INTRODUCTION
As a global health problem sickle cell anemia affects many world populations. Knowledge of a disease to early death has existed in Africa for over a century. 

1.1 HISTORICAL BACKGROUND: The ancient lore and more modern beliefs about sickle cell disease in Africa have been summarized by Edelstine. Sickle cell disease under various names was thought by Konotey-Ahulu. In 1910, Dr. J. B. Herrick, a physician in Chicago, first described sickle cell, having observed curious poikilocytes on the stained blood smear of a dental student from Grenada. The student subsequently had a painful crisis, which Herrick suggested might be related to his abnormal red cells. The demonstration of induced sickling in wet sealed preparations was made by Emmel in 1917 and oxygen dependence of the change to the sickle shape by Hahn and Gillespie in 1927. The later investigators showed that the sickle shape appeared in red cell suspension at oxygen tensions < 45 mm Hg and that sickling was inhibited at pH > 7.4; sickled cells would revert to normal shape on reoxygenation, and cells exposed to carbon monoxide did not sickle.

Sherman noted that sickling was more readily in red cells obtained from anemic patients with sickling than in cells from non anemic individuals with sickle cell trait. Using a polarizing microscope Sherman also in 1940 noted that sickled cell were birefringent, reflecting as others pointed out, alignment of certain molecules within the cell. A New York pediatric hematologist, Janet Watson and his colleagues suggested in 1948 that paucity of sickle cells in newborn African – American reflected an abnormality of hemoglobin in adults with sickle cell disease that was not present in the fetal hemoglobin of the infants.

Against the background of hard-won knowledge two major advances occurred in the late 1940s: First, in 1949, Linus Pauling and his associates demonstrated that hemoglobin prepared from the red cell of patients with sickle cell anemia differed electrophoretically from the hemoglobin of normal individuals and the hemoglobin of individuals with the asymptomatic sickle cell trait appeared to be a mixture of normal and sickle hemoglobin. The second advance came from formal
genetic analyses of families, carried out by several investigators\textsuperscript{10,11,12}, with the most complicated studies performed by Neel\textsuperscript{11}, who showed that both parents of children with sickle cell anemia had sickle cell trait and concluded that sickle cell anemia represented homozygosity for a gene that in the heterozygous state was manifest as sickle cell trait.

In 1950, Harris\textsuperscript{13} demonstrated gelling of deoxygenated Hb S, and Perutz and Mitchison\textsuperscript{14} reported that crystals of deoxy Hb S were birefringent and had decreased solubility. The cardinal properties of hemoglobin as a transport protein for oxygen and carbon dioxide were known by 1910: its oxygen affinity permitted reversible combination with oxygen at atmospheric oxygen pressure, and its oxygen affinity increased with oxygenation and decreased with increasing pH\textsuperscript{15}. It was not until about 1960 that two landmark observations began to provide a structural basis for normal hemoglobin function and thereby impacted clinical and chemical considerations of all hemoglobins: (a) the work of several groups established the subunit structure and primary sequences of subunits(\( \alpha, \beta, \gamma \)) of human hemoglobin and (b) the model of hemoglobin based on x-ray crystallography was published by Perutz and his associates\textsuperscript{16} in 1960. Vernon Ingram\textsuperscript{17} discovered that the defect of the disease was a single amino acid substitution in the hemoglobin molecule of sickle cell.

Millions of people worldwide affected by sickle cell disease, the most commonly observed Haemoglobinopathy poses significant challenges for clinician and scientist. Treatment for the symptoms and complication of the condition are available, but in most cases there is no cure. Some researchers believe that bone marrow transplant may offer a cure in a small number of cases\textsuperscript{18}.

It is an autosomal recessive disease, commonly found in tropical countries. It is the most common single genetic mutation in human and abundantly present in large part of the world i.e. Africa, Mediterranean countries, Middle East and parts of South American countries, India and others parts of the globe where people originating from these countries have settled. In India the Sickle Cell belonging to the same haplotype and is stated to have evolved independency. Clinical and hematological also the sickle cell disease prevalence in India is different from the
rest of the world\textsuperscript{19}. In India the clinical manifestation of sickle cell anemia seems to be milder than in Africa and Jamaica\textsuperscript{20}.

