ZINC STATUS IN RELATION TO GROWTH AND MATURATION IN CHILDREN WITH SICKLE CELL ANAEMIA IN KHARTOUM STATE

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Dedication

To My Original Family
My Father, Mother, Sisters,
My Dear Husband Alargam,
My Lovely Children Mohamed, Khalid and Mysam
I offer my grateful appreciation to Dr. Yahia Shakir, associate professor of Paediatrics and Childhealth, University of Khartoum for his guidance and unlimited support.

I extended my grateful thanks to Dr. Bakhita Attallah, Amarthelab technician and my colleagues for their kind help.

My sincere appreciations to my kind mother, father, dear husband and lovely kids for their help and unlimited support.
Abstract

One hundred and twenty sickle cell anaemia patients were studied between June and October 2006 to assess their growth and maturation and its relation to serum zinc level. They were randomly collected from referred clinic of Khartoum and Omdurman Teaching Hospitals.

They were studied by means of:

1. Questionnaire.
2. Clinical examination.
4. Investigations.

The growth (weight and height) and sexual maturity (by Tanner staging) were assessed and compared by their serum zinc level.

The study revealed that weight is significantly affected and low weight for age is related to low serum zinc level (P < 0.05). In contrast to height for age and sexual maturity which were found not to be related to low serum zinc level.

The severity of illness of the study group was assessed by number of hospital admissions, febrile and painful episodes, diarrhoeal diseases and number of blood transfusions. The nutritional status was assessed by the quantity and quality of food taken.

The Medical care was assessed by history of vaccination and drug intake.
خلاصة الاطروحة

الدراسة تتناول وتشمل في اكتوبر وحتى يونيور من الفترتين 2006، وتبين أن
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3 - بشرية
4 - معملية

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- السن
- السرير
- البريد
- المعلم

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- النشاط في دائرة القطاع، والتنفس، والتنبؤ

وتشمل تطبيق الصحة العامة خلال كل وقائعة، والجودة

- الغذاء ونوع، والجودة، والصحة العامة خلال كل وقائعة، والجودة
- التركيز في دوري والبيئة الرائعة، والصحة العامة خلال كل وقائعة، والجودة

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- لتطوير، وتحسين النظام، والصحة العامة خلال كل وقائعة، والجودة
Chapter One

1. INTRODUCTION AND LITERATURE REVIEW

Definitions:

Sickle cell disease (SCD): Applies to all patients with at least at single HBS chain and one another abnormal \( \beta \) globulin.

Sickle cell anemia (SCA): is a hemolytic anemia characterized by production of abnormal hemoglobin chain that tend to polymerize when deoxygenated causing distortion of RBCs morphology (sickling), with attendant vascular occlusion. It results from inheritance of abnormal HB from both parents (homozygous state).

Sickle cell trait: a carrier state (Hb AS) sickling occur on extremes of hypoxia and acidic PH\(^{(1)}\).

1.2 Historical Background:
The first published account of SCA was by Herrick in 1910, who described the clinical hematological manifestation of the disease in a 20 years old medical student from Grenada\textsuperscript{(2)}.

Pauling et al\textsuperscript{(3)} determined that a point mutation in the gene coding the B chain of HB molecule.

In 1977 Walter Gilbert and Fridrick Sanger working separately in US and England developed a new technique for DNA sequencing. This lead to identification of mutations in B globulin chain gene.

In 1984 a bone marrow translation in a child with leukemia and sickle cell anaemia produce a first reported cure of the disease.

In 1995 hydroxyurea become the first and only drug proven to prevent complications of SCA.

\textbf{Sickle cell disease in Sudan:}
A study done in Sudan in Khartoum Teaching Hospital between 1996 and 2000, with 189 of SCD patients and 118 controls. They found that 93.7% belong to families of single ethnic descent.

The SCD was found to be predominant among the Afro-asciatic groups (68.4%). Those patients clustered in western Sudan (Kordofan and Darfor) from where 73% of all cases originate(4).

**SCD in the world:**

SCD is the most common single gene disorder in black Americans.

SCA is prevalent in other ethnic groups as well, including those from Mediterranean area, Turkey and Indian subcontinent. It may also be seen in people of Spanish descent and those from Caribbean, South and Central America(5,6).

**Pathophysiology of SCA:**
**Biochemistry of Hb:**

The normal human Hb molecule consists of four globulin chain: tow α and tow β chains. When α and β chains are normal this abbreviated Hb A.

Abnormal Hb is designated by the type of abnormality in the globulin chain; for example presence of one sickle β chain and one C β chain abbreviated Hb SC.

Homozygous SCD is designated Hb SS.

**Biochemistry of Hb S:**

Hb S is formed when the amino acid valine is substituted for glutamic acid at the 6 position of β chain. This single amino acid substitution has far-reaching effects on Hb interactions, RBC morphology and hemodynamics. Hbs β chain has an unusual propensity to bind with other Hb S chains when deoxygenated. On to this basic polymer, other Hb molecule may also polymerize leading to a large polymer strands. These rigid strands distort RBCs into a variety of elongated shape and decrease its deformability \(^7\). This sets the stage for vascular obstruction and hemolysis.
Polymerization is an ongoing process and its extent depends on a number of factors; with the most important being extent of deoxygenation, Hb concentration in the cell, the intracellular composition of other Hb variants, PH and temperature.

Polymerization cause non-selective increase in membrane cations permeability with egress of water, RBCs dehydration and accelerate polymerization.

The end result of multiple episodes of polymerization and dehydration is dense irreversibly sickle cell, when oxygenated it may contain no polymer but distorted in shape and contribute to vaso-occlusion (7-9).

RBCs in SCA also appear to have an increased binding affinity for vascular endothelium. It has been shown that adherent sickled RBCs inhibit vasorelaxation (10).

**Clinical Presentation of SCA and Management:**

**Age and sex:**
Usually newborns have no features of SCA, but hemolytic anemia develops over the 3-4 months during replacement of Hb F by Hb S.

**Clinical features:**

Clinical features in SCA are mainly due to hemolytic anemia and vaso-occlusive components which is the most common and earliest manifestation of the disease. Other problems in SCA include osteomyelitis, osteonecrosis, splenic infarct and sequestration, acute chest syndrome, papillary kidney necrosis and renal insufficiency.

Clinical features based on organ approach.

**The acute painful vaso-occlusive:**

The most common and earliest manifestation half of all SCA patients will experience pain by 4.9 years of age. The pain is described as bone pain, but any organ may be involved. It is caused by microvascular occlusion with subsequent tissue ischemia. In young children it most commonly manifest as dactylitis.

**Management:**
Dehydration and acidosis should be corrected, increasing oxygen tension, treating infection and control of pain by acetaminophen or if not responding by morphine.

**The lung:**

It is the most common site of involvement in SCA.

Injuries range from acute processes such as pneumonia and acute chest syndrome to chronic entities such as pulmonary fibrosis.

Pulmonary complications constitute the second cause of hospitalization and now the leading cause of death\(^{(11)}\).

**Pneumonia:**

It is estimated that children with SCA are 100 times more susceptible to develop pneumonia than other children, and they have 30% recurrence rate\(^{(12)}\).

