# INTRODUCTION

Sickle cell disease (SCD) is a hemolytic anemia, characterized by abnormal hemoglobin production of autosomal recessive inheritance. SCD may lead to acute and chronic tissue ischemia and many organ dysfunctions due to intermittent small vascular obstructions ***(Ozen et al., 2013)***.

In contrast to many inherited anaemias, in SCD, iron overload does not occur without blood transfusion ***(Porter and Garbowski, 2013)*** Sequential transfusions are related to iron overload and, eventually, to organ damage. Endocrine dysfunction is one of the most important complications ***(Alves and Braid, 2011)***.

The main complications in SCD are impairment of microcirculation and functional abnormalities of the organs ***(Ballas, 2002).***

Investigators propose that disruptions of tissue vitalization during vaso-occlusive crisis and inflammatory mediators may also cause thyroid dysfunction ***(Ozen et al., 2013)***.

Doppler ultrasound allows the measurement of blood flow velocity in major arteries supplying the thyroid gland, and blood flow velocities and other Doppler indices maybe more objective parameters in the diagnosis and follow-up of diffuse thyroid disease ***(Yazici et al., 2007)***. Previous studies have established role of Doppler ultrasound in many thyroid

disorders ***(Ishay et al., 2010; Kumar et al., 2009; Kumar et al., 2009; Bogazzi et al., 1999)***.

Researchers have suggested that intraparenchymal Doppler measurements may be more reliable for detecting alternations of thyroid microcirculation and disease activity and is a useful index of thyroid function before any invasive tests ***(Karazincir et al., 2013)***.

# AIM OF THE WORK

**The aim of this work is**

1) To evaluate the intrathyroidal hemodynamic changes and thyroidal volume in sickle cell disease (SCD) patients and its relation to disease severity and iron overload state.

2) To assess the relation of these hemodynamic changes and thyroidal volume and the thyroid functions tests.

# SICKLE CELL DISEASE

## Definition

Sickle cell disease (SCD) is a hereditary hemoglobinopathy characterized by abnormal hemoglobin (Hb) production, hemolytic anemia and intermittent occlusion of small vessels, leading to acute and chronic tissue ischemia, chronic organ damage and organ dysfunction ***(Smiley et al., 2008).***

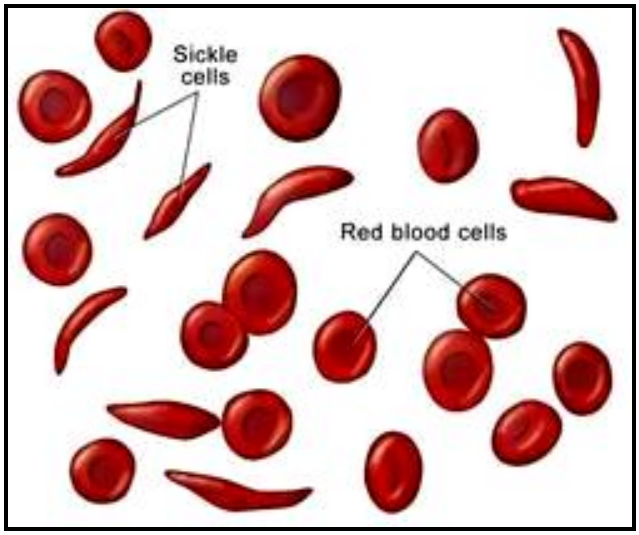


**Figure (1):** The difference between the sickle cell and the normal red blood cell ***(www.vanguardngr.com).***

## Epidemiology and Geographical distribution

Worldwide estimates for neonates born with SCD each year is 400.000 including 300.000 with Sickle cell anemia (SCA) ***(Piel et al., 2013).***

HbS was identified in Malarious regions across Sub-Saharan African, parts of Mediterranean including Greece,

