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A Review on Pathophysiology of Sickle cell Anemia and its Impact on Various Organ System

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ABSTRACT:

Sickle cell anemia is a hemoglobin disorder which is affecting relatively under privileged population like a tribal population who is belonging to economically poor background so might be lack of education and awareness about current health facility provided by the government and other helping organizations. While on the other hand the medical and para medical people too found difficulty in understanding about the sickle cell anemia and handling patients of it. No doubt so much work already done on understanding the pathophysiology of the disease and newer treatment for this lifelong disease. The current review is an initiative attempt to highlight the basic what kind of changes pathophysiologically occurs in sickle cell anemia and what kind of effect can be occur on various body organ systems are studied. This review can be helpful to the all health care provider and it might be helpful even to the general population to be aware about the disease and its complication.

KEY WORDS: Sickle cell anemia, hemoglobin disorder, Adhesion, Reperfusion, Vasoocclusion.

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INTRODUCTION:

Sickle cell anemia is a common hereditary hemoglobin disorder.[1] Hemoglobin, as we know, is a tetrameric protein composed of two pairs of globin chains. Normal adult red blood cells contain mainly adult hemoglobin ($\alpha_2\beta_2$), along with small amounts of A_2 hemoglobin ($\alpha_2\delta_2$) and fetal hemoglobin ($\alpha_2\gamma_2$). Sickle cell anemia is caused by a point mutation in the sixth codon of β-globin chain and that leads to the replacement of a glutamate with a valine. The abnormal physiochemical properties of the resulting sickle hemoglobin are responsible for the disease.[2] The prime objective of making review of such a disease is its prevalence and complications in south Gujarat region which needs a lot of attention from health care department.

Pathophysiology of Sickle Cell Anemia: - When deprived of oxygen, sickle cell molecules undergo polymerization a process sometimes called as gelation or crystallization. The change in physical state of sickle hemoglobin distorts red blood cells and turned into sickle shape.[1] Change in shape of red blood cells is initially reversible upon re- oxygenation to oxygen. However membrane damage occurs with each episode of sickling and eventually the cells accumulate calcium, loss potassium and water and eventually become irreversibly shape changed. Many factors affect this change in shape of red cells.[2] Therefore to understand the basic pathophysiology of sickle cell anemia first we have to understand the mechanism of sickling or change in shape of red blood cell in sickle cell anemia and its rheology and then the various theories which thought to play a significant role in sickle cell anemia. That is why

pathophysiology of sickle cell disease is not limited to abnormal red blood cells. The clinical explanation of sickle cell anemia covers complex pathways and occurrence of events like activation of endothelial cells, inflammatory response, bioavailability of nitric oxide, free radical mediated stress and oxidative adhesiveness of a variety of blood cells in the body.

Mechanism of Sickling: - Glutamate is a polar amino acid and it is replaced by a non polar amino acid valine which causes a marked decrease in the solubility of sickle hemoglobin in deoxygenated form. However solubility of oxygenated sickle hemoglobin is not affected. The substitution of amino acid which is non polar in nature (valine) by glutamate occur in a sticky patch on outer surface of β-chains of hemoglobin. It is present on oxy and deoxy sickle hemoglobin but absent on adult hemoglobin. There is a site or receptor complementary to sticky patch on deoxy sickle hemoglobin. The sticky patch of one deoxy sickle hemoglobin binds with receptor of other deoxy sickle hemoglobin and this process continues resulting in formation of long aggregates molecules of deoxy sickle hemoglobin. Thus, the polymerization of deoxy molecules leads to long fibrous precipitates. These stiff fibers distort the erythrocytes into a sickle shape and are highly vulnerable to lysis.[1] In case of oxy sickle hemoglobin the complementary receptor is masked, although the sticky patch is present. Hence the molecules of oxy sickle hemoglobin can't bind among themselves or with molecules of deoxy sickle hemoglobin.[1] Normal deoxy adult hemoglobin lacks sticky patches but contains receptors. Absence of sticky patches does not allow deoxy adult hemoglobin to precipitate in formation of aggregates sickling is due to polymerization of deoxy sickle hemoglobin. Therefore if sickle hemoglobin is maintained in oxygenate form or (minimum deoxy sickle hemoglobin) sickling can be prevented.[1]