Impaired immune status, a result of functional asplenia and other abnormalities in the immune system render patients with SCA prone to infections, mostly pneumonia\(^{(13)}\).

Pneumonia in SCA is most commonly caused by streptococcus pneumoniae, hemophilus influenzae, staph-aureus, Chlamydia pneumoniae and salmonella\(^{(14)}\).
**Prevention:** is by oral penicillin prophylaxis begun by age 3 month and continued to at least 5 year of age\(^{(14)}\).

**Acute chest syndrome (ACS):**

It is an acute pulmonary illness characterized by a new pulmonary consolidation, fever, chest pain and signs of distress.

Causes are infection, fat emboli and bacteremia which is more common in children than adult.

Pulmonary vascular occlusion may lead to acute chest syndrome, and microvascular occlusion has been shown at thin section C.T. in ACS\(^{(15,16)}\).

Other factors linked to ACS include opioid use, pulmonary edema and parvovirus B19\(^{(17)}\).

**Treatment:** consist of hydration, transfusion, supplemental oxygen and analgesia. Incentive inspirometry to improve atelectasis, antibiotic therapy for suspected infection and steroids may also be used\(^{(17)}\).

**Chronic pulmonary disease (CPD)**
CPD occur in about 4% of patients due to repeated episodes of pneumonia and acute chest syndrome\(^{(14)}\).

At histology CPD in SCA consists of pulmonary fibrosis, pleural scaring, adhesion and pulmonary arteriolar intimal hyperplasia with resultant pulmonary hypertension\(^{(17,18)}\).

In children with SCA, a marked increase in airway hyper-reactivity which is typically asymptomatic, has been shown in pulmonary function testing (73% of patients)\(^{(19)}\).

**The skeletal system:**

The skeletal system of patients with SCA is remarkable for its life long preservation and frequent expansion of red (cellular) marrow, even in their epiphysis.

Skeletal complications include infraction and oestomyelitis. Both of these problems are assumed to be caused by congested cellular marrow. The cellular marrow impedes blood flow, enhances stasis, regional hypoxia and sickling and infract may result, these render the marrow susceptible to pathogens; oestomyelitis may result\(^{(20,21)}\).

**Infraction:**
Bone marrow infraction is thought to be the underlying cause of most pain crises in SCA.

Patients with SCA are also prone to silent infraction, and the discovery of oestonecrosis may be incidental finding (22).

In the spine, infraction appears as central square-shaped endplate depression, resulting from microvascular occlusion and subsequent overgrowth of the surrounding portion of endplate. This appearance approximately seen in 10% of patients, and it is pathogonomic of SCA and has been called H. shaped deformity.

Epiphyseal infraction in SCA has predilection for proximal humeri and femora, although any bone may be involved.

SCA is the most common cause of oestonecrosis of the hip in children and approximately half of patients will develop epiphseal oestonecrosis by the age of 35 (23).

**Treatment:**

Generally supportive with analgesics, hydration and antibiotics if infection is suspected.
When joint affected especially weight bearing joints, replacement may be necessary\(^{(24)}\).

**Osteomyelitis:**

It’s most common in the diaphyseal region of bone and most often found in the femur, tibia and humerus.

Patients with osteomyelitis present with pain, fever, erythma and elevated white blood count.

The most common organisms are salmonella followed by staph-aures and gram negative bacilli.

Although osteomyelitis much less common than infraction, may be difficult to discriminate from infraction even with clinical, laboratory and radiological information.

MR imaging is the prefer modality for evaluating marrow.

**The brain:**
Stroke, atrophy and cognitive impairment are major consequences of SCA. 25% of all patients with SCA will have a neurologic complication over their life time.

Many children will experience “silent infraction” (defined as absence of clinical symptoms with MR imaging findings of infract), it is twice as common as clinical infraction and may occur in up to 22% of children by 12 years of age.

Other less common problems include intraparenchymal and subarachonoid hemorrhage and aneurysm.

Infraction in patient with SCA is usually ischemic, embolic and thrombotic strokes are unusual\(^{18,26}\).

Infacts both silent and clinical are best detected by MR imaging.

Infacts in patients with SCA tend to occur in the white matter and at the peripheral supply zones of middle and anterior cerebral arteries.

**Management:**

Because of life long cognitive and functional impairments that result from stroke, efforts directed toward
identifying patients at risk for stroke to institute preventive therapy.

Transcranial Doppler ultrasound is a valuable tool for assessing large cerebral artery flow dynamics.

Studies showed that elevated velocities in the distal internal carotid artery and middle cerebral artery correlate with increased risk of stroke\(^{(27,28)}\).

Although studies very slightly in the mean velocities that correlate with stroke, generally velocities greater 170-200 cm/sec indicate increased risk.

Preventive therapy, maintenance transfusion on monthly basis is now offered to these patients.

Screening by transcranial Doppler ultrasound begins by the age of 3 years.

Patients with two consecutive elevated velocities are offered maintenance transfusion therapy, with the goal of reducing Hb S concentration to 30% or less of total hemoglobin concentration.
**Moya moya:**

Reduced cerebral blood flow from any cause may result in development of fine collateral vascular channels. These usually arise from thalamoperferate and lenticulosrrriate arteries in response to occlusion of distal internal carotid artery. This process is called moya moya for its angiographic appearance, such collaterals are seen in 35% or SCA patients at angiography\(^{26,29}\).

**The liver:**

The liver is frequently involved by SCA complications. Hepatitis is frequent, likely from repeated transfusions\(^{33}\).

Intrahepatic biliary duct stones and cholestasis are also seen, which are hypothesized to be result from infraction\(^{34}\). Pigmented gall stones are evident in up to 50% of adults and 20% of children with SCA.

The liver may manifest changes of iron overload in transfusion dependant patient with SCA.

**The heart:**

Studies showed that cardiac changes in patients with SCA are electrical system fibrosis. In some patients with
sudden death, dilated champergs with septal hypertrophy, but normal contractility\textsuperscript{(35)}.

**The eyes:**

Patients with SCA may experience acute retinal artery occlusion with sudden loss of vision in one eye: this typically resolves in several days, although some long term visual impairment may result.

Orbital compression syndrome may result from infarcts of osseous walls of orbit, which develop edema and subperiosreal hematomas\textsuperscript{(36)}.

**The ears:**

Large series report prevalence of hearing loss of 11\textsuperscript{Æ}41\% in SCD\textsuperscript{(37)} the cochlear microvasculature in young may be susceptible to occlusion\textsuperscript{(38)} and children should have audiometry after SCA crises to exclude readily manageable cause of educational handicap and preventable disability.

**Priapism:**

It is a prolonged painful erection of the penis that commonly occurs in children and adolescents with SCD. It occurs in 2 form: stuttering episodes that last fewer then 4
hours but are often recurrent and may precede severe episodes; and severe episodes that last more than 4 hours and may eventually result in importance severe, episodes require urgent evaluation and treatment that may include hydration, analgesics, aspiration and irrigation by a urologist and some times blood transfusion\(^{(39)}\).

**Neonatal Screening and Diagnosis:**

Most infants with SCD are healthy at birth and become symptomatic later in infancy or childhood after fetal hemoglobin levels decrease. Most infants with SCD born in United States are identified by routine neonatal screening\(^{(40,41)}\). Screening can done by electrophoresis of fetal blood after 18 week of pregnancy or by chorionic villous sampling from 9 week of pregnancy or amniotic fluid sampling aspirated at 16 weeks of pregnancy for SCD.