Turkey, various Oases on the eastern &western coast of Arabian Peninsula, India**.** In contrast, HbS was absent in Americans, Northen European and Oceanian populations ***(Piel et al., 2010).*** And became relatively prevalent in African –American populations as in USA, Brazil and Carribean ***(King et al., 2007).***

The greatest burden is seen in Sub-Saharan Africa, where more than 75% of all SCD occurs, with this proportion projected to increase by 2050 ***(Piel et al., 2013).*** As in Sub-Saharan Africa and Uganda, 20.000 babies per year are thaught to be born with SCD ***(Ndeezi et al., 2016).***

Four haplotypes are associated with HbS in Africa (Benin, Central African Republic, Senegal and Cameroon) and the fifth haplotype is thaught to have arisen in (India and Arabian Peninsula), suggesting that these haplotypes have an effect on the severity of the disease ***(Bitoungui et al., 2015).***

In Egypt; along the Nile Valley, The HbS gene is almost non existent, but in the Western desert near the Libyan border, variable rates of 0.38% in the coastal rates to 9% in the New Valley Oases have been reported. HbS carrier rates vary from 9 to 22% in some regions ***(El-Beshlawy, 2009; Moez and Younan, 2015).***

The major haplotypes with SCD mutation in Egypt are of Senegal and Benin ***(Powars et al., 2002).***

## Genetics

Sickle cell disease (SCD) is an Autosomal Recessive (AR) disorder that result from an abnormal gene found on short arm of Chromosome 11; this lead to the production of a mutated form of Hemoglobin (Hb) and Hemoglobin S (HbS), where a single amino acid (a.a), Glutamic acid is replaced by Valine at sixth position of the 146 amino acids of Hb β chain ***(AL-Salem, 2016).***

The interaction between $\beta^s$ gene and $\beta^c$ gene lead to a typically very mild sickling disorder known as" HbSC" disease; While a $\beta^s$ gene interacts with a β-Thalassemia gene, the severity of the resulting sickling disorder depends on the severity of Co-inherited β-Thalassemia ***(Frenette and Atweh, 2007).***

When the mutation of the β-Thalassemia is mild, the resulting Sβ-Thalassemia tends to be mild clinically as in African descent people; if the mutation is severe, the sickling disorder tends to be moderate clinically as in Mediterranean people ***(Kaur et al., 2013).***

## Fetal hemoglobin (HbF) as 2ry modification in SCA:

HbF is the most powerful genetic modulator of the clinical and hematological features of SCA, this is dependent on its ability to prevent deoxy HbS polymerization ***(Ngo and Steinberg, 2014).*** It is genetically regulated, and its level and distribution among sickle erythrocytes is highly variable ***(Akinsheye et al., 2011).***

In addition; HbF appears to benefit some complications of sickle cell disease more than others due to premature destruction of erythrocytes that do not contain HbF even if concentration of HbF is high ***(Akinsheye et al., 2011).***

Accordingly; the high level of HbF during the infancy has been recognized as an important factor predicting increased life expectancy and reducing the frequency of both acute pain and leg ulcers ***(Rees et al., 2010).***

## Sickle cell variants

### *a) Sickle cell trait (HbSC);*

It is a heterozygote form of SCD, having both HbA and HbS. The heterozygous individuals are not anemic and have normal red cell indices with HbS percentage typically near 40%; Therefore the amount of HbS present is insufficient to produce sickling disorders, these individuals are asymptomatic but at risk for several complications ***(Bender and Gabrielle, 2014).***

### *b) Sickle cell anemia (HbSS):*

It is a homozygote form of SCD, and is generally considered the most severe form of SCD ***(Booth et al., 2010)***, having red cell containing 90-100% HbS ***(Nathan et al., 2000).***

### *c) Sickle βthalassemia ( HbS/β-thalassemia):*

It is due to co-inheritance between sickle beta globin S allele with beta thalassemia allele ***(Escourt et al., 2016);*** including:

#### I. HbS/$\beta^0$-thalassemia:

It results from a completely co-inherited β thalassemia mutation, causing the sickling disorder to be as severe as that of homozygote form ***(Kaur et al., 2013)***, having red cell containing 80-90% HbS and 2-15% HbF ***(Embury et al., 2004).***

#### II. HbS/β+-thalassemia:

It results from partially active of the co-inherited β thalassemia leading to the sickling disorder with a variable spectrum of clinical severity ***(Kaur et al., 2013)***, having red cell containing ≥ 50% HbS ***(Kanter and Jarres, 2013);*** and 2-10% HbF ***(Embury et al., 2004);*** and 10-30 % HbA ***(Paul et al., 2007).***

#### III. HbSE syndrome:

It is a very rare heterozygote form. It is predominantly asymptomatic sickling disorder ***(Chui and Dover, 2001)***; having red cell containing 30-40% HbE, 50-60% HbS and 0-10% HbF ***(Acipayam et al., 2015).***

## Pathophysiology of SCD

Polymerization of HbS and Cell Sickling are the prime pathophysiological events in SCD. So; Oxygen tension and

intracellular HbS concentration are the 1ry molecular drivers of this process ***(Archer et al., 2015).***

## *A) HbS Polymerization:*

HbS arise from a mutation in the β-globin gene. This mutation produces a hydrophobic motif in the deoxygenated HbS tetramer which results in binding between β1 & β2 chains of two hemoglobin molecules. This crystallization produces a polymer nucleus, which grows and fills the erythrocyte, causing disruption in its architecture and flexibility and promoting cellular dehydration, with physical and oxidative cellular stress ***(Rees et al., 2010).***

The rate and extent of HbS polymerization is proportionate to the extent and duration of hemoglobin deoxygenation that is affected by co inheritance of genetic factors which modify the intracellular HbS or HbF concentration for example; the co-inherited of α-thalassemia or hereditary persistence of HbF ***(Rees et al., 2010).***

## *B) Vaso-occlusion "Cell Sickling":*

- **Sickle cell adhesion**

It is generally believed that vaso-occlusion develops from adhesion of sticky sickle cell RBCs to endothelium followed by trapping and polymerization of rigid less deformable cells as intercellular cell adhesion molecule-1, vascular cell adhesion molecule-1 and selectins ***(Kaul, 2008;***

***Archer et al., 2015).*** All interact with endothelial cells, RBCs and variety of soluble proteins within plasma, such as; thrombospondin (from platelets) and Von Willebrand factor from endothelial cells to mediate vasoocclusion within macro- and microvasculature ***(Makani et al., 2013).***

- **Role of Inflammation**

It enhances the expression of adhesion molecules, further increasing the tendency of sickled erythrocytes to adhere to the vascular endothelium and worsen vaso-occlusion ***(Rees et al., 2010).***

Ischemia-reperfusion injury release free hemoglobin and heme 2ry to RBCs lysis and increased placental growth factor (PLGF) production, all may be contributing to the inflammatory vasculopathy ***(Manawani and Frenette, 2013).***

Reperfusion of ischemic tissue promotes chronic inflammation by increased oxidative damage and adhesion of leukocytes (mainly neutrophils) to the endothelium followed by extravasation into the tissues and damage tissues ***(Manawani and Frenette, 2013).***

- **Oxidative stress**

The cycles of ischemia-perfusion injury causing activation of xanthine-xanthine oxidase system that disturbs normal redox state promoting intravascular oxidant stress and disrupting nitric oxide (NO) homeostasis ***(Wood et al., 2008).*** Chronic

proinflammatory response in sickle cell patients induced by constant recruitment of neutrophils and monocytes proved to play an important role in causing complications. So; the oxidation that is mediated by oxidants and free radicals which is called Reactive Oxygen Species (ROS) are formed as a byproduct of oxygen metabolism and nitric oxide. The increase in the normal redox state of a cell cause toxic effects resulting in cell and tissue damage ***(Queiroz and Lima, 2013).***