Rheology of Sickle Cells: - Clinical features of sickle cells are related to increase viscosity of the blood. The viscosity of plasma in sickle cell anemia is slightly higher than that of plasma from normal subjects, as results of higher total protein concentration. However viscosity of oxygenated sickle blood is lower than that of normal blood at all shear rates, mainly as a result of lower hematocrit level. The viscosity of sickle cell containing sample increases with decreasing oxygen saturation primarily because of reduced cellular deformability. Cellular dehydration as well as resulting increase in cytoplasmic viscosity is a major determinant of abnormal rheological behavior of oxygenated sickle cells. Sickle cell membrane demonstrates extensional stiffness and persistent deformation. The rheological property of sickle cell hydration and it will increase for oxidative damage to the membrane.

Adhesion: - Abnormal adherence to vascular endothelium, monocytes, macrophages, and model lipid membrane compare with normal red blood cells, sickle cell are two to ten time more adherent to human endothelial cells. This property of sickle blood is imparted by deformable sickle cells rather than irreversible sickle cells perhaps because rigid cells are unable to form multiple surface contacts with endothelial cells.[3] Individual who generate a relatively greater number of irreversible sickle cells has decreased red cell deformability and milder diseases compare with those red blood cells are deformable. Rigid irreversible sickle cells are unable to enter the capillary or to adhere tenaciously to capillary endothelium, where as deformable sickle cells enter capillary readily and adhere to endothelium and compromise blood flow. Conditions which promote the expression of adhesion receptor by endothelial cells include hypoxia, thrombin, tumor necrosis factor and interleukin-1.these factors also increase adhesion of sickle cells to endothelium in vitro.[4] the level of thrombospondin are elevated in sickle cell patients during crisis conditions, perhaps may be as a result of activation of thrombocytes in blood.[5] Patients with sickle cell who had acute painful episodes have higher level of circulating endothelial cells than patients with no recent events. Circulating endothelial cells were predominantly microvascular (CD36+) and expressed markers of endothelial cells activation [6, 7] (the cell mediators are Selectin, interacellular adhesion molecule-1, vascular cell adhesion molecule-1) [8, 9] Macrophages have an increasing affinity for sickle cells. Excessive immunoglobulin is found on the surface of sickle cells, which are ingested by macrophages resulting in a positive anti-globulin test. Increased phagocytosis is inhibited by partially blockage of macrophage Fc fragment.

Pathogenesis of Vaso-occlusion: - Potential risk factor for vaso-occlusion includes: - polymerization & sickle cell deformability and viscosity, the fraction of dense cells & sickle cell endothelial adherence and activation, hemostatic activation & vascular tone and acidosis, dehydration, menstrual cycle, high altitude & stress, etc. Because of the higher concentration of sickle hemoglobin, the densest cells are least deformable and they are at higher risk for the intracellular polymerization. The abnormal interaction between sickle cell and vascular endothelium may be of greater relevance for vaso-occlusive events then are alterations in red cell morphology or viscosity of the blood. The sickle shape cell may have an effect on local regulation of vascular tone. An abnormal state of vasodilation and low vascular resistance in subjects with sickle cell anemia occur during steady state periods, substances like inflammatory mediators such as prostacyclin and an increase in

vasoconstrictor substance including endothelin and prostaglandin. These shifts in balance e.g. vascular flow, further obstruction are more profound during absence of oxygen of sickle cells. Adhesion of red blood cells to the endothelial cells alters vascular flow specific ligand and it might mediate adhesion of sickle red cells to endothelium include v WF, thrombospondin, fibrinogen, fibrinopectin, laminine, factors which can act as vasoconstrictors such as free radicals prostaglandins PGI_2, PGD_2, and endothelin may enhance adhesion of sickle cell to endothelium. Infection or tissue inflammation may intensify erythrocytes adhesion through inflammatory cytokines such as tumor necrosis factor. [4, 9, 10, 11] Generally adhesion and increase stickiness of neutrophils to the membrane also observed in this condition. Leucocytes may also interfere with micro-vasculature flow by lodging in capillary.[12] Increase in white blood cells in sickle cell anemia may associated with mortality and silent infarction in brain.[6]

