TO STUDY THE ASSOCIATION OF ELEVATED PULSE PRESSURE WITH HAEMOLYSIS, PROTEINURIA AND CHRONIC KIDNEY DISEASE IN SICKLE CELL DISEASE PATIENTS
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ABSTRACT
BACKGROUND
The aim of this study is to explore and assess the relationship of elevated pulse pressure with haemolysis, proteinuria and chronic kidney disease in sickle cell disease (SCD) persons.

MATERIALS AND METHODS
This was a cross-sectional study. About 102 patients who were admitted during March 1, 2015 to September 30, 2016 at MYH and MGM Medical College Hospital, Indore were examined for study purpose. The patients of sickle cell disease were selected on the basis of inclusion and exclusion criteria. All patients enrolled were submitted for a clinical examination and later a laboratory work up. Results were analysed using Student’s t-test (two tailed, independent) and Pearson’s correlation test to assess any possible correlation of elevated pulse pressure with different biomarkers of haemolysis, proteinuria and chronic kidney disease.

RESULTS
In this study, we found that the elevated pulse pressure had a positive correlation with the presence of protienuria, chronic kidney disease and elevated serum creatinine in patients with sickle cell disease. In addition it also had a positive correlation with raised liver enzymes, reticulocyte count and systolic blood pressure suggesting a positive correlation with haemolysis and liver disease.

CONCLUSION
Elevated pulse pressure is closely linked to haemolysis, proteinuria and chronic kidney disease in SCD patients and further studies may be warranted to prove it as an independent predictor.

KEYWORDS
Sickle Cell Disease, Biomarker, Elevated Pulse Pressure, Haemolysis, Proteinuria, Chronic Kidney Disease.

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BACKGROUND
Sickle cell disease is a group of blood disorders with an autosomal recessive inheritance, which is found globally. When erythrocytes get sickled and deoxygenated due to a mutation in the β globin gene of haemoglobin, this type of blood disorder is called sickle cell disease (SCD). SCD is associated with a number of acute and chronic health problems. In certain SCD patients, probably with increased pulse pressure and normal blood pressure there is increased risk of complications like haemolysis, cardiovascular complications and kidney diseases.¹

Haemolysis is the breakdown of the RBC’s membrane and release of haemoglobin and other internal components into plasma. Haemolysis in SCD is caused by endothelial dysfunction via multiple mechanisms and both haemolysis and endothelial dysfunction may be independently linked to elevated pulse pressure.²,³,⁴,⁵,⁶,⁷

Proteinuria is the excretion of increased proteins in the urine. Proteinuria maybe a sign of renal (kidney) damage. Among patients with sickle cell disease, the prevalence of proteinuria has been estimated to be 20- 25 % and decreased kidney function has been reported in about 5-30 % of patients. Among patients with other sickling haemoglobinopathies, albuminuria and/or proteinuria have been reported to be present in about 8-30 % of patients with increasing prevalence with age. Decreased kidney function is seen in about 6 percent of patients.⁸,⁹,¹⁰,¹¹ CKD, also known as chronic kidney disease is the progressive loss of kidney function over a period of months or years. Renal disease is seen in 15-18% of all SCD patients and is a cause of early death.¹²,¹³
AIM AND OBJECTIVES
The aim of this study was to explore and evaluate the relationship between the elevated pulse pressure and haemolysis, proteinuria and chronic kidney disease in sickle cell disease patients.

Inclusion Criteria
- Diagnosed sickle cell disease patients.
- Age Group- above 10 years.

Exclusion Criteria
- Prisoners.
- Mentally ill patients.
- Patients not giving consent.

MATERIALS AND METHODS
About 102 patients were enrolled for the study. All the personal information and vital statistics were obtained in the form of a questionnaire. All the patients were submitted for a complete physical examination. Laboratory investigations including Hb, total blood count, albumin, creatinine, AST, ALT and LDH were done in the laboratory of MGM Medical College and MY Hospital, Indore. Reticulocyte count was measured by new methylene blue reagent. Urine protein test, urine sugar, urine dipstick test and microscopic examination were done for urine samples. CKD-EPI formula was used for e-GFR estimation.

Statistical Methods
The statistical software namely SPSS 15.0, Stata 8.0 and GraphPad were used for the analysis of the data. Student’s t-test (two tailed, independent) and Pearson’s correlation test has been used for to find the association between elevated pulse pressure and other parameters.

RESULTS
The results are as tabulated in the table below. The p-value and r-value of different clinical and laboratory parameters and their correlation and possible statistical significance with elevated pulse pressure in SCD patients were summarised in the table. These results showed that the elevated pulse pressure is associated with haemolysis, proteinuria and chronic kidney disease in SCD.

