Evaluation of renal function in sickle cell disease patients in Jaafer Ibn Ouf Peadiatric teaching hospital, Khartoum state, Sudan

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فَسِيرَ ١٠٥

وقال السجدة

صدق الله العظيم

سورة التوبة - اية 105
DEDICATON

To my parents ...  

Who encouraged me at all stages of life

To my brother and sisters ... 

For their unlimited support ...
I would like to express my sincere gratitude and thankfulness to my supervisor Dr. Abdelwahab A'bdin for his guidance, meticulous supervision, revising and discussing all aspects of this study. His valuable advices and comments are highly appreciated.

My great thanks also extend to the patients, others who contributed in a way or another for the success of this study especially.
# ABBREVIATIONS

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Full Form</th>
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<tbody>
<tr>
<td>AKI</td>
<td>Acute Kidney Injury</td>
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<td>CKD</td>
<td>Chronic Kidney Disease</td>
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<tr>
<td>CRF</td>
<td>Chronic Renal Failure</td>
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<tr>
<td>ESRD</td>
<td>End-Stage Renal Disease</td>
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<tr>
<td>GFR</td>
<td>Glomerular Filtration Rate</td>
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<tr>
<td>HbSC</td>
<td>Hemoglobin Sickle Cell Disease</td>
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<tr>
<td>NO</td>
<td>Nitric Oxide</td>
</tr>
<tr>
<td>SCD</td>
<td>Sickle Cell Disease</td>
</tr>
<tr>
<td>SPSS</td>
<td>Statistical Package for the Social Sciences</td>
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<td>WHO</td>
<td>World Health Organization</td>
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ABSTRACT

Sickle cell disease (SCD) is the most prevalent genetic disease worldwide. In the classical form of the disease, there is heterozygosity in the mutation that causes hemoglobin S, while in other rare forms of the disease, hemoglobin S coexists with another abnormal hemoglobin (hemoglobin C, β-thalassemia). Renal involvement can occur throughout the life of a patient with SCD. The study aimed to investigate renal function abnormalities in sickle cell patients in Sudan, 2018. It is case control study conducted in Khartoum state in period between March and August 2018. Data collected, cleaned and analyzed using SPSS version 25.0.

This study covered 80 study participants that divided into two comparison groups, Cases group that represented (62.5%) and Controls group that represented (37.5%). Our study found that (62.5%) of the study participants were above 5 years in age. The age distribution were similar among both study groups (cases versus controls). Concerning the gender distribution, our study found that more than half of the study participants were females (56.3%) with male female ratio 0.7:1 among cases and 0.9:1 among controls. Nearly three quarters of cases (74%) had positive history of urinary tract infections compared with controls (13.3%). Regarding the results of renal function tests, our study found that the overall means were urea 4.8 ± 1.35 mmol/L, Creatinine 0.89 ± 0.7 mg/dl, Serum Na 141.29 ± 3.82 mmol/L, Serum K 5.99 ± 0.4 mEq/L and Serum Chloride 102.04 ± 3.05 mEq/l. Our study found that there was a significant difference in the level of potassium (p value < 0.001) and in the creatinine even with in the normal ranges (p = 0.0422). The study did not found a significant difference in the levels of urea, Sodium and chloride. This study has explained renal profile (urea & creatinine) and their role in sickle cell anaemia which could be used in designing of the better management of sickle cell patients in Sudan.
الخلاصة
مرض الانيميا المنجلية (SCD) هو المرض الوراثي الأكثر انتشارًا في جميع أنحاء العالم. في الشكل الكلاسيكي للمرض، يمكن أن تحدث المشاكل الكلوية طوال حياة المريض بالانيميا المنجلية، هدف الدراسة هو التعرف على حالات اضطراب وظائف الكلى لدى مرضى الانيميا المنجلية بالسودان في الظروف الكلاسيكية. دراسة مقارنة بين حالات مصابة بمرض الانيميا المنجلية مع افراد آخرين صحّة، وذلك بمستشفى جعفر ابن عوف بولاية الخرطوم بالسودان في الفترة بين مارس وأغسطس 2018. تم جمع البيانات واعداها وتحليلها باستخدام SPSS الإصدار 25.0. غطت هذه الدراسة 80 مشاركًا في الدراسة التي قسمت إلى مجموعتين للمقارنة: مجموعة الحالات (مرضى بالانيميا المنجلية) التي مثلت (62.5%) ومجموعة المضات (الصحّة) التي مثِلت (37.5%). وجدت دراستنا أن (62.5%) من المشاركين في الدراسة كانوا فقّر 5 سنوات. كان التوزيع العمرى متشابهًا بين مجموعتي الدراسة (الحالات مقابل المضات) وجدت دراستنا أن أكثر من نصف المشاركين في الدراسة كانوا من الإناث (56.3%) مع نسبة الإناث الذكور 0.7: 1 بين الحالات و 0.9: 1 بين المضات. في حين أن ما يقرب من ثلاثة أرباع الحالات (74%) لديهم تاريخ إيجابي من التهابات المسالك البولية مقارنة مع مجموعة الاصحاب أو المضات (13.3%). في ما يتعلق بنتائج اختبارات وظائف الكلى، وجدت دراستنا أن متوسط مستوى الليبريا هي 4.8 ± 1.35 مليمول / لتر، الكرياتينين 0.89 ± 0.7 mg / dl، الصوديوم mEq / L 141.29 ± 5.99، الوتاسيوم L 3.82 ± 0.4 مليمول / لتر، الكرياتينين 102.04 ± 3.05 مليمول / لتر، البوتاسيوم 5.99 ± 0.4 مليمول / L، والكلوريد 120.29 ± 0.4 mEq / L، الكرياتينين 3.82 ± 0.4 mEq / L. وجدت دراستنا أن هناك فرقًا ذو جدوى إحصائية في مستوى البوتاسيوم في الكرياتينين (قيمة p = 0.001) وفي الكرياتينين ورغم أن المستوى في المجموعتين هو في الحد الطبيعي، لم نجد الفرقًا كبيرًا في مستويات البوتاسيوم والكلوريد والبوتاسيوم والكلوريد. أوضحت هذه الدراسة ملخصًا لوظائف الكلى (الليبريا والبوتاسيوم) ودورها في تقدير وضع المرضى بفقر الدم المنجل، هذه النتائج يمكن استخدامها في تصميم خطة معالجة أفضل لمرضى الانيميا المنجلية في السودان.
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Chapter One