Confirmatory testing of infants with positive neonatal screening results and diagnosis of older patients who present with symptoms require hemoglobin separation by electrophoresis (cellulose acetate and cirate agar), isoelectric
focusing and/or high performance liquid chromatography (HPLC)\textsuperscript{(41)}.

**Health supervision for children with sickle cell disease:**

The provision of comprehensive medical care decreases morbidity and mortality during childhood. The provision of comprehensive care is a time-intensive endeavor that includes ongoing patients and family education, periodic comprehensive evaluation and other disease-specific health maintenance services, psychological care and genetic counseling.

**Family and patient education:**

Identification of an infant with SCD through neonatal screening provides an opportunity to educate families before symptoms develop\textsuperscript{(40,41)}. Initially the focus should include the genetics, basic pathophysiology of SCD and importance of regularly and scheduled health maintenance visits, penciling
prophylaxis and immunization. Education about the need for urgent medical evaluation for treatment of febrile illnesses, acute chest syndrome, a plastic and sequestration crisis is critical.

Sequestration crises includes the need for medical attention immediately if the child is pale and listless, and instruction about abdominal palpation for determining spleen size.

Recognition and appropriate management of dectylitis and painful event should be reviewed. As the child ages, other topics such as stroke, enuresis, priapism, cholelithasis delayed puberty, proliferative retinopathy, a vascular necrosis of hip and shoulder, and leg ulcers are introduced.

During middle childhood and adolescence, it includes genetic basis and issues related to contraception, carrier of partners, genetic counseling and prenatal diagnosis.

The ultimate goal is to enable families to cope with the child’s complex chronic illness and enhance the child’s potential for successful transition to adulthood.
**Health maintenance:**

In addition to ensuring compliance with “recommendations for preventive pediatric health care” of American Academy of Pediatrics (AAP), the following SCD related issues should be addressed periodically:\(^{(42)}\):

**Prophylactic medications:**

All infants with Hb SS receive penicillin prophylaxis, 125 mg, and twice daily initiated by 2 months of age\(^{(40)}\). The dose is increased to 250 mg orally, by 3 years of age and continued at least until the 5\(^{th}\) birth day\(^{(45)}\). Erythromycin is used in children with proven penicillin allergy.

**Immunization:**

Timely administration of routine immunizations recommended by the AAD is essential\(^{(47)}\). Children with SCD should receive 7-valent pneumococcal conjugate and 23-valent pneumococcal polysaccharide vaccines. Yearly influenza immunization is recommended.
**Comprehensive medical evaluations:**

All patients should have regularly scheduled comprehensive medical evaluations to review previous disease manifestation, document important baseline physical findings and laboratory, values, monitor growth and development, detect early signs of chronic organ damage and develop individualized patient care plans\(^{(41)}\).

The clinical course of each patient with SCD should be regularly reviewed by pediatric hematologist. Oncologist generally at the time of comprehensive evaluations, the possibilities of chronic transfusions, hydroxyurea, and stem cell transplantation should be considered.

**Acute illness:**

Is characterized by relatively common childhood signs and symptoms, such as fever, cough, abdominal pain, pallor and limping, can rapidly become life threatening. Unfortunately, delayed or inadequate evaluation and treatment of acute illness remains an important cause of preventable morbidity and mortality\(^{(48)}\). The goal of ensuring timely medical treatment for acute illness also is facilitated by
providing anticipatory guidance to patients and families about early recognition, appropriate medical evaluation and treatment of common acute complications\textsuperscript{40,41}.

**Growth and Development in SCA patients.**

Sickle cell anemia is a severe congenital and chronic illness, which, even today shows critical rates of morbidity and mortality\textsuperscript{49}. About 25\% of children with this disease have satural deficit and retarded skeletal maturation and pubertal development\textsuperscript{50}. Besides anemia and peripheral tissue hypoxia and growth hormone deficiency (GH) and starvation also reported in SCD, factors well known to have a negative influence on growth.

The mean heights and weights of SCD children are within normal parameters at birth, but fall below those of normal children by 1-2 years of age\textsuperscript{51}.

Platt et al\textsuperscript{49} reported across sectional analysis of growth data in 2115 patients with sickle cell hemoglobinopathies (age 2 to 25 years) participating in the co-operative study of SSD and showed that patients with SS and SB were consistently
shorter and weighted less than normal controls and patients with SC and SB\(^+\). These differences increased with age so that the greatest degree of growth failure was observed in adolescents\(^{(52)}\).

Henderson et al\(^{(53)}\) in a study of 63 patients with SCA found that 25% had impaired growth (< 5\(^{\text{th}}\) percentile for height, weight or weight/height). Among the adolescents 46% had poor growth. Similar findings have been reported in other cross-sectional and longitudinal studies\(^{(54)}\). The pathophysiology of growth failure in a SCD is poorly understood. The cooperative study of SCD data did not detected the effect of socio-economic status on growth; however other studies have suggested that nutritional and other micronutrients factors such as zinc may play a role in growth failure\(^{(53)}\).

One study showed an improvement in both growth parameters and the clinical course following caloric supplementation. A variety of micronutrients deficiencies have been suggested in SCD. Numerous case reports describing an
exacerbation of the chronic anemia that was reversed by folic acid therapy led to routine folic acid supplementation\(^{(55)}\).

One study done by Heyman MB and his colleagues report gain in height and weight in two children with SCD given a high caloric nutritional supplement by nasogastric feeding\(^{(56)}\). However, most studies and growth retarded children with SCD have shown adequate caloric and nutritional intake, indicating growth retardation cannot be explained by nutritional factors alone in most patients\(^{(57)}\).

The influence of sickle cell hemoglobinopathies on growth and development, including the height, weight and sexual maturation of 2115 patients aged 2 → 25 years old who had homozygous SCD SS, SC disease, sickle beta thalassemia was studied. Using regression analysis of these and maturation curves for each hemoglobinopathy, it was found that all hemoglobinopathy groups were found significantly different from published normal, and that subjects with SS were consistently smaller and less sexually developed than others\(^{(52)}\).
The relationship of growth with hemoglobin and fetal hemoglobin showed potentially interesting gender differences, high hemoglobin and fetal hemoglobin concentration being related to attained height and weight at 5 and 7 years and to height increment from 3-9 years in boys not in girls. Gender differences were only significant for the relationship between hemoglobin and weight and weight/height. Further analysis suggested that the apparent effect of total hemoglobin on height and weight was mediated through an effect of fetal hemoglobin. Gender differences in anthropometric indices and in nutrient intake were also confined to males in a Nigerian study (58).

**Zinc Deficiency and Supplementation in Children:**

Zinc is an essential trace element. Its intake is closely related to protein intake; as a result, it is an important component of nutritionally related morbidity worldwide.

The usual oral intake is approximately 4 – 14 mg/day and dietary. Sources include animal products such as meat,
sea food and milk. Ready to eat cereals contains the greatest amount of zinc from plant product\(^{(59)}\).

Lacto Vegetarians need more milk, eggs, grains, nuts and seeds to increase requirement.