<table>
<thead>
<tr>
<th>Sl. No.</th>
<th>Parameters</th>
<th>p-value</th>
<th>r-value</th>
<th>Correlation</th>
<th>Significance</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>SBP</td>
<td>0.00</td>
<td>0.379</td>
<td>Positive</td>
<td>Yes</td>
</tr>
<tr>
<td>2.</td>
<td>DBP</td>
<td>0.001</td>
<td>-0.312</td>
<td>Negative</td>
<td>Yes</td>
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<tr>
<td>3.</td>
<td>Hb</td>
<td>0.052</td>
<td>-0.193</td>
<td>Negative</td>
<td>No</td>
</tr>
<tr>
<td>4.</td>
<td>Reticulocyte count</td>
<td>0.01</td>
<td>0.31</td>
<td>Positive</td>
<td>Yes</td>
</tr>
<tr>
<td>5.</td>
<td>LDH</td>
<td>0.002</td>
<td>0.298</td>
<td>Positive</td>
<td>Yes</td>
</tr>
<tr>
<td>6.</td>
<td>Total bilirubin</td>
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<td>0.375</td>
<td>Positive</td>
<td>Yes</td>
</tr>
<tr>
<td>7.</td>
<td>Serum creatinine</td>
<td>0.003</td>
<td>0.292</td>
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<td>Yes</td>
</tr>
<tr>
<td>8.</td>
<td>Proteinuria</td>
<td>0.00</td>
<td>0.424</td>
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<td>9.</td>
<td>eGFR</td>
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<td>-0.339</td>
<td>Negative</td>
<td>Yes</td>
</tr>
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<td>10.</td>
<td>CKD</td>
<td>0.00</td>
<td>0.463</td>
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<td>Yes</td>
</tr>
<tr>
<td>11.</td>
<td>AST</td>
<td>0.027</td>
<td>0.220</td>
<td>Positive</td>
<td>Yes</td>
</tr>
<tr>
<td>12.</td>
<td>ALT</td>
<td>0.026</td>
<td>0.220</td>
<td>Positive</td>
<td>Yes</td>
</tr>
<tr>
<td>13.</td>
<td>Alkaline phosphatase</td>
<td>0.021</td>
<td>0.228</td>
<td>Positive</td>
<td>Yes</td>
</tr>
</tbody>
</table>

Table 1. Statistical Analysis of Different Parameters with Elevated Pulse Pressure in SCD Patients

DISCUSSION
A seeming paradox of sickle cell disease is that patient’s do not suffer from a high prevalence of systemic hypertension in spite of endothelial dysfunction, chronic inflammation and vasculopathy. However, some patients do develop systolic hypertension and increased pulse pressure, an increasingly recognised major cardiovascular risk factor in other populations. Pulse pressure, in spite of never been thoroughly investigated in SCD is an important risk factor for the damage of end-organ damage, cardiovascular morbidity and mortality in many conditions.

Two major studies analyses the effects of blood pressure including pulse pressure on haemolysis and end organ damage.

According to The Cooperative Study of Sickle Cell Disease (CSSCD) the SCD patients (a natural history study of SCD cohort in the pre-hydroxyurea era) particularly those with HbSS had lower overall median systolic BP (113±14.5 mmHg) than normative control, a difference observed for all age groups and both sexes.

According to walk-PHaSST study, a international multicenter cross-sectional cohort study, the pulse pressure is predicted by haemolysis in the patient with HbSS. In the hydroxyurea era, the UNC (University of North Carolina) cohort had a higher systolic blood pressure (122±15 mmHg) as in the age-matched African-American control subjects.

These studies shown that the elevations of systolic blood pressure in SCD patient over baseline are detrimental, which have a risk of vascular dysfunction, including stroke, kidney disease and pulmonary hypertension.

In SCD patients, the pulse pressure is increasingly recognised as a cardiovascular risk factor. walk-PHaSST study findings suggest that elevated pulse pressure maybe more reflective of the peculiar vasculopathy of SCD where haemolysis resulted in increased arterial stiffness from nitric oxide depletion and decreased peripheral vascular resistance from anaemia leading to elevated pulse pressure.
We found that most of the patients in group of lower haemoglobin levels were having elevated pulse pressure in our study. There is increased level of reticulocyte count in these patients and there is also increased level of LDH in patients having elevated pulse pressure. Also the levels of haemolysis markers are much higher than the upper limit of normal values in patients with elevated pulse pressure. In our study, we found that markers of haemolysis were correlating positively with elevated pulse pressure.

In our study, we found that markers of renal function deterioration reflected by increased level of creatinine and proteinuria were present in patients with elevated pulse pressure and the level of these markers were markedly elevated in these patients. Hence it may be concluded that elevated pulse pressure can reflect deteriorating renal functions in sickle cell patients. 56% of patients with sickle cell disease were having chronic kidney disease ranging from stage 1 to stage 3. However there is a negative correlation between elevated pulse pressure and estimated GFR in this study.

Since abnormalities in kidney function are among the most sensitive and earliest biomarkers of microvascular dysfunction in SCD, it may be important to therapeutically target blood pressure early and aggressively to prevent kidney dysfunction and its complications. The angiotensin-converting enzyme inhibitors may reduce proteinuria in SCD patient, but there is no clear evidence to know which subgroup of patients may benefit from such intervention. The optimal blood pressure at which these angiotensin-converting enzyme inhibitors should be initiated is however unknown and neither it is certain that the therapy would indeed delay the reduction of albuminuria and slows the long-term clinical outcomes such as need for kidney replacement therapy and death.

Based on our results, treatments aimed at reducing haemolysis may, however, also benefit the prevention of microvascular renal complications independently of other therapeutic interventions.

In walk-PHASST, an international multicenter cross-sectional cohort study, there was no correlation between pulse pressure and liver enzymes (AST, ALT, alkaline phosphatase) But, in our study, we found a significant association of elevated pulse pressure with AST, ALT and alkaline phosphatase. These findings suggest that liver functions are also deranged in patients with elevated pulse pressure. It may due effect of acute derangement of liver functions in crisis state of sickle cell disease patients.

**CONCLUSION**

Our results show that elevated pulse pressure is closely linked to haemolysis, proteinuria and chronic kidney disease in SCD and it can be taken as a marker to predict these complications of occurrence of haemolysis and CKD in these patients. However a larger study may be required to further substantiate this claim.

**REFERENCES**