- Activation of endothelial cells on post-capillary venules.
- Conscription of adherent leucocytes in endothelium.[3]
- Interaction of sickle cell with adherent endothelium.
- Vascular clogging by white blood cell and or sickle cell resulting in ischemia.
- It's also possible that platelet may involve in process through formation of platelets sickle hemoglobin red cell aggregates.

In above figure the inflammatory mediators released can lead to the activation of the vascular endothelium. Sickle cell themselves may also stimulate endothelial cells directly by causing adhesion. The stimulated endothelial cells are balanced to recruit rolling and adherent white blood cells in blood vessels by expressing chemokines and cell adhesion molecules such as the selectin and immunoglobulin based members of mediators. On activation, firmly adherent neutrophils capture circulating sickle-shape red blood cell, leads to transient episodes of vaso- occlusions that are initiated in the smallest post-capillary venules. Interactions between red blood cells and white blood cells tend to occur at vessel junctions, where white blood cells recruitment is the most active. The large arrow indicates the blood flow direction.[3, 12-13]

Role of Dehydration: - The irreversible sickle cell exhibits several perturbations in cation hemostasis, related to physical distortion of cation permeability barrier by bundle of sickle hemoglobin polymers. The amount of intracellular calcium increased as much as four folds. Two pathways play a major role in formation of dense cells. The calcium activated potassium channel and the potassium-chloride transport channel.[14, 15] The transient increase in free calcium induced by red cell deoxygenation leads to activation of calcium and potassium channel and subsequent activation of potassium-chloride co-transport, [14] which results in further loss of potassium ions. In irreversible sickle cell unlike reversibly sickle cells potassium loss exceeds sodium gain and there is over loss of intracellular hemoglobin. The rate of dehydration of sickle cell is uneven and those destined to become irreversible sickle cells dehydrated by a fast track process. Reversible permeability pathway for Na^+, K^+, Mg^{+2} and Calcium and the results of ionic shifting affecting cell dehydration. The direct effect on calcium permeabilization activates gardos (K-Cl) channel which trigger the loss of potassium-chloride and water and is associated with red cell acidification.[17-18] In reticulocyte and young red blood cells expression of potassium-chloride co-transporter, the acidification further consequences in loss of potassium-chloride, acidification and potassium-chloride co-transport stimulation. The rapid dehydration of young sickle cells are due to combined effect of gardos channel of potassium-chloride co-transport.[15] The level of magnesium is reduced in sickle red blood and increasing cell magnesium produce decreasing in activity of potassium-chloride.

The Endothelial role in chronic vasculopathy:- The role of the endothelium in normal physiology is wide-ranging,[20] including its glandular role with autocrine and paracrine a chemical mediator, and even endocrine functions as a distributed signaling network; its task in regulating the pro- versus anticoagulant balance of the blood and vessel wall; while its critical function as a regulator of vascular pressure and flow; and its participation in actualizing inflammation signaling through adhesion molecule and its control of vessel wall permeability. The endothelial physiology has shifted from a state of physiologic usefulness to a state of some degree of harmful function.[20] Candidate contributory factors include polymerization-induced red cell sickling; a systemic inflammatory state[21] with abnormal expression of adhesion molecules for white blood cells and red blood cells [7,22,23]; activation of the coagulation system in terms of both platelets[24] and plasmatic coagulation, from its proximate end[25] through its amplification and effector aspects[26]; a bio-deficiency of nitric oxide[23] plus nitric oxide resistance[6], a sign of vessel wall disease; and accompanying vascular instability with up-regulation of non-nitric oxide vaso-regulatory systems[27-28]; stasis (due to sickling and/or abnormal blood cell adhesion to endothelium and/or thrombotic activity) causing reperfusion injury physiology[29-30]; disruption of the signaling function of endothelium[20]; and, of course, largely undefined—

but unquestionably-genetic influences on endothelial biology.[31-33]