Zinc circulates at concentration of \(70 \rightarrow 120\) microg/dl. It is an important internisic metal component or activating cofactor for more than 70 important enzyme systems, including carbonic anhydrase, alkaline phosphatases, dehydrogenases and carboxy peptidases. It is involved in regulation of nucleoproteins and activity of various inflammatory cells and plays a role in growth, tissue repair and wound healing, carbohydrate tolerance and synthesis of testicular hormones.

10 to 40\% of dietary zinc is absorbed in the small intestine; absorption is inhibited by the presence of fiber and phytates in the diet that binds to zinc as well as dietary iron and cadmium.

**Zinc deficiency:**

It is important problem in children and adolescents particularly in developing countries. The true incidence of
zinc deficiency is not known because of non specificity of symptoms and imprecise diagnostic methods.

Symptoms attributed to severe zinc depletion include growth failure, primary hypogonadism, skin disease, impaired taste and smell, impaired immunity and resistance to infection.

Zinc supplementation in populations likely at risk for zinc deficiency appears to have beneficial effects on incidence and outcome of serious childhood infectious diseases.

Zinc deficiency occurs in breast fed babies – especially preterm whose mothers have low zinc, in hereditary zinc malabsorption (acrodemitis enteropathica), Crohn disease, liver and renal diseases and sickle cell disease.

Zinc depletion in sicklers appear to reflect increased urinary excretion caused by a renal tubular defect and perhaps chronic hemolysis or impaired absorption, not in adequate dietary intake\(^{60}\).

**Diagnosis:** Zinc status can be assessed by measurement of zinc in plasma, erythrocytes, neutrophils, lymphocytes and
hair. A low plasma zinc is usually defined as a less of 60 microg/dl (61).

**Zinc Supplementation:**

Zinc deficiency is associated with impaired immunity and propensity to infections, is said to be common in children in developing countries in which children experience high rates of serious infections. Zinc supplementation has been evaluated both as a therapeutic and as a potential prophylactic agent in children in these populations (62).

Several randomized studies have shown that zinc supplementation reduces the duration and severity of acute diarrhea in children who are likely to be zinc deficient (61).

Numerous studies in multiple underdeveloped countries have shown a preventive effect of oral routine zinc supplementation on the incidence of diarrheal diseases and pneumonia (62,63).

Some studies have described improved linear growth in infants who received zinc supplementation, especially in those
who were stunted or had low plasma zinc concentrations at base line\textsuperscript{(64)}.

A meta-analysis study confirmed the effect of zinc supplementation in enhancing linear growth velocity and weight gain in children with growth retardation\textsuperscript{(65)}. Because zinc has no pharmacological effect on growth, a growth response to zinc is taken as evidence of a preceding growth-limiting zinc deficiency\textsuperscript{(66)}.

Zinc supplementation has improved linear growth in otherwise healthy non-SCD children with mild growth failure\textsuperscript{(67,68)}.

Zinc supplementation has improved linear growth in otherwise healthy, non-SCD children with mild growth failure in North America\textsuperscript{(67)}, Guatemala\textsuperscript{(68)}, Chile\textsuperscript{(69)}, Ecuador\textsuperscript{(70)} and Ethiopia\textsuperscript{(71)}.

A recent meta analysis study of 25 Zinc supplementation trials conducted in children between 1969 and 1996\textsuperscript{(72)} showed a small but significant improvement in height (0.22SD) with zinc supplementation (P < 0.0001), especially in
those children with the greatest degree of stunning (-2 SD) and lowest baseline plasma zinc concentrations.

**Zinc Status in SCD patients:**

It has been recognized for several decades that children with SCD especially those with SCD. SS has poor growth and delayed maturation\(^{(73)}\).

Increased nutritional requirements, poor nutritional status or both have been documented in children with SCD\(^{(74,75)}\).

Zinc deficiency has been suggested as a contributing factor to growth failure in SCD on the basis of case reports and cross-sectional studies\(^{(75,76)}\). In a large cross-sectional survey of plasma zinc status in children with SCD-SS, low growth status, low fat-free mass and delayed skeletal were associated with low plasma zinc concentrations\(^{(75)}\).

In adults with SCD given Zinc supplements, improved immune function (fewer illnesses and increased natural killer cell activity) and red blood cell integrity (reduced number of
irreversibly sickle cells and increased RBC survival) were also observed\(^{(77,78)}\).

The etiology of zinc deficiency in SCD is not known. Possible mechanisms include increased requirements secondary to erythrocyte hemolysis, chronic inflammation, increased protein turnover and urinary zinc losses, inadequate zinc intake because of poor diet, and inadequate net intestinal absorption. Possible zinc deficiency is suggested by poor growth and delayed skeletal and sexual maturation commonly observed in children with SCD\(^{(73,79)}\).

At birth infant with SCD-SS are normal in size, but significant growth deficits become apparent by 5 year of age\(^{(80)}\).

In recent study survey of 36 children with SCD in Baltimore, 25% had height, weight and weight for height values were less than the 5\(^{th}\) percentile of the NCHS standards\(^{(81)}\).

A study done on the effect of zinc supplementation on growth and body composition in children with SCD in
children’s hospital of Philadelphia Nutrition Center, General Clinical Research Center and the comprehensive sickle center.

It showed that an improved in linear growth in prepubertal children with SCD-SS whose diets were supplemented with 10 mg elemental zinc per day as zinc sulphate in randomized, placebo-controlled study(73).

In one study, for example, 44% of 104 children with SCD had low plasma zinc concentrations (57). These children, when compared to those with normal plasma zinc levels, had significant reduction in height, weight, upper arm muscle area, and in older children delayed sexual maturation. Whether zinc deficiency promotes infection in children with SCD remains controversial(77).

Although the etiology of mild zinc deficiency in SCD is unknown, the significant declines in height for age and weight for age Z-scores observed in the control group, which are typical of the gradual growth failure that occurs in children with SCD, suggest that children with SCD are unable to meet their zinc requirements through diet.
A study conducted by Olivera et al.\textsuperscript{(82)} revealed zinc levels are low in children with SCD in comparison to normal children without SCD. However there was no difference in zinc levels in children with or without growth failure, suggesting other metabolic disturbances are involved. However most studies of growth retardation have shown adequate nutritional and caloric intake, indicating that growth retardation can not be explained by nutritional factors alone in most patients.

Inadequate zinc intake is another possible mechanism of zinc malnutrition in SCD. Poor appetite is frequently reported by care providers of children with SCD, and anorexia associated with painful or febrile episodes is common\textsuperscript{(83)}. However the few studies of nutrients intake in children with SCD are based on small sample sizes\textsuperscript{(84)} and therefore have limited generalizability in a comparison of 9 children with SCD and control subjects, lower RBC zinc was not associated with differences in zinc intake\textsuperscript{(84)}, similarly Phebus et al.\textsuperscript{(85)} documented lower serum zinc concentrations in 80 children with SCD than in 44 healthy control subject aged 3 to 18 and found no significant differences in dietary zinc intake.
A small randomized trial of zinc supplementation in 10 male subjects aged 14-17 years with SCD and growth retardation showed significantly improved growth and skeletal maturation over 1 year\(^{(86)}\).