Introduction, Objectives and Justification
1.1 Introduction

Sickle cell disease (SCD) is the most prevalent genetic disease worldwide. In the classical form of the disease, there is heterozygosity in the mutation that causes hemoglobin S, while in other rare forms of the disease, hemoglobin S coexists with another abnormal hemoglobin (hemoglobin C, β-thalassemia). The disease is endemic in sub-Saharan Africa where it is associated with higher morbidity and mortality, and as a consequence, almost half of children with SCD die before their fifth birthday. [1]

Sickle cell disease (SCD) is an inherited anemia resulting from mutations in the β-globin chain of adult hemoglobin (HbA; α2β2). Homozygous HbSS (α2βS2) is most common, but approximately one third of adults with SCD have compound heterozygous HbSC (α2βsβc). [1-2] Anemia, painful vaso-occlusive episodes, hemolysis, widespread vasculopathy, and early mortality are characteristic of HbSS. Retinopathy, avascular necrosis of the bones, and chronic pain are more typical of HbSC. Participants with HbSC have a more normal life expectancy. [2]

Continuous improvement in the quality of care has allowed SCD patients to live longer. In many affluent countries, the life expectancy has increased from ~15 years in the 1970s to the present ~50 years. This improved survival is also associated with increasing occurrence of multiple organ lesions secondary to long-standing disease. [3]

The kidneys are the sixth most affected organ in SCD, and chronic renal failure is one of the main causes of death in adults with SCD. The kidney lesions start in childhood and mainly include glomerular and tubulo-
interstitial lesions. The glomerular lesions evolve from hyperfiltration state characterized by an increase in glomerular filtration rate and effective renal plasma flow in association with glomerular hypertrophy to the progressive focal and segmental glomerulosclerosis, then glomerular obsolescence, proteinuria and impaired renal function. \[4\]

Tubular lesions are characterized by damages in the vasa rectae system, disruption of the countercurrent exchange, impairment of urinary concentration causing hyposthenuria and polyuria, and papillary necrosis causing hematuria.\[3\]

The glomerular lesions in SCD start in the early years of life with the prevalence of albuminuria correlating with increasing age and decreasing creatinine clearance. Ultimately, kidney lesions in SCD progress to end-stage renal disease in 4.2–18% of the patients. \[3-4\]