Reperfusion Injury: In this mechanism some vascular wall perturbation and damage may results from the vascular occlusion by what so ever reason it was but mainly a greater amount results from the reoxygenation which occurs upon the resolution of the occlusion. That's why it's said that occlusion from reversible red cell sickling argue that sickle cell anemia must be the typical example of reperfusion injury. There are examples in experimental manner to justified this theory.[29,30] The blood cell adhesion to endothelium might help in occurrence of sickling, by satisfying the requirement for slowed flow to accommodate the polymerization delay time.[34]

As it is known that the reperfusion injury is well known to involve inflammatory pathways, [35] virtually all of the implicated and potential causal factors are known to be able to be derived from such a condition. It includes adhesion molecule expression, vascular stasis, and enhanced lysis of red blood cell (due to oxidant effects, red cell sickling, plus activation of immune/macrophage), signaling disruption, oxidative stress, nitric oxide consumption, coagulation pathway activation, and abnormal permeability in vasculature. It is likely that the systems biology of chronic sickle vasculopathy might be derived from the several influential factors and all activated by reperfusion injury physiology which is explained in Fig. 3.
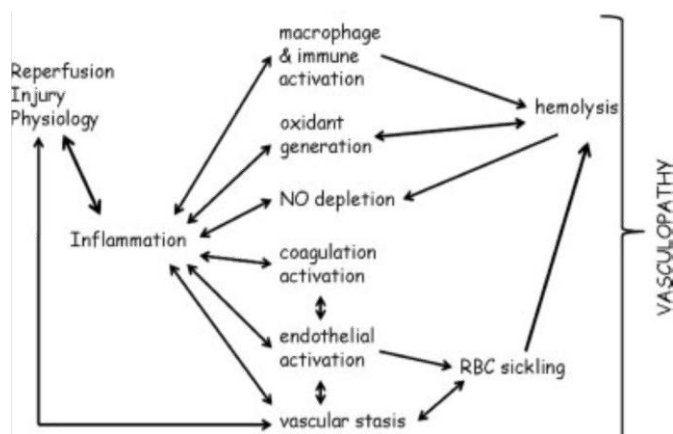
Figure1: role of reperfusion physiology in red blood corpuscle sickling and hemolysis

Hemolysis and Nitric Oxide: - Hemolysis may be due to repeated cycles of sickling and un-sickling which interact to produce changes in irreversible red cell membrane, and red blood cell dehydration and its destruction. Hemolysis might be associated with endothelial dysfunction, vasculopathy and hypercoagulability. Free radical nitric oxide is produced by the endothelium and is a critical regulator of normal vascular function. This nitric oxide regulates basal vasodilator tone and inhibits platelet and hemostatic activation and also inhibits transcriptional expression of adhesion molecules such as

