± 12	
Chest pain	Negative	15.9 ± 14.8	0.47	Negative	2.5 ± 3.3	0.2
	Positive	4.3 ± 3.6		Positive	8.6 ±14.5	
Kidney pain	Negative	10 ± 9.9	0.1	Negative	3.9 ± 8	0.7
	Positive	3 ± 2.9		Positive	6.39 ± 8	
Hepatic pain	Negative	7.9 ± 8.9	0.3	Negative	3.8 ± 8	0.4
	Positive	3.6 ± 4		Positive	6.9 ± 5.7	
Cholethiasis	Negative	8.3 ± 9.7	0.3	Negative	3.8 ± 8.1	0.4
	Positive	4 ±3.4		Positive	6.9 ± 5.7	
Brain stroke	Negative	7.6 ± 8.4	0.2	Negative	Not applicable	
	Positive	2.7 ± 3.8		Positive	Not applicable	

Discussion:

Sickle cell disease (SCD) is one of the major health problems in Saudi Arabia as there is high prevalence of sickle cell gene especially in Southern, Western and Eastern areas. In Al- Hasa region (Hofuf area, Eastern province), it was reported that the frequency of sickle cell gene ranges from 0.1%-0.25% of the screened newborn babies (Nasserullah *et al*., 1998). Patients in the Eastern areas have different haplotypes than Southern and Western areas (Pearson, 1999). The present study was designed to evaluate the potential role of survivin, Lp (a) and sICAM-1 in patients with sickle cell anemia from Al- Hasa region.

Survivin is a 16.5 kDa protein that has an essential role in mitosis. Its expression is generally cell-cycle regulated with expression peaking during G2/M, where it functions as an essential chromosome passenger protein to regulate cytokinesis (Matsui *et al*., 2001). Also, it is essential for the viability of proliferating cells (Li *et al*., 1999)**.**

Comparison of the serum levels of survivin in the control, SCT, and SCD groups showed insignificant elevation of serum survivin in patients with SCD than in the other two groups. Meanwhile, serum survivin was significantly correlated with the MCV in the SCD group. This may indicate the need for survivin during erythroid formation. It could also support the

observation that inhibiting survivin may interfere with the continued production and/ or the survival of red blood cells (Gurbuxani *et al*., 2005).

Vaso-occlusion has traditionally been ascribed to plugging of the microcirculation by deformed sickle erythrocytes generated by deoxygenation-induced polymerization of mutated hemoglobin. The ancillary events of polymerization that contribute to cell sickling include erythrocyte and leucocyte adhesion to an activated endothelium (Driscoll, 2007). Moreover, evidence suggests that sickle erythrocytes may also induce changes in the vascular wall that contribute to the occlusive process (Hebbel, 1997).

sICAM-1 is normally expressed at low levels on the luminal surface of endothelial cells. Its expression is induced by a variety of biological stimuli. It provides an adhesive surface for specific ligands present on the surface of leucocytes physiologically recruited as part of the inflammatory programme. Therefore, subsequent shedding of soluble adhesion molecules into blood plasma can serve as markers of endothelial dysfunction (Kato *et al*., 2005). The current study revealed that the concentration of s ICAM-1 didn't significantly differ between the three examined groups. This might indicate lack of endothelial dysfunction in the examined patients. At the start of this year, Mera et al published that extracellular survivin up-regulates adhesion molecules on the surface of leucocytes in patients with rheumatoid arthritis. On the other hand, our results demonstrated positive but statistically insignificant relationship between both survivin and s ICAM-1 expression in patients with sickle cell anemia.

Recently, Leung *et al*., (2007) reported that survivin depleted mice had lower hemoglobin compared with the control animals. In our SCD patients, the total hemoglobin concentration was significantly reduced than in SCT and control groups. This could be explained by the exacerbated peripheral erothrocytic destruction as indicated by the increased reticulocytic count, and suggest a trial of the body to compensate for the decreased hemoglobin by elevating survivin in this group.

Sickle cells are less deformable in the microcirculation and provoke a cascade of events that results in vascular occlusion, organ ischemia, and eventually, chronic end-organ damage. Thus, the clinical manifestations of SCD are diverse and any organ system may be affected (Alabdulaali, 2007). The current study demonstrated higher percent of complications in SCD patients than in the SCT group. In the SCD group, the most frequent complication was pain in the bones and kidneys. On the contrary, leg ulcers,

pulmonary hypertension and brain stroke were detected only in 10-20 % of cases. In the SCT group, bone and chest pains were also the most frequent symptoms. The lower frequency of severe complications in both groups confirms the previously (Alabdulaali, 2007) reported finding that patients in Hofuf area have mild form of the disease with good outcome. This could be attributed to their Asian haplotypes (El-Hazmi *et al*., 1999) and/ or the effective inhibition of deoxyhemoglbin S polymerization by Hb F as reported by Borba *et al*. (2003).

Although statistically insignificant, SCD patients with different symptoms had lower survivin concentrations than SCT patients with the same symptoms. In this study, the patient with the highest serum survivin concentration (26.4 pg/ml) was of special interest. Surprisingly; his Hb S, Hb F and Hb A 2 concentrations were 71.7%, 25.6% and 2.7%, respectively. He was on folic acid and was the only patient in SCD group who didn't have history of hemolytic crisis. Taken together; these findings might reflect the protective effect of hemoglobin F and/ or survivin against the development of clinical complications in sickle cell anemia.