In the literature, reports showing zinc deficiency in SCD did not separate groups by stature and compared individuals with a large age gap and at different stages of sexual development\(^{(87,88)}\). This reinforces the fact that there is no unifocal relationship between zinc and growth in patients with SCD, although they frequently present low serum levels. This strongly suggest that zinc does have some influence, but implies the existence of additional factors.

Although several studies did not succeed in relating low s. zinc level in SCD with nutritional status\(^{(84,89)}\), we cannot rule out any interference of malnutrition in the zinc results and also as a cause of short stature. Probably in the presence of chronic and severe disease as SCA, conditions of malnutrition and mild nutritional deficiencies are often difficult to establish by clinical or laboratory data.
In 1994 Ilham M. Omer studied the physical growth and school performance among SCA patients. She found that the weight and height is significantly lower than the control group within all age group.
Justification and Objectives

- Sickle cell disease is a common chronic problem in Sudan affecting significant number of children.
- Children with SCD have poor growth and delayed maturation, which may be partially due to zinc deficiency.
- Poor growth and delayed maturation in children with SCD-SS may be improved with adequate nutritional care, particularly zinc supplementation.

Objectives:

- To measure zinc level in patients with SCA.
- To evaluate the relation between zinc level, linear growth and sexual maturation of patients with SCA.
Chapter Two

2- MATERIALS AND METHODS

3.1 Study Design:

Is a cross-sectional hospital based case control study.

3.2 Selection of Cases:

Study Population:

The study was done for SCA patients who presented to Gafar Ibn Oaf Hospital and Omdurman SCA referred clinic from June to October 2006. Patients are selected randomly from those attending the referred clinic.

Inclusion Criteria:

120 patients were included in the study. Their age ranged from one to seventeen years, who are proved sickler by hemoglobin electrophoresis.

Exclusion Criteria:

Patients excluded from the study those who are known to have chronic medical problem other than SCD as malabsorption (inflammatory bowel disease, intestinal by pass
surgery and nephrotic syndrome). Also patients on hydroxyurea or supplements containing zinc or those who refused to participate were excluded from the study.

Verbal consent was taken from all parents or accompanying care takers of children with SCA, and from physicians caring for them especially before taking blood sample.

3.3 Study Design:

A control group in the study are sickler patients whom were zinc levels are normal and compared to those with low zinc levels.

Zinc levels of cases and control group were compared to anthropometric measurements and sexual maturation in older age group (≥ 9years old).

3.4 Data Collection:

A questionnaire was completed for all cases. Answers were taking from accompanying care takers or the child himself.

The questionnaire consists of:
3.4.1 Clinical history:

Personal history including full name, age, sex, residence and tribe.

Age at diagnosis of disease. (for how long patient is known sickler).

PH of hospital admissions by febrile illnesses, diarrhoeal diseases, painful crises or blood transfusions.

Nutritional history including amount (number of meals per day), quantity (particularly meat, milk, seafood), to determine adequacy of nutrition.

Social history was taken about the income, housing condition (number of room, kitchen, latrines and a availability of safe water supply and electricity, and number of family members.

Vaccination history was taken and patients were either completely, partially or not vaccinated at all.

Family history of consanguinity, similar problem or deaths.
Drug history including folic acid, prophylactic antibiotic or other drugs was also taken.

3.4.2 Clinical examination:

All patients were examined generally for pallor, fever, jaundice, respiratory and cardiovascular examination and signs of art failure.

Abdominal examination for organomegaly.

Searching for leg ulcers, oestomylites and hemiplegia.

Anthropometric measurements:

Weight: Patient were weighted with light clothes and without shoes (to within 0.1 kg) and weight was expressed in z-scores and compared to international NCHS standards.

Height: height is taken to all patients without shoes and child standing with heels and back in contact with height stadiometer (to within 0.1 cm) and expressed in z-scores and compared to international NCHS standards.

Assessment of Maturation:
Any patient ≥ 9-years and < 18 year was assessed for sexual maturity in a private room; genital and pubic hair for males and breast and pubic hair for females compared to the drawings of Tanner stages.

➢ Tanner stages for males are as follow:

  o Stage I: is preadolescent; tests, scrotum and penis about the same size as in early childhood.

  o Stage II: Enlargement of scrotum and tests and reddening and change of texture of scarcel skin. Little or no enlargement of penis (10.5 to 12.5 years).

  o Stage III: Enlargement of penis mainly in length, further growth of tests and scrotum (11.5 to 14 years).

  o Stage IV: Increased size of penis development of glans, further enlargement of tests and scortum and darkening of scrotal skin.

  o Stage V: Gentilia of adult size and shape (14 years to adult).
**Tanner stages for females:**

*Stage I:* Preadolescents. No breast budding.

*Stage II:* Continued enlargement of breast.

*Stage IV:* Areola and papilla from 2ndry mound. *Stage V:* Mature female breast.

### 3.5 Investigation:

Two ml of blood is taken from every patient with SCA in a plane tube and plasma is separated into glass and stored at 20 °C. Serum can be used within 24 hours.

Serum plasma zinc was measured chemically by spectrophotometry (zinc present in the sample is deleted by 5-Br-PAPS (5-bromo-2 pyridyiazol) -5- (N. propyl-N-sulphopropylamino)-phenol in the reagent.

The formation of this complex is measured at a wave length of 560 nm. The measurement must be done within 60 minutes when serum mixed with reagent.

Serum zinc level is measured in µmol/L and the normal range is between 9.8 – 16.8.
3.6 **Research Team:**

- The researcher himself
- Lab technician.

3.7 **Statistical Analysis:**

The questionnaire was coded, and a master sheet was constructed to arrange the raw data. The tables were then drawn and description statistics measured.

Data were entered into statistical package for social science (SPSS); computer programme for analysis. The growth parameters (weight and height for age), serum zinc level were performed with chi-square test. Level of significance was set at p value < 0.05.

EPI info 2002 statistical package computer programme was used to determine the nutritional status of children\(^{(90)}\).
Chapter Three

3- Results

3.1 Age and Sex of Patients with SCA included in the Study:

*Table 1:* shows that 46.7% of total numbers are males while the remaining 54.3% are female.

*Table 2:* shows that 50 patients are below 5 years of age (about 33%) and 48 patients are above 8 years old (40%).

3.2 The Tribes of Cases Involved in the Study:

It shows that almost all patients are from tribes belonging to western Sudan, while only 2 patients (1.7%) are belonging to Alzandi tribe.