vascular cell adhesion molecule-1.[36-40] The half-life of nitric oxide in the vasculature is very short because of rapid reactions with red cell hemoglobin to form methemoglobin and nitrate.[41] The activity of nitric oxide as vasodilation is only possible because all of the hemoglobin is compartmentalize within red blood cell, which creates diffusional barriers for nitric oxide entry into the red blood cells and reduces the scavenging of nitric oxide with intracellular hemoglobin.[42] Intravascular hemolysis releases hemoglobin into plasma, which will then potently scavenge nitric oxide via a de-oxygenation reaction with oxyhemoglobin which converts nitric oxide to nitrate.[41] Hemolysis disrupts the red cell nitric oxide diffusion barriers and results in a potent inhibition of all nitric oxide bioactivity, leading to a clinical state of endothelial dysfunction and nitric oxide resistance.[43-45] Hemolysis also releases red blood cell arginase into plasma. Arginase metabolizes plasma arginine into ornithine, which reducing the required substrate for nitric oxide synthesis and compounding the reduction in nitric oxide bioavailability in sickle cell anemia.[22] Endothelial function is also compromised in sickle cell anemia patients who have lower levels of apolipoprotein A-I.[46] Chronic nitric oxide depletion may contribute to constriction of vessels, pulmonary hypertension endothelial adhesion molecules activation such as vascular cell adhesion molecule-1, activation of platelets, mitogen, and endothelin explained in Fig. 2.[46] Because free radical nitric oxide is a potent inhibitor of platelet activation, this pathway is activated in patients having sickle cell anemia secondary to direct inhibition of nitric oxide by plasma hemoglobin and increased intracellular platelet expression of arginase.[47-48] Clinical studies of patients with sickle cell anemia reveal correlations between the intrinsic rate of intravascular hemolysis and the level of procoagulant factors in blood.[49,50]
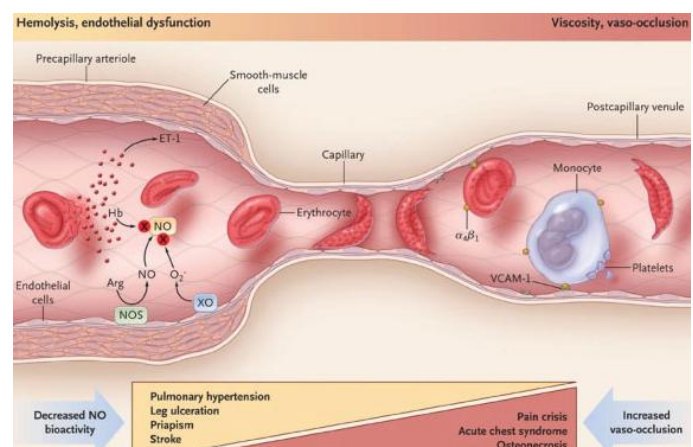
Figure 2.Relationship of hemolysis to vascular dysfunction.

Changes in central nervous system and stroke: - In sickle cell anemia red cell contains sickle hemoglobin, which polymerizes

when deoxygenated. When sickle hemoglobin is polymerized, the affected red blood cells become rigid and may block small blood vessels; stasis causes platelet adherence and fibrin deposition. This cascade is repeated until the vessel is severely narrowed, causing the manifestations of cerebro-vascular disease. These complications include transient ischemic attacks, overt and silent cerebral infarction, cerebral hemorrhage, infections, Moya–moya pattern, posterior reversible encephalopathy syndrome, dural venous sinus thrombosis, thickness of the diploic space, and cerebral atrophy.[51]

Stroke: - It affects almost 6-12% of patients in sickle cell anemia. Most common cause is cerebral infarction with sign and symptoms of hemiparasis, aphasia, cranial nerve palsies, and high risk of recurrent stroke in long term transfusion. Intracranial hemorrhage becomes more common with advancing age. In hemorrhagic stroke generalized phenomenon like coma, headache, and seizures are occur. A transient ischemic attack is a focal neurologic deficit persisting for less than 48 hours. Infarction usually occurs in a segmental pattern that suggests damage to the cerebral arteries. Vessel narrowing is the consequence of intimal and medial proliferation that is thought to be caused by endothelial damage from sickle red blood cells. Damaged irregular endothelium can serve as nidus for the adhesion of platelets and sickle cells and thereby resulting in thrombus formation. Intra-cerebral hemorrhage may also occur years later in patients who had prior cerebral infarction as a result of a rupture of fragile collateral vessels (Moyamoya).[52]

Changes in pulmonary system: - Lung is the major target organ for acute and chronic complication of sickle cell disease. Lung as the recipients of deoxygenated sickle cell that escape from the spleen or bone marrow may be at special risk for vaso-occlusion and infarction. These pulmonary problems not directly related to sickle cell vaso-occlusion, such as pneumonia or asthma, but they can worsen the sickle cell disease because local or systemic hypoxia increases polymerization of sickle hemoglobin.[52]