Knowing the level of Hb F in an individual is insufficient to foretell the likely complications due to the differential clinical response among patients achieving similar Hb F levels (Steinberg, 2005). In the present study, patients with SCD had Hb F with a range of 16.8 - 26.9%. Surprisingly, patients with symptoms had a trend for lower survivin than patients without symptoms. This might indicate decreased viability of RBCs in symptomatic patients and might confirm the previous finding (Li *et al*., 1999) that survivin is essential for the viability of proliferating cells. Consequently, further studies are needed to prove that the expression of survivin in SCD patients may be more reliable indicator of good prognosis than Hb F.

Examining the relationship of s ICAM-1 with the different clinical variables revealed positive but insignificant correlation with age or gender in the SCD and SCT groups. Similarly, Kato *et al*. (2005) didn't find significant association between s ICAM-1 and both age and gender in patients with SCD. Meanwhile, the positive significant association between s ICAM-1 and ALT in the SCT group might potentially reflect pathological activation of hepatic vascular endothelium. Supporting this interpretation, Kato *et al*. (2005) as well as other investigators has found association between s ICAM-1 and both direct bilirubin and alkaline phosphatase in patients with SCD. On the other hand, the pattern of s ICAM-1 expression in relation to the different symptoms was not uniform. Thus, it needs further investigation to be explained.

Serum Lp (a) was first identified by Berg (1963). It is a particle with an unusual structure consisting of apo (a), which is linked to apo B-100 of an LDL-like particle through disulfide bonds. Apo (a) itself seemed to be responsible for the over expression of ICAM-1 induced by Lp a (Takami *et al*., 1998**)**. The current study revealed insignificant increase in Lp (a) concentrations in patients with SCD than in the other two groups. Moreover, it is significantly correlated with serum ALT and creatinine levels in the same group of patients. This might indicate its correlation with s ICAM-1expression and endothelial activation in the livers and kidneys of this group of patients.

The association between Lp (a), survivin and s ICAM-1 in patients with sickle cell anemia was not examined before. Our results showed positive association between Lp (a) and survivin ($P \leq 0.05$) as well as an insignificant association between Lp (a) and s ICAM-1. Moreover, the significant positive correlation between Lp (a), survivin and s ICAM-1 in one hand and MCV, reticulocytic count, ALT and creatinine in the other hand, suggest differential tissue expression of these three markers.

In conclusion:

our study confirms that the hematopoietic system is extremely sensitive to survivin expression. More studies are urgently recommended to support the findings of the current study which indicate that survivin expression might provide reliable predictor of good prognosis in patients with sickle cell anemia.

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دور السيرفيفين والجزيء الذائب اللاصق للخلايا (١) فى مرض فقر الدم المنجلى

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الملخص:

مما لا شك فيه أن المقدرة على التنبؤ بتطورات مرض فقر الدم المنجلي يساعد على تحديد العلاج المناسب لهؤلاء المرضى. أثبتت الدراسات السابقة أن الجزيئات المسببة للالتصاق الخلايا، ذات علاقة وثيقة بالمضاعفات الناتجة عن التهابات الأوعية الدموية في بعض الأمراض. كما أثبتت دراسات أخرى أن كل من السيرفيفين والليبوبروتين ـ أ، يحفز تكوين الجزيء اللاصق الذائب- ١. لذلك افترضت الدراسة الحالية أن تؤثر هذه الجزيئات في حدوث المضاعفات التي تظهر لمرضى فقر الدم المنجلي.

احتوت هذه الدراسة على أربعين مريض بفقر الدم المنجلي وكذلك على ثلاث وثلاثين شخص أصحاء من منطقة الأحساء بالمملكة العربية السعودية. تم فصل أنواع الهيموجلوبين المختلفة بواسطة الرحال الكهربائي، وتحديد عدد الخلايا الشبكية, كذلك قياس بعض وظائف الكلى والكبد ومستوي والليبوبروتين ـ أ، السيرفيفين، والجزيء اللاصق الذائب ـ ١ في مصل المرضى باستخدام الطرق القياسية.

أظهرت النتائج زيادة مستوى السيرفيفين والليبوبروتين ـ أ في مجموعة مرضى فقر الدم المنجلي عن المجموعتين الأخريين بصورة لا يعتد بها إحصائيا. وقد كان مستوي السيرفيفين أعلى في المرضى الذين لم يعانوا من مضاعفات المرض عن المرضى الذين يعانون من تلك المضاعفات. ولم تظهر أي نوبة لتكسير كريات الدم الحمر في المريض الذي ظهر عنده أعلى تركيز السيرفيفين. وقد أكدت العلاقة الايجابية بين السيرفيفين وكل من حجم كريات الدم الحمر وعدد الخلايا الشبكية على أهميته في تكوين وحيوية هذه الخلايا. كما أكدت العلاقة الإيجابية بين كل من والليبوبروتين أ والجزيء اللاصق الذائب مع وظائف الكلى والكبد على ارتباطهم بالخلل الموجود في الغشاء المبطن للأوعية الدموية. وأظهرت الدراسة وجود علاقة موجبة بين كل من والليبوبروتين ـ أ والسيرفيفبن والجزيء اللاصق الذائب- ١.

استخلص البحث أنه من المحتمل أن يقدم مستوى السيرفيفين مؤشراً مناسبا يدل على تحسن الحالة الصحية لمرضى فقر الدم المنجلي.