### *C) Hemolysis:*

It is caused by HbS polymerization and it is evidenced by its development of progressive vasculopathy ***(Kato et al., 2006)***. Hemolysis results in the release of Hb and arginase from erythrocytes increasing the consumption and decreasing production of Nitric Oxide (NO) respectively. NO is a critical regulator of vasodilation and vascular homeostasis whose inactivation produces vasoconstriction and proliferative vasculopathy ***(Rees et al., 2010).***

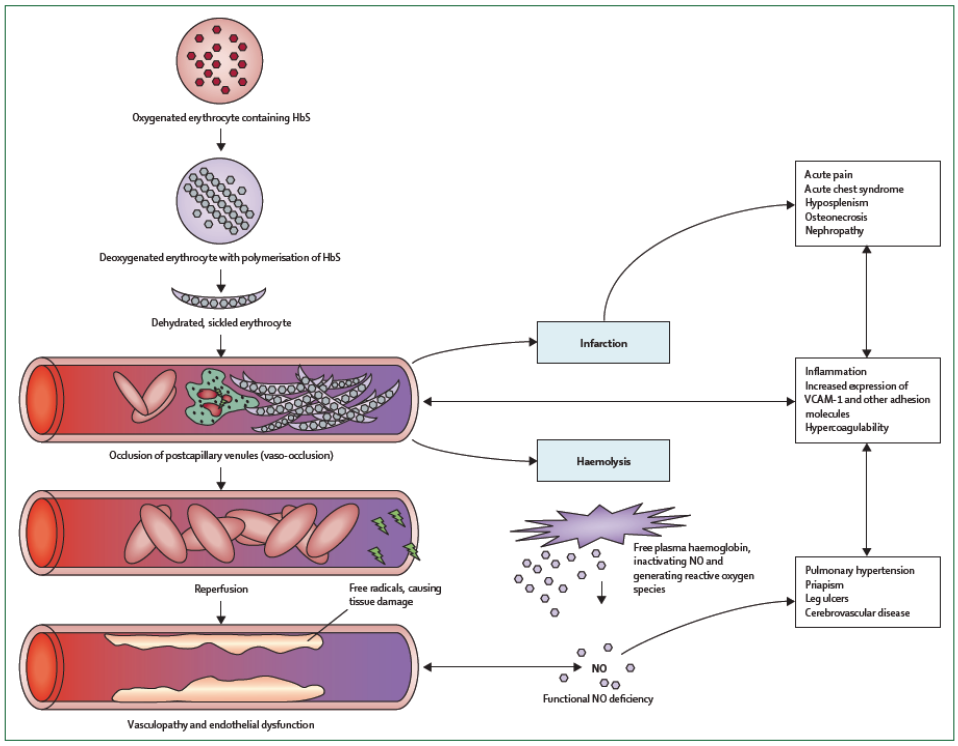


**Figure (2): The pathophysiology of sickle-cell disease.** The roles of HbS polymerisation, hyperviscosity, vaso-occlusion, hemolysis, and endothelial dysfunction. Deoxygenation causes HbS to polymerise, leading to sickled erythrocytes. Vaso-occlusion results from the interaction of sickled erythrocytes with leucocytes and the vascular endothelium. Vaso-occlusion then leads to inflammation which enhances the expression of adhesion molecules, further increasing the tendency of sickled erythrocytes to adhere to the vascular endothelium and to worsen vaso-occlusion. Reperfusion of the ischaemic tissue generates free radicals and oxidative damage. The damaged erythrocytes release free haemoglobin in to the plasma, which strongly bind to nitric oxide, causing functional nitric oxide deficiency and contributing to the development of vasculopathy. HbS=sickle haemoglobin. NO=nitric oxide. VCAM=vascular cell-adhesion molecule ***(Rees et al., 2010)***.