The large number of patients are from Messeryia and Bargo tribe. *(Table 3).*
Table 1: Distribution according to sex of patient involved in the study group

<table>
<thead>
<tr>
<th>Sex</th>
<th>Frequency</th>
<th>Percentage (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male</td>
<td>56</td>
<td>46.7</td>
</tr>
<tr>
<td>Female</td>
<td>64</td>
<td>53.3</td>
</tr>
<tr>
<td>Total</td>
<td>120</td>
<td>100.0</td>
</tr>
</tbody>
</table>
**Table 2: Distribution of patients according to age**

<table>
<thead>
<tr>
<th>Age (Years)</th>
<th>Frequency</th>
<th>Percentage (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 – 2</td>
<td>11</td>
<td>9.2</td>
</tr>
<tr>
<td>2.1 – 4</td>
<td>29</td>
<td>42.2</td>
</tr>
<tr>
<td>4.1 – 8</td>
<td>32</td>
<td>26.7</td>
</tr>
<tr>
<td>9 – 17</td>
<td>48</td>
<td>40</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>120</strong></td>
<td><strong>100.0</strong></td>
</tr>
<tr>
<td>Tribe</td>
<td>Frequency</td>
<td>Percentage (%)</td>
</tr>
<tr>
<td>---------------------</td>
<td>-----------</td>
<td>----------------</td>
</tr>
<tr>
<td>Messerya</td>
<td>24</td>
<td>20</td>
</tr>
<tr>
<td>Bargo</td>
<td>22</td>
<td>18.3</td>
</tr>
<tr>
<td>Foor</td>
<td>10</td>
<td>8.3</td>
</tr>
<tr>
<td>Hawsa</td>
<td>9</td>
<td>7.5</td>
</tr>
<tr>
<td>Tama</td>
<td>12</td>
<td>10</td>
</tr>
<tr>
<td>Zandi</td>
<td>2</td>
<td>1.7</td>
</tr>
<tr>
<td>Others (Falata, Gawama, Barno, Dago, Rizigat)</td>
<td>41</td>
<td>34.2</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>120</strong></td>
<td><strong>100.0</strong></td>
</tr>
</tbody>
</table>
3.3 Age of Patients at Time of Diagnosis:

Table 4: shows that (30.8%) are diagnosed at 4 month of age, while (45.8%) are diagnosed before 1 year of age. That means most of patients (76.6%) are diagnosed early (before 1 year), but (12.6% are diagnosed late after (5 years of age).

3.4 Number of Previous Hospital Admissions:

Table 5 shows that of 120 patients only 11 are not admitted at all, while 50.8% are admitted less than 5 times and 27.5% are admitted frequently (more than 9 times).

3.5 Number of Blood Transfusions Given to the Patients:

Table 6 shows that 25.8% are not transfused at all while 15.8% patients are transfused more than 5 times.

3.6 Number of Hospital Admissions by Febrile Illnesses:

Table 7 shows that only 10% of cases did not develop febrile illness that necessitate hospital admission. All the rest of patients are admitted by febrile illness and (27.5%) are admitted more than 8 times.
### Table 4: Age of patients at diagnosis

<table>
<thead>
<tr>
<th>Age</th>
<th>Frequency</th>
<th>Percentage (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0 – 4 months</td>
<td>37</td>
<td>30.8</td>
</tr>
<tr>
<td>5 months – 1 year</td>
<td>55</td>
<td>45.8</td>
</tr>
<tr>
<td>1.1 – 5 years</td>
<td>13</td>
<td>10.8</td>
</tr>
<tr>
<td>&gt; 5 years</td>
<td>15</td>
<td>12.6</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>120</strong></td>
<td><strong>100.0</strong></td>
</tr>
</tbody>
</table>
### Table 5: Number of previous hospital admissions

<table>
<thead>
<tr>
<th>Admissions</th>
<th>Frequency</th>
<th>Percentage (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No admission</td>
<td>11</td>
<td>9.2</td>
</tr>
<tr>
<td>1 – 5</td>
<td>61</td>
<td>50.8</td>
</tr>
<tr>
<td>6 – 9</td>
<td>15</td>
<td>12.5</td>
</tr>
<tr>
<td>&gt; 9</td>
<td>33</td>
<td>27.5</td>
</tr>
<tr>
<td>Total</td>
<td>120</td>
<td>100.0</td>
</tr>
</tbody>
</table>
Table 6: Number of blood transfusions given to the SCA patients

<table>
<thead>
<tr>
<th>Transfusion</th>
<th>Frequency</th>
<th>Percentage (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No of transfusion</td>
<td>31</td>
<td>25.8</td>
</tr>
<tr>
<td>1 – 2</td>
<td>45</td>
<td>37.6</td>
</tr>
<tr>
<td>3 – 5</td>
<td>25</td>
<td>20.8</td>
</tr>
<tr>
<td>&gt; 5</td>
<td>19</td>
<td>15.8</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>120</strong></td>
<td><strong>100.0</strong></td>
</tr>
</tbody>
</table>
Table 7: Hospital admission by febrile illnesses

<table>
<thead>
<tr>
<th>Febrile illnesses (attack)</th>
<th>Frequency</th>
<th>Percentage (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No attack</td>
<td>12</td>
<td>10</td>
</tr>
<tr>
<td>1 - 2</td>
<td>18</td>
<td>15</td>
</tr>
<tr>
<td>3 – 5</td>
<td>44</td>
<td>36.7</td>
</tr>
<tr>
<td>6 – 8</td>
<td>13</td>
<td>10.8</td>
</tr>
<tr>
<td>&gt; 8</td>
<td>33</td>
<td>27.5</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>120</strong></td>
<td><strong>100.0</strong></td>
</tr>
</tbody>
</table>
3.7 Hospital Admissions by Diarrhoeal Diseases:

*Figure 1:* shows that diarrhoeal diseases are not a common presentations. 75% are not admitted at all by diarrhea and only 10% of patients are admitted by diarrhoeal more than 5 times.

3.8 Admission by Hand Foot Syndrome:

*Table 8:* shows that only 24% are not admitted before by this problem and 34.2% are admitted more than 5 times by hand foot syndrome.

3.9 Nutritional Status in Children included in the Study:

*Figure 2:* shows that the majority of patients has adequate nutritional status (65.2%). (34.8%) had poor nutritional status.

3.10 Consanguinity Among Patients with SCA:

*Table 9:* shows that a considerable number are a product of consanguineous marriage (68.3%) while only 31.7% are not a product of consanguineous marriage.
Figure 1: Sex of the study group with SCA
n = 120

53.3% Male
46.7% Female
Figure 2: Distribution of the study group according to tribes

- Messerya: 30%
- Bargo: 18.3%
- Foor: 8.3%
- Hawsa: 7.6%
- Tama: 10%
- Zandi: 8.3%
- Others: 4.2%

$n = 120$
Figure (3): Hospital admissions by diarrhoeal disease
n = 120

- 75%: More than 5 attacks
- 15%: 1-5 attacks
- 10%: No attack
Figure (4): Nutritional status among SCA patients
n = 120

65.2%
34.8%
Figure (5): Social Class of SCD
n = 120
Figure (6): Height for age in SCA patients
\[ n = 120 \]
Figure (7): Weight for age in SCA patients included in the study

n = 120
Table 8: Hospital admission by hand foot syndrome

<table>
<thead>
<tr>
<th>Hand foot syndrome (times)</th>
<th>Frequency</th>
<th>Percentage (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No attack</td>
<td>29</td>
<td>24.2</td>
</tr>
<tr>
<td>1 – 3</td>
<td>50</td>
<td>41.6</td>
</tr>
<tr>
<td>&gt; 3</td>
<td>41</td>
<td>34.2</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>120</strong></td>
<td><strong>100.0</strong></td>
</tr>
</tbody>
</table>
## Table 9: Family history of consanguinity

<table>
<thead>
<tr>
<th>Family history</th>
<th>Frequency</th>
<th>Percentage (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yes</td>
<td>82</td>
<td>68.3</td>
</tr>
<tr>
<td>No</td>
<td>38</td>
<td>31.7</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>120</strong></td>
<td><strong>100.0</strong></td>
</tr>
</tbody>
</table>
3.11 Family History of Similar Problem and Death:

Table 10 and 11: shows that (35.8%) of patients had similar problem in their families, while (18.3%) showed a history of death by similar problem.