Acute chest syndrome: - The term acute chest syndrome is used because more precise etiology is not known. Acute chest syndrome is the most common about 25% cause of hospitalization in sickle cell patients and it is the most common complication of surgery, laparoscopy and anesthesia. Acute chest syndrome is related to anemia, low fetal hemoglobin, high hemoglobin level, high steady state hematocrits, infection, hypoventilation intrapulmonary sickling, and fat embolism. These insults are believed to involve "sludging of blood" in the pulmonary microvasculature

secondary to erythrocytes with high polymer content, and resulting infarction of the pulmonary parenchyma.51 Sign and symptom of acute chest syndrome are fever, cough, chest pain, shortness of breath, wheezing, dullness, tachypnea, etc54 Even though acute chest syndrome is self-limited when it involves small area of pulmonary parenchyma but it can progress to failure of respiratory system function, which is characterized by pulmonary edema and severe hypoxemic condition.54 Nitric oxide production is reduced during sickle vaso-occlusive crisis and that's why it can be used as the therapeutic aim as the nitric oxide reduced adhesion of sickle cell to endothelial cell after exposure to hypoxia.51 Causes of acute chest syndrome are as follow:- 1) Sickle hemoglobin consequences: Direct consequences like pulmonary infarction in situ where etiology is unknown, hypoventilation to ribs/sternum, postoperative alteration, embolism infarction, necrotic bone marrow, sickle cells from distal site like spleen or pulmonary edema secondary to fluid overload. 2) Indirect consequences like infection.

Pulmonary hypertension: - A central risk factor for the development of pulmonary hypertension in patients with sickle cell anemia is the rate of chronic intravascular hemolysis, which is characterized by low steady-state level of hemoglobin, high lactate dehydrogenase enzyme level, high billirubin levels, and high reticulocyte counts.[55, 56]

Cardiovascular changes: - Cardiac exam finding are rarely normal in sickle cell patients. Heart is usually enlarged and the pericardium hyperactive, systolic murmurs are found in most patients and premature contractions are often present in adults' having sickle cell anemia.[51, 57] But generally contractility is normal and over congestive heart failure is uncommon and even if heart failure is present it must be due to secondary to other causes, such as fluid overload.[58] Reduced oxygen carrying capacity due to anemia may lead to increase demand on heart with an increase in cardiac output.

Bone marrow changes: - Skeletal manifestation of sickle cell is result of changes in bone and bone marrow caused by chronic tissue hypoxia that is exacerbated by episodic occlusion of the microcirculation by abnormal sickle cells. In sickle cell anemia arterial vessels in bone marrow show significantly increase in fibrous connective tissue and changes in muscle that very with age and vessel size.[59] When rigid erythrocytes are jam in the arterial and venous sinusoids of skeletal tissues that resultant effect is intravascular thrombosis, which might cause infarction of bone and bone marrow. In sickle cell anemia bone or bone marrow infarction can lead to changes like osteolysis in acute infarcts, osteonecrosis, articular disintegration, myelosclerosis, H-vertebrae (step like end plate depression also known as Raynoid or Dystrophic medullary calcification like bone within bone)[60, 61] In children, sickle cell

anemia cause Hand-foot syndrome in bones, it's a bilateral painful swelling of the dorsa of hands and feet occurs as a result of sickling and capillary stasis; it is Hand-foot syndrome or sickle cell dactylitis. It last for 2 weeks is accompanied by changes of periostitis. As observed by changes of periostitis does not occur after 4 years. It is self limited and bones heals themselves without permanent deformity so except hydration and analgesics does not require special treatment.[62]

Figure 3: hand- foot syndrome in bones of sickle cell child.