1.2 CRISIS\textsuperscript{S:} Four major types of crises are recognized in sickle cell anaemia: aplastic, acute sequestration, hyper-haemolytic, and vaso-occlusive crises. Hyper-haemolytic crises are less commonly reported in literature from the temperate climates\textsuperscript{21,22,23}. This continues to be a major problem among patients with sickle cell anaemia in tropical Africa where the natural history of the disease is somewhat complicated with recurrent episodes of malarial infection\textsuperscript{24, 25, 26}. Apart from the vaso-occlusive crises, the first three listed above could lead to severe anaemia in patients with sickle cell anaemia.

1.2.1 Vasoocclusive Crisis:- The hallmark of sickle cell disease is the vasoocclusive pain crisis. It is the most common clinical manifestation but can occur with varying frequency in different individuals. It results from the complex interplay between sickled red cells, neutrophils, endothelium and plasma factors. The end result is that of tissue hypoxia leading to tissue death and accompanying pain. Crisis may affect any tissue, but patients typically complaint of pain in the chest, lower back and extremities. Abdominal pain occurs and may mimic acute abdomen from other causes. Fever is often present, even in the absence of infection episodes may be precipitated by dehydration, infection and cold weather, although in about half of cases no precipitating factor is found.\textsuperscript{27} repeated splenic infarction in childhood typically results in “autosplenectomy” and loss of splenic function by age 6 to 8 years.\textsuperscript{28} phases of vasoocclusive episodes have been described in children and adults.\textsuperscript{29, 30} These include a prodormal phase characterized by low intensity pain, parasthesias, decreased red cell deformability and an increase in irreversibly sickled cells followed by an initial, evolving phase characterized by increasing pain and worsening of hematologic parameters. This is then followed by and established phase with steady, severe pain, increased hemolysis, increase neutrophils and increased acute phase reactant, at which time patients typically seek medical care. The characterization of phases has implications for clinical research.

1.2.2 Aplastic Crisis:- Aplastic crisis in sickle cell anemia is akin to that seen in other hematologic disorders where there is a cessation in red cell production in the face of
ongoing hemolysis resulting in an acute, severe drop in hemoglobin levels. The characteristic laboratory finding is a decrease in reticulocytes count to less than 1 percent. It is usually associated with infections. The most common causative agent is parvovirus B19, which attaches to the P antigen receptor on erythroid progenitor cells, causing a temporary arrest in red cell production.\textsuperscript{31, 32} Recurrent aplastic crises by parvovirus B19 is rare because of the development of protective antibodies. Although classically responsible for decreased red cell production, pancytopenia may occur. Other rare complications associated with parvovirus B19 include acute splenic sequestration, hepatic sequestration, acute chest syndrome, marrow necrosis, and renal dysfunction.\textsuperscript{33-38}

\textbf{1.2.3 Sequestration Crisis}:- This type of crisis is characterized by sudden, massive pooling of red cells, especially in the spleen, which may result in hypovolemic shock and cardiovascular collapse.\textsuperscript{39} It is typically seen in infants and children (usually <5 years of age) prior to autoinfarction of the spleen but can be seen in adults with Hb SC disease or Hb Sβ-Thalassemia with persisting splenomegaly.\textsuperscript{40, 41, 42} A minor sequestration episode is usually accompanied by a hemoglobin of more than 7g/dL, and a major episodes usually is one in which the hemoglobin has decreased by 7 g/dL or the hemoglobin has decreased by 3 g/dL from baseline.\textsuperscript{43}

\textbf{1.2.4 Hyperhemolytic Crisis}:- This is a term used to describe the occurrence of episodes of accelerated hemolysis characterized by decreased blood hemoglobin, increasing reticulocytes, and other markers of hemolysis like hyperbilirubinemia, increased LDH. Episodes of hyperhemolysis are known to occur in certain conditions; resolution phase of a vasoocclusive crisis during which irreversibly sickled red cells and dense red cells trapped in the microcirculation are rapidly destroyed is one such example.