3.12 Vaccination among Children Included in the Study:

Table 12: shows that almost all of children completed their recommended vaccination (98%). Only one patient are not vaccinated at all and another one patient partially vaccinated.

3.13 Drug History of Patient:

Table 13: shows that (98.3%) of patients are taking folic acid, while only (20%) of patients are taking prophylactic antibiotic although (40%) of patients are below 5 years of age.
Table 10: Family history of similar problems

<table>
<thead>
<tr>
<th>Similar problems</th>
<th>Frequency</th>
<th>Percentage (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yes</td>
<td>43</td>
<td>35.8</td>
</tr>
<tr>
<td>No</td>
<td>77</td>
<td>64.2</td>
</tr>
<tr>
<td>Total</td>
<td>120</td>
<td>100.0</td>
</tr>
</tbody>
</table>
Table 11: Family history of death by a similar problem

<table>
<thead>
<tr>
<th>Family history</th>
<th>Number</th>
<th>Percentage (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yes</td>
<td>22</td>
<td>18.3</td>
</tr>
<tr>
<td>No</td>
<td>98</td>
<td>81.7</td>
</tr>
<tr>
<td>Total</td>
<td>120</td>
<td>100.0</td>
</tr>
</tbody>
</table>
Table 12: vaccination among cases included in the study

<table>
<thead>
<tr>
<th>Vaccination history</th>
<th>Number</th>
<th>Percentage (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Not vaccinated</td>
<td>1</td>
<td>0.85</td>
</tr>
<tr>
<td>Partially vaccinated</td>
<td>1</td>
<td>0.85</td>
</tr>
<tr>
<td>Vaccinated up to age</td>
<td>118</td>
<td>98.3</td>
</tr>
<tr>
<td>Total</td>
<td>120</td>
<td>100.0</td>
</tr>
</tbody>
</table>
Table 13: Drug history of the sickler

<table>
<thead>
<tr>
<th>Drug history</th>
<th>Number</th>
<th>Percentage (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Folic acid</td>
<td>118</td>
<td>98.3</td>
</tr>
<tr>
<td>Prophylactic antibiotic</td>
<td>20</td>
<td>17</td>
</tr>
<tr>
<td>Other drugs</td>
<td>13</td>
<td>10.8</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>120</strong></td>
<td><strong>100.0</strong></td>
</tr>
</tbody>
</table>
3.14 Social Class of SCA Patients Included in the study:

*Figure 3:* shows that most of patients are of low socio-economic class (71.7%) while only two patients (1.7%) are of high class.

3.15 Clinical Presentation of SCA Patients at Time Attending the Referred Clinic:

*Table 14:* shows that most of patients are pale (83.3%) and having jaundice (55.8%). 27.5% of patients are presented in painful crises and only (6.7%) have or had a history of oestomylities.

2.5% develop CVA and hemiplegia.

3.16 *Figure 4:* shows the growth parameters for SCA patient. It shows that weight is more affected than height, (3.3%) of patients their height is severely affected, while (12.5%) of patients their height is moderate for age the remaining 101 patients (84.2%) were within normal for age (-1.99 SD up to the SD).
Table 14: Clinic presentation of patients at time of attending referred clinic

<table>
<thead>
<tr>
<th>Clinical presentation</th>
<th>Frequency</th>
<th>Percentage (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pallor</td>
<td>100</td>
<td>83.3</td>
</tr>
<tr>
<td>Jaundice</td>
<td>67</td>
<td>55.8</td>
</tr>
<tr>
<td>Fever</td>
<td>26</td>
<td>21.7</td>
</tr>
<tr>
<td>Hand foot syndrome</td>
<td>14</td>
<td>11.7</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>15</td>
<td>12.5</td>
</tr>
<tr>
<td>Chest pain</td>
<td>4</td>
<td>3.3</td>
</tr>
<tr>
<td>Hepatomegaly</td>
<td>48</td>
<td>40</td>
</tr>
<tr>
<td>Splenomegaly</td>
<td>22</td>
<td>18.3</td>
</tr>
<tr>
<td>Oestomycities</td>
<td>8</td>
<td>6.7</td>
</tr>
<tr>
<td>Hemiplegia</td>
<td>3</td>
<td>2.5</td>
</tr>
<tr>
<td>Heart failure</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>
Figure 5: shows weight for age and were 9 (7.5%) patients are their weight are > - 3 SD for age, while 43 patients their weight is -2.99 SD to -2 SD. The remaining 68 patients were normal for age -1.99 SD to +ve SD.

3.17 Table 15: shows Tanner stages of 48 patients whom were ages between 9 $\rightarrow$ 17 years; it shows that only 12 (25%) had normal tanner stage, while the remaining 36 patients (75%) had delayed tanner stage for age.

3.18 Table 16: shows s-zinc level of the 120 patients and only 36 patients their zinc level is low (< 9.8 micromol/L) while the remaining 84 patients their zinc level is within normal.

3.19 Table 17: shows the relation between zinc level and height for age of the patients, and the results are; 4 patients with low zinc level are moderately short for age and 32 patients with low zinc level are within normal height for age. It shows that there is no significant relation between zinc and height.
Table 15: Tanner stages of the 48 patients of SCA (ages between 9 → 17 years)

<table>
<thead>
<tr>
<th>Tanner stage</th>
<th>Number</th>
<th>Percentage (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal Tanner stage</td>
<td>12</td>
<td>25</td>
</tr>
<tr>
<td>Delayed Tanner stage for age</td>
<td>36</td>
<td>75</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>120</strong></td>
<td><strong>100.0</strong></td>
</tr>
</tbody>
</table>
### Table 16: S. zinc level in SCA patients included in the study

<table>
<thead>
<tr>
<th>Result of blood sample</th>
<th>Number</th>
<th>Percentage (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal s. zinc &gt; 9.8 µmol/L</td>
<td>84</td>
<td>70</td>
</tr>
<tr>
<td>Low s. zinc level &lt; 9.8 µmol/L</td>
<td>36</td>
<td>30</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>120</strong></td>
<td><strong>100.0</strong></td>
</tr>
</tbody>
</table>
Table 17: Height for age of sickle patients versus serum zinc level

<table>
<thead>
<tr>
<th>Result of blood sample</th>
<th>Severe (&gt; - 3 SD)</th>
<th>Moderate (-2.99 SD → - 2 SD)</th>
<th>Mild (&lt; 1.99 SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low s. zinc</td>
<td>0</td>
<td>4</td>
<td>32</td>
</tr>
<tr>
<td>Normal s. zinc</td>
<td>4</td>
<td>11</td>
<td>61</td>
</tr>
</tbody>
</table>

P = 0.441
Table 18: shows the relation between zinc level and weight for age of the 120 patients and results are; 2 patients of severely low weight for age (> -35D) had low s-zinc level. 20 patients of moderate low weight for age (-2.99 SD to -2 SD) had low s. zinc level, and 14 patients with normal weight for age their zinc level is low.