Because of anatomic distribution of blood vessels supplying the vertebrae, the infarction affecting the central part of vertebrae which is fed by a spinal table giving the skull the characteristics hair on-end appearance) [51]

Changes in hepato-billiary system: - The pathophysiology of hepatic dysfunction was attributed to classic histologic features of kupfer cells hyperplasia, erythrophagocytosis and engorgement of sinusoids by aggregates of sickle cells.[63]

Gall stones: - The prevalence in patients with sickle hemoglobin increased to 75% at the age of 30 and 85% by the age of 33 years.[64] In all forms of hemolytic anemia turnover of heme increases, reflecting level of unconjugated and conjugated billirubin produced by liver and excreted in bile. As a result, in long term chronic hemolytic state, over production of bile salts results in pigment gallstones and consequent gall bladder disease.[65]

Hepatic venous outflow obstruction: - hepatic thrombosis or (Budd-chiari syndrome) is an acute and fatal thrombotic occlusion of hepatic veins. The definition has now been expanded to sub-acute and chronic occlusive syndromes characterized by hepatomegaly, increase weight, ascites and abdominal pain. Centrilobular fibrosis develops in instance in which thrombosis is more slowly developing. [2, 66]

Cirrhosis & Acute hepatic failure - prolonged hepatic vein outflow obstruction or viral infection or chronic blood transfusion can lead to cause acute hepatic failure or cirrhosis.[66, 67]

Viral hepatitis: - Chronic blood transfusion or infections are the main risk factor for causing hepatitis in sickle cell anemia patients. The common clinical findings of viral hepatitis in sickle cell anemia are malaise, jaundice, low-grade fever, tender hepatomegaly, elevated transaminase and bilirubin.[68]

Hepatic iron overload: - Patients with sickle cell anemia are at higher risk of iron overload and damage to the liver from chronic transfusion. Serum ferritin levels in these patients correlate with the number of units of blood transfused. Increased iron deposition occurs within reticulo-endothelial cells, including Kupffer cells. Iron chelation therapy with intravenous or subcutaneous deferoxamine is recommended, as untreated, this condition can progress to cirrhosis.[69]

Acute splenic sequestration crisis: - Acute splenic sequestration crises are a life-threatening complication of sickle cell anemia. It is rare in adults due to progressive splenic fibrosis as a result of repeated infarctions and occurs mainly in infants and young children aged less than 8 years; 30% are under the age of 5 years.[70] Major crisis is identified by a fall in hemoglobin level to less than 6 g/100 ml. Hemoglobin of more than 6 g/100 ml indicates a minor episode.[71]

Splenic abscess: - Patients with sickle cell anemia are at greater risk of developing splenic sepsis. Splenic abscess occur secondary to infection of splenic infarcts. Two predisposing factors were recognized (a) repeated splenic infarctions which are more likely to occur with spleenomegaly and (b) exposure to systemic bacterial infection to which sickle cell anemia patients are susceptible as a result of hyposplenism with upper abdominal pain presented, usually at the left upper quadrant, and fever. The spleen may be palpable and tender. Percutaneous drainage is an attractive option in sickle cell anemia and should be tried first to avoid the high morbidity associated with surgical intervention and to avoid splenectomy with its attendant risks.

Changes in renal function: - The distribution of blood flow in kidney and the hyperosmolarity of renal medulla create a situation where red blood cell s containing sickle hemoglobin undergo deoxygenation in an acidic and hyperosmolar environment which can cause them to sickle more easily. Hypoxia, acidosis and hypertonicity in renal medulla lead to stasis in vasa recta and ischemia at renal medulla and papillary tip leads to cause pyelonephritis, atrophy, tubular dysfunction, etc.[51]

Tubule Dysfunction: - Defective urinary acidification also is well described in sickle cell anemia. Typically patients have normal aldosterone and renin responses. The primary

abnormality is an incomplete distal renal tubular acidosis and the severity of the acidification defect is related in part to the severity of hyposthenuria. Defects in potassium excretion are also seen in sickle cell anemia. Although hyperkalemia does become manifest as over all renal function deteriorates. The medullary region of the kidney is composed of renal tubules and medullary blood vessels that are collectively referred to as vasa recta system. The environment of renal medulla is characterized by decreased oxygen, acidosis, and hypertonicity. This condition promotes polymerization and sickling so this area of the kidney is susceptible to malfunction.[51]