Sickle haemoglobin and β-thalassaemia these two haemoglobinopathies are common in Central India and are important from clinical and disease burden point of view. These disorders are mainly present in Scheduled Tribes and Scheduled Castes as compared to other endogamous groups of Central India. There is heterogeneity in the distribution of these deleterious genes in the area. In some
endogamous groups like Jharia, Mehra in Scheduled Caste group and Pradhan. Panika, Barela, Bhilala in Scheduled Tribe group, sickle haemoglobin has high prevalence and β-thalassaemia is very low or absent. In some primitive tribes like Saharia, Hill Korba, Kamar sickle haemoglobin is either absent or with low prevalence but β-thalassaemia is common. The distribution of the ethnic (caste & tribe) groups is also uneven in the various pockets of Madhya Pradesh and Chhattisgarh. For examples Jhabua, Dhar, Badwani and Mandla districts of Madhya Pradesh and Bastar, Surguja and Narayanpur districts of Chhattisgarh has high (>60%) proportion of tribes whereas in many districts the proportion of tribal population is less than 20 percent. Both these states need micro level planning to develop the infrastructural facilities, based on the type of abnormal gene and population size of STs and SCs, to diagnose manage and prevent the disease in the area.

There are large variations in prevalence of sickle hemoglobin in various tribal/scheduled caste populations of a geographical area/district and within a tribe/caste population scattered over a large area.

Marriage patterns/customs of the people are the main cause for the transmission of the disorder. The tribal populations as well as other non-tribal populations of Central India are strictly endogamous and generally the marital distances are small. Hence it requires to map the prevalence of sickle cell gene and β-thalassaemia gene in various population (ST and SC communities) groups at district level in Central India (states of Madhya Pradesh and Chhattisgarh). Out of 45 districts of the state, 27 districts fall under the sickle cell gene belt. These districts (arranged in descending order according to percentage of ST and SC population) are Jhabua, Barwani, Dindori, Mandla, Dhar, Shahdol, Umaria, Betul, Seoni, West Nimar, Chhindwara, Harda, East Nimar, Jabalpur, Ratlam, Dewas, Katni, Damoh, Hoshangabad, Sagar, Satna, Balaghat, Ujjain, Indore, Mandsaur, Neemuch and Narsimhpur. Similarly in Chhattisgarh, the sickle haemoglobin is common in central and southern parts.44

The clinical manifestations of sickle cell disease greatly outnumber its conspicuous features, anemia and “pain crisis”. Chronic anemia is not an everyday
concern in sickle cell disease, but exacerbations of the anemia may be life-threatening and are thereby important clinical considerations. Among the organ rendered dysfunction earliest by sickle cell disease is spleen, and its genotype dependent damage, autoinfarction, hypertrophy, sequestration, abscesses, and hemorrhage pose lifelong dangers to patients and challenges to clinicians. Recent advances in understanding, diagnosing and treating of complications have enhanced the clinical well-being of sickle cell disease patients, but further improvements are needed. Life-long overproduction of Bilirubin due to overproduction chronic hemolysis places a great burden on the liver and biliary tract; a majority of adult patients with sickle cell anemia develop gallstones. The liver is at further risk from circulatory impairment, inspissations of sludge in the biliary tree, and exposure to transfusion-transmitted infectious agents. The exquisite susceptibility of the kidney to the ravages of sickle cells is illustrated by the fact that renal complications occur even in sickle cell trait. Renal manifestations range from the generally benign hyposthenuria and hematuria of both sickle cell trait and disease to the more serious acidosis, hyperkalemia, nephrosis, and renal insufficiency of sickle cell disease. Acute pulmonary complications are life threatening, and chronic sequelae are the source of considerable morbidity.

Clinical approaches to these complications currently lack the benefit of complete pathophysiological and biochemical understanding.

Blood counts, erythrocyte indices, and measurements of various biochemical parameters vary greatly within and among the various anemic crises present in genotype of sickle cell disease. Laboratory values beyond the expected abnormal range may signify accelerated organ damage or a new disease complication.

Therefore, present study is aimed to assess the apparent role of biochemical indices in various anaemic crises present in sickle cell disease to enhance our understanding of sickle cell disease.