There are suggestions that SCD may already be contributing to the burden of kidney disease among Africans \[9\]. However, little is known about the importance and determinants of kidney disease in SCD in equatorial Africa, where the highest global prevalence of the disease occurs.\[4\]

Kidney disease is seen in most with SCD and may affect glomerular and/or tubular function. CKD in SCD is associated with excess mortality at clinical baseline and during treatment with hydroxyurea (the current standard of care for HbSS). However, the clinical picture is incomplete. Reports of CKD in SCD have focused primarily on patients with HbSS. Furthermore, the life expectancy of adults with SCD has lengthened, and more recent
multicentered studies are likely to be more informative about the current status of renal disease in this population.[4]

Few diseases give rise to such diverse renal manifestations as does sickle cell disease (SCD). Such involvement adversely affects virtually all major physiological processes in the kidney, and leads to complications that are common and chronic on the one hand (such as impaired urinary concentrating ability), and those that are rare and uniformly fatal on the other (such as renal medullary carcinoma).[5]

Renal involvement can occur throughout the life of a patient with SCD. Manifestations such as hyperfiltration, hypertrophy, and impaired urinary concentrating ability are described as early as in infancy. Microalbuminuria is observed in some patients in childhood, whereas haematuria and acute kidney injury (AKI) can occur at any age. [5]

Macroalbuminuria tends to occur in early to middle adulthood, and can be accompanied by regression of the glomerular filtration rate (GFR) to the normal range. In the later decades, the risk of chronic kidney disease (CKD), progressive reduction of GFR, and end-stage renal disease (ESRD) increases. [5]

In this context, the main purpose of our study was to investigate renal function abnormalities in SCD patients in Sudan, 2018.
1.2 Objectives

1.2.1 General objective:

Investigate renal function abnormalities in sickle cell disease patients in Sudan, 2018.

1.2.2 Specific objectives:

1. Measure the level of urea and creatinine among patients with sickle cell anaemia
2. Measure the level of sodium, potassium and chloride among patients with sickle cell anaemia
3. Correlate between the values of renal functions results with some relevant patients characteristics such as the age, gender and the duration of the disease
1.3 Justification

According to the best knowledge of the researcher, there is no available of published research work that evaluate investigate renal function abnormalities in SCD patients in Sudan, with in the few previous years.

Moreover, this study may help to offer valuable rationalized information for variety of beneficiaries such as the SCD patients themselves and their families by availing the updated information about the possible levels of renal functions hazards among patients with SCD.

Similarly, for laboratory specialists, pathologists, pediatricians and relevant medical staff; in order to be more critical in investigation to be more precise in overall management outcome for the patients with SCD in Sudan.
Chapter Two

Literature Review
2. LITERATURE REVIEW

2.1 Background and definition

Sickle cell disease (SCD) is a multisystem disorder and the most common genetic disease in the United States, affecting 1 in 500 African Americans. About 1 in 12 African Americans carry the autosomal recessive mutation, and approximately 300,000 infants are born with sickle cell anemia annually. The understanding of the phenotypic expression of the disease is still limited although environmental factors such as cold weather and air quality, infections, fetal hemoglobin level, and other genetic subtypes play a role in the manifestation of the disease. Clinical manifestations are variable and affect multiple systems and generally cause lower life expectancy.\textsuperscript{[6]}

Sickle cell is caused by a mutation in the hemoglobin beta chain in which glutamic acid is substituted with valine at position six on chromosome 11. \textsuperscript{[7]}

Sickle cell disease (SCD) and its variants are genetic disorders resulting from the presence of a mutated form of hemoglobin, hemoglobin S (HbS). The most common form of SCD found in North America is homozygous HbS disease (HbSS), an autosomal recessive disorder first described by Herrick in 1910. \textsuperscript{[7]} SCD causes significant morbidity and mortality, particularly in people of African and Mediterranean ancestry. Morbidity, frequency of crisis, degree of anemia, and the organ systems involved vary considerably from individual to individual.\textsuperscript{[8]}

Although carriers of sickle cell trait do not suffer from SCD, individuals with one copy of HbS and one copy of a gene that codes for another abnormal
variant of hemoglobin, such as HbC or Hb beta-thalassemia, have a less severe form of the disease.[9] SCD usually manifests early in childhood. For the first 6 months of life, infants are protected largely by elevated levels of Hb F; soon thereafter, the condition becomes evident.[9]