Hyposthenuria: - An inability to concentrate urine maximally is perhaps the most common renal abnormality in sickle cell anemia. Hyposthenuria typically becomes apparent during early childhood as enuresis. Despite having increased secretion of uric acid, patients with sickle cell anemia often have hyperuricemia because of increased erythropoiesis and are vulnerable to secondary gout. Increased creatinine secretion causes a lower serum creatinine level and thus an overestimation of glomerular filtration rate.[51]

Hematuria: - It results from sickle hemoglobin polymerization and sickling in the renal medulla. The treatment of hematuria in sickle cell anemia involves bed rest; maintain input and output, if blood loss is more than blood transfusion. If life threatening bleeding from only one kidney occurs then the local resection of bleeding segment is preferred.[51]

Acute & chronic renal failure: - Acute renal failure occurs as a component of acute multi organ failure syndrome in patients with sickle cell anemia. Pathophysiology of acute multi organ failure syndrome appears to be due to diffuse small blood vessel occlusion which in turn results in tissue ischemia and organ dysfunction.[51] Protein urea which can progress to the nephritic syndrome is the most common manifestation of the glomerular injury in sickle cell anemia. Moreover, more than 40% of sickle cell anemia patients with nephritic syndrome may go on to develop end-stage renal failure.[51]

Leg ulcer: Sickle cell ulcer usually begins as small elevated, crusting sores on the lower third of leg, above the toes and over and around the medial and lateral malleolus. Occasionally, ulcers are seen over the tibial area or the dorsum of foot. They can be single or multiple. In the early phase, neighboring skin appears to be healthy but as the ulcer develops the surrounding skin appeared hyper pigmentation with a loss of subcutaneous fat and hair follicles. These ulcers are painful and often accompanied by reactive cellulites and regional adenitis.51Low hemoglobin F, warm temperature; infection may appear to enhance ulcer formation. Clean and

wash the ulcerated area regularly. The current available treatments are zinc oxide bandages, Ardigene gel or transfusion. Skin graft is the alternate and only option for the long term unhealed ulcer.

Priapism: - Priapism defined as a sustained, and unwanted erection with pain, is a well identified complication of the sickle cell anemia. Boys and young men and their family should know that they should be prepared as soon as an episode begins and that if untreated can results in impotence and other complications like skin necrosis, fistula, damaged or strictures of the urethra.[51] Male should know that a full bladder can trigger priapism and therefore they need to urinate frequently but with kept in mind not to lead to dehydration state otherwise the complication will worsen also. They should also avoid prolonged sexual activity which can trigger an episode. Mean age at which priapism occurs is 12 years and by the age of 20 years 89% of the males with sickle cell disease have experienced one or more episode of the priapism. Priapism is due to vaso-occlusion which causes obstruction of the venous drainage of the penis. Priapism can be classified into two types (1) prolonged and (2) stuttering. Prolonged if it last for more than three hours and stuttering if it last for more than few minutes and less than three hours and resolves spontaneously. Recurrent episodes of the priapism can result in fibrosis and impotence, even when adequate treatment is attempted.[51] Patients should advised to drink extra fluids and use oral analgesics and attempt to urinate as soon as priapism begins.

Ocular system: - Almost any ocular tissue can be affected by sickle cell anemia and the eye provides a unique opportunity for direct observation of the sickle cell anemia vaso-occlusive process.[51]

Proliferative sickle retinopathy: - In this, lesions develop in the areas of abnormal arteriovenous communications at the border between the vascular and avascular retina, usually at the temporal periphery, and develop at posterior, with regression of the vascular arcades. Classification for peripheral retinal vascular changes in sickle cell anemia is as below[51] Degeneration and fibrosis of vitrous cavity can lead to tractional detachment of the retina, sometimes followed by detachments.[51]

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