## Clinical Features and Complications

The major features are related to hemolytic anemia and vaso-occlusion, which can lead to acute & chronic pain and tissue ischemia or infarction ***(Vichinsky, 2016).***

## *1) Hemolytic Anemia:*

SCD is characterized by severe chronic hemolytic anemia which gradually develops over the first 2-4 months, parallel to the replacement of much of fetal hemoglobin by HbS ***(Quinn et al., 2004).***

As a result of hemolysis, the bone marrow becomes very active with immature RBCs or reticulocytes in the peripheral blood with increase platelets and WBCs as a consequence of increased erythropoiesis (ineffective erythropoiesis) ***(Roseff, 2009).***

### A) Acute Sequestration:

- ***Splenic sequestration***

The incidence of acute splenic sequestration occur in young age mostly under the age of 5 years ***(Roseff, 2009).***

It is most common in children with homozygous sickle cell disease (HbSS), however, children with variant disease can have acute splenic sequestration crisis at any time during childhood ***(McMahon, 2006).***

With splenic sequestration crisis, vasoocclusion within the spleen and splenic pooling of red cells producing a marked drop in Hemoglobin concentration accompanied by persistent reticulocytosis and a rapidly enlarged spleen. Parvovirus B19 infection may be a risk factor for splenic sequestration ***(Vichinsky, 2011).***

- ***Hepatic sequestration***

It is best described as a syndrome consisting of pain in Rt upper quadrant, hepatomegaly, a falling hematocrit and elevated ALT (usually <300 IU/L) ***(Ebert et al., 2010; Ballas et al., 2012).*** A rapid falling in the hematocrit paralleled a dramatic increase in the liver size ***(Banerjee et al., 2001).***

A reverse hepatic sequestration is a fatal case that has been described in which resolution of hepatic sequestration accompanied by a spontaneous and rapid rise in Hb over 24 hours, with the release of viable sequestered cells into the circulation causing death from hypervolemia, hypertension, heart failure and intracerebral hge ***(Banerjee et al., 2001).***

## B) Aplastic crisis:

It is characterized by a transient arrest of erythropoiesis, leading to sudden reductions in Hb concentration and red cell precursors in bone marrow and a markedly reduced number of reticulocytes in the peripheral blood ***(Vichinsky, 2011).*** The contributory factors are (lack of folic acid) or impaired its production by Human Parvovirus B19 which is responsible for 80% of crisis, as it can suppress bone marrow production by destroying the RBC precursor cells in marrow ***(Roseff, 2009).***

## C) Hyperhemolytic crisis:

It is defined as acute exacerbation of anemia along with the evidence of reticulocytosis ***(Vichinsky, 2011).*** It occurs

during the sitting of transfusion ***(Roseff, 2009).*** It can occur mostly due to infection and acute chest syndrome. Also, malaria and glucose 6-phosphate dehydrogenase deficiency in patients with SCD can lead to hyperhemolysis. It is characterized by a rapid drop in Hb & increased reticulocyte count ***(McMahon, 2006).***

## ***2) Vasoocclusive crisis:***

It is due to involvement of both macro and micro-circulation leading to end organ damage. As well as, the micro-circulation involvement causes acute painful crises ***(Embury et al., 2004).***

### A) Vasoocclusive pain

It is intense in SCD patients, although there is significant variability in the severity of frequency of acute painful episodes ***(George et al., 2013).*** Acute episodic pain is the most common reason for admission to hospital for both children and adults ***(Rees et al., 2010).*** However, the majority of pain episodes are managed at home with up to a third of patients having pain as often as daily ***(Smith et al., 2008).***

Recent studies show that the quality improvement methods (Home Pain Management Plans) was incorporated successfully into the daily work flow of the outpatient SCD clinic. So; using this intervention improve patient outcomes by decreasing avoidable Emergency Department Visits as well as reducing overall health care costs ***(Crosby et al., 2014).***