Screening for HbS at birth is currently mandatory in the United States. This method of case finding allows institution of early treatment and control. Obtaining a series of baseline values on each patient to compare with those at times of acute illness is useful.[9]

2.2 Epidemiology and disease burden

Sickle cell anemia is the most common monogenic disorder. Prevalence of the disease is high among the people of Sub-Saharan Africa, South Asia, Middle East, and the Mediterranean. It is estimated that in the United States, the population of sickle cell disease is approximately 100,000 and likely to increase. [10] The most common genotype is homozygous hemoglobin SS (HbSS), and common heterozygous conditions are hemoglobin sickle beta zero thalassemia, hemoglobin sickle beta plus thalassemia (hemoglobin sickle beta plus thalassemia), and hemoglobin sickle cell disease (HbSC).[10]

An extensive literature search was carried out accessing the US National Library of Medicine, the WHO Eastern Mediterranean Region resources, the Catalogue for Transmission Genetics in Arabs and papers and documents published in Sudan that included data on the prevalence of sickle cell anaemia and trait. [11] Rates of SCA and trait varied in different areas in Sudan with the highest rates reported from Western and Eastern Sudan where one in every 123 children born in Messeryia tribe in Western Sudan is at risk of
having SCD. High consanguinity rates and malaria endemicity are strong related factors with sickle cell gene in Sudan. This review will present what is known about the rates of sickle cell gene in different ethnic groups in Sudan. \[11\]

### 2.3 Mechanism and pathology

The genetic mutation described causes polymerization of the Hemoglobin molecule that alters the erythrocyte shape and its ability to deform. There is increased adhesion of erythrocytes followed by formation of heterocellular aggregates, which physically cause small vessel occlusion and resultant local hypoxia. \[12\] This process triggers a vicious cycle of increased HbS formation, the release of inflammatory mediators and free radicals that contribute to reperfusion injury. Hemoglobin also binds to nitric oxide (NO), a potent vasodilator, and releases oxygen. Erythrocytes are more likely to sickle and become rigid in the presence of dehydration. \[12\]

### 2.4 Renal insufficiency in sickle cell disease

Nephropathy is a serious complication of SCD that begins in childhood and may progress to overt renal failure. Sickle cell nephropathy involves damage to multiple structures within the kidney, including the glomeruli within the renal cortex and the renal tubules and vasa recta within the hypoxic, hyperosmolar renal medulla. ESRD develops in 4.2 to 11.6% of adults with HbSS and is an independent predictor of premature mortality in young adults. \[13\] Common clinical markers of renal function such as serum creatinine are
not reliable indicators of early stage glomerulopathy in SCD because of the increased GFR, lower muscle mass, and increased tubular secretion of creatinine in individuals with SCD.\[13\]

Glomerular changes begin as early as the first decade of life in otherwise asymptomatic SCD patients. Early glomerular changes in SCD are characterized by high renal blood flow, glomerular hyperfiltration and hypertrophy, and a gradual loss of glomerular filtration permselectivity such that larger molecules such as albumin abnormally permeate the restrictive pores of the glomerular capillary wall. Thus, albuminuria is a sensitive and early clinical marker of glomerulopathy.\[14\]

Studies previously demonstrated a significant loss of glomerular permselectivity and ultrafiltration coefficient in albuminuric adults with SCD and normal GFR, with the greatest reductions in permselectivity observed in patients with renal insufficiency, suggesting that progressive glomerular injury is a major determinant in the development of renal failure in SCD.\[15\] Additionally we demonstrated that the ultrafiltration coefficient correlates inversely with the fractional clearance of albumin, providing evidence that albuminuria is a reliable indicator of sickle glomerulopathy.\[15\]

Moreover, abnormal albuminuria becomes increasingly prevalent with age and occurs in most adults with SCD. In our study of SCD patients at the Georgia Comprehensive Sickle Cell Center, we found that 68% of adults with HbSS and 42% of adults with non-HbSS SCD had abnormal albuminuria. In adults 40 years of age and older, these frequencies increased to 79% for HbSS and 59% for non-HbSS SCD. Other cohort studies of younger
populations have shown abnormal albuminuria in 16% to 28% of children and young adults with HbSS and HbSβ0.[16]

The kidney is an organ of considerable impact on the clinical course of sickle cell patients. In DRC, the main haplotype of SCD globin gene, the most severe form of the disease. The CAR βs globin gene haplotype was found significantly more often in patients with chronic renal failure (CRF) suggesting a genetic predilection.[17]