This shows that there is a significant relation between weight and height.

Table 19: shows the relation between zinc level and sexual maturation.

This table shows that 14 patients with delayed tanner stage have low serum zinc level while 22 patients with delayed tanner stage have normal zinc level. The p value of the test 0.157 indicating no significant relation between sexual maturity and zinc level.
Table 18: weight for age versus s. zinc level

<table>
<thead>
<tr>
<th>Result of blood sample</th>
<th>Severe (&gt;-3 SD)</th>
<th>Moderate (-2.99 SD → -2 SD)</th>
<th>Mild (-1.99 SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low s. zinc</td>
<td>2</td>
<td>20</td>
<td>19</td>
</tr>
<tr>
<td>Normal s. zinc</td>
<td>7</td>
<td>23</td>
<td>54</td>
</tr>
</tbody>
</table>

P = 0.032
Table 19: Tanner stage versus serum zinc level

<table>
<thead>
<tr>
<th>Zinc level</th>
<th>Tanner stage</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Normal</td>
<td>10</td>
<td>22</td>
</tr>
<tr>
<td></td>
<td>Low</td>
<td>2</td>
<td>14</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>12</strong></td>
<td><strong>36</strong></td>
<td></td>
</tr>
</tbody>
</table>

P = 0.157
Chapter Four

4- DISCUSSION

This is conducted among sickle cell anemia children in Khartoum State. Sickle cell anemia is one of the commonest inherited disorder affect children especially of western ethnic descent. It studied the relation between growth parameter (height and weight for age), sexual maturity and their serum zinc level.

The age group involved is between 1 and 17 years about two third of them are below 5 years and the other one third is above 5 years of age. The sex of patients in the study is nearly canal, but the differences in sex are not an objective. However their age was considered, because sexual maturity is one of the objective of the study.

Almost all of the patients are from tribes of western Sudan and this because the consanguous marriage is still a problem need to be discussed in detail with these families of inherited disorder.
Wethers DL from Colombia University, studied the effect of sickle cell anaemia on growth and sexual maturation. He found delayed growth at all ages and in both sexes and demonstrated delay is sexual maturation in SCA children\(^{(91)}\). He studied only the growth and maturation and not relate it to serum zinc level.

The study showed that there is a significant relation between reduction of weight for age and low serum zinc level (P < 0.05), compared to sicklers with normal serum zinc level. Similar results was obtained by University of Lorin, Nigeria, which found an anthropometric values were lower than the 50\(^{th}\) percentile for SCA children. Of all parameters weight for age was particularly deficient\(^{(92)}\). However this study did not relate growth parameters to serum zinc level.

This result is also similar to the study done by Zamel BS, Stalling VA and their colleagues, university of Pennsylvania, about serum zinc and relation to growth and maturation. It found that decreased plasma s. zinc level is common in sickle cell disease (SS genotype) and is associated with decreased linear growth, skeletal and sexual maturation\(^{(75)}\).
The height for age and sexual maturity are found not to be related to serum zinc level in this study (P > 0.05) of both. This is similar to one study that failed to show an association between s. zinc concentrations and growth parameters\(^{(93)}\). This results are also similar to the study conducted by Olivera et al\(^{(82)}\), which found there is no difference in zinc level in children with SCA with or without growth failure, suggesting other metabolic disturbances are involves.

Plasma zinc may not be a sensitive indicator of growth-limiting zinc deficiency, especially in patients with SCD for whom hemolyzed red blood cells may contaminate plasma samples.

A measurable effect on growth in a controlled study is considered to indicate pre-existing growth-limiting zinc deficiency that has been at least partially corrected by provision of zinc supplements\(^{(67)}\).

In the study done by Zamel BS and his colleagues about effect of zinc supplementation on growth and body composition in children with SCA\(^{(73,73)}\) they found there were no differences in growth related to baseline plasma zinc
concentrations. However, zinc supplementation was associated with greater linear growth and other indicators of nutritional status. This finding suggest that the gradual growth failure in children with SCD-SS may be preventable with adequate nutritional care, particularly zinc supplementation.

Several factors may contribute to growth failure in SCA patients. The study revealed that most patients are admitted frequently to hospital by febrile illnesses and painful crises, and significant number of them received blood transfusions several times in their course of illness indicating that chronicity and severity is a strong factor affecting their growth and maturity. However diarrhoeal diseases are found to be irrelevant to their problem, because only 10% of them are admitted by diarrhoeal disease more than 5 times.

The nutritional history of patients included in the study was satisfactory (79% showed adequate nutritional history). Most of the families insist that they take sufficient amount of zinc containing food, like milk, meat and cereals, although most of them are of low socioeconomic classes (86%).
However most studies of growth retarded children with SCA have shown adequate caloric and nutritional intake, indicating that growth failure can not be explained by nutritional factors alone in most patients(83).

The vaccination history of patients is excellent, because 98.3% are completed their vaccination programme up to age and this because of availability of vaccines and probably repeated hospital admission may be a reason for completion of their vaccine programme.

Previous reports have linked zinc to growth abnormalities in children with SCD(75,76,87). Relative to normal plasma zinc concentrations, low plasma zinc concentrations are associated with poorer growth status (i.e, a height for age z-score less than the 5th percentile) (89) a significantly lower height, weight, elbow breadth, upper arm muscle mass and delayed skeletal age(75).

The effect of zinc supplementation on prepuberal children with sickle cell disease has not been evaluated.

CONCLUSION
1- Most of studied group children are from western tribes, of them a considerable number (68.3%) are a product of consanguious marriage.

2- Patients are frequently admitted by febrile illnesses (mean 5.4.9) painful crises (mean = 4) and received blood transfusion (mean = 2.16), however diarrhea is not a common presentation among them (mean 1.26).

3- Vaccination history is excellent, almost all of them are completed their vaccination (98.3%), taking their folic acid (98.3%), but only 17% of the 40% whom their age is 5 years or less are taking their prophylactic antibiotic.

4- The commonest presentation is pallor, jaundice, fever and painful crises respectively, only minority are presented by oestomylities and CVA.

5- Of their growth parameter, weight was found to be affected more (mean is -1.66) and was found to be related to low serum zinc level (P < 0.05). The height
for age was less affected (mean height for age is 
0.56) and was found to not related to zinc level.

6- The sexual maturity is significantly delayed (75% had 
delayed Tanner stage for age, but found not to be 
related to their serum zinc level.
RECOMMENDATIONS

- Screening of the families belonging to tribes with high incidence of sickle cell anaemia is important for early detection and proper management.

- Health education is important to decrease the degree of consanguous marriage, education about immunization prophylaxis, acute crises and comprehensive medical evaluation is mandatory for those patients.

- The follow up of those patients should be by regular monitoring of growth parameters and nutritional assessment and control of acute crises, maintenance of hemoglobin level near normal; factors well known to affect their growth.

- Although several studies fail to relative low s. zinc level with nutritional status in SCA patients, we can’t rule out any influence of malnutrition in the zinc results, so adequate nutritional intake particularly zinc may
improve growth, immunity and wound healing in those children.
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