Despite this high prevalence of the disease in our midst and the risk of CRF, information about renal complications in pediatric population suffering from SCD in DRC are unknown. Probably this renal impairment is under-reported in African children, poverty and the paucity of pediatric nephrologists and hematologists in this region should contribute to this fact. In addition, SCD and renal diseases are not regarded as a major health problem confronted to infectious diseases and malnutrition.[17]

2.5 Renal function tests

Kidney function tests is a collective term for a variety of individual tests and procedures that can be done to evaluate how well the kidneys are functioning. The kidneys, the body's natural filtration system, perform many vital functions, including removing metabolic waste products from the bloodstream, regulating the body's water balance, and maintaining the pH (acidity/alkalinity) of the body's fluids. Approximately one and a half quarts of blood per minute are circulated through the kidneys, where waste chemicals are filtered out and eliminated from the body (along with excess
water) in the form of urine. Kidney function tests help to determine if the kidneys are performing their tasks adequately\(^{[18]}\)

2.5.1 Serum urea

Urea is the end product of protein catabolism. The urea is produced from the amino group of the amino acids and is produced in the liver by means of the Urea cycle. \(^{[19]}\)

Urea undergoes filtrations at the glomerulus as well as secretion and reabsorption at the tubular level. The rise in the level of serum urea is generally seen as a marker of renal dysfunction specially glomerular dysfunction. Urea level only rises when the glomerular function is reduced below 50%. The normal serum urea level is between 20-45 mg/dl. But the level may also be affected by diet as well as certain non kidney related disorders. \(^{[20]}\)

A high protein diet may increase the blood urea level. Similarly a low protein diet may decrease blood urea level. Other causes of protein catabolism such as any hyper metabolic conditions, starvation etc also cause increased blood urea levels. \(^{[21]}\) Similarly the level of urea may also be decreased in case of hepatic injury. So even though blood urea is not an excellent marker of renal dysfunction as it rises quite late in the dysfunction and its rise is also not exclusive to kidney dysfunction, but for practical purposes serum urea level is still one of the most ordered test and forms an important part of the kidney function test. Urea is measured in diagnostic labs either by UV kinetic method using á ketoglutarate as an NH3 + acceptor in presence of enzyme glutamate dehydrogenase. It is also measured calorimetrically by Berthelot’s end point method and is read in visible range using a calorimeter\(^{[22]}\).
Sometimes the Serum urea level is expressed as blood urea nitrogen. BUN can be easily calculated from the serum urea level. The molecular weight of urea is 60 and it contains two nitrogen atoms of combined atomic weight of 28. Hence the contribution of nitrogen to the total weight of urea in serum is 28/60 that is equal to 0.47. Hence the serum urea levels can be easily converted to BUN by multiplying it by 0.47.[23]

2.5.2 Serum Creatine

Creatine is a small tripeptide found in the muscles. It stays in its phosphorylated form and releases energy for any burst of muscular activity. It is released from the muscles during regular wear and tear and is converted to creatinine (its internal anhydride). [24] It is to be remembered that unlike urea, creatinine is not a toxic waste. It is simply used as a marker of renal function. Creatinine is freely filtered at the glomerulus and is also to a very small extent secreted into the tubules. So any problem with glomerular filtrations has a significant effect on the excretion of creatinine resulting in a much substantial rise in serum creatinine level. [25-27]

Normal serum creatinine level is 0.6 to 1.5 mg/dl. Serum creatinine is a better indicator of renal function and more specifically glomerular function than urea. For a particular individual the creatinine level is dependent on the muscle mass and muscle wear and tear. [28] There may be significant difference in creatinine level of individuals with vastly differing muscle mass. For example a body builder or athlete will have higher creatinine levels than a sedentary desk worker. Similarly creatinine level will also increase in case of any muscle trauma or excessive wear and tear as seems in athletes.
and people involved in hard physical labor. Creatinine is most commonly measured in laboratories calorimetrically by Jaffe’s method.[29, 30]

2.5.3 Electrolytes

- The purpose of the kidney is not just water balance and excretion but also to maintain the electrolyte balance of the body. Kidneys actively reabsorb or excrete electrolytes to maintain the electrolyte balance of the body. [31] Owing to their small size almost all electrolytes are filtered at the glomerulus. After filtration most of the electrolytes are absorbed back at the tubular level but any problem at the tubular level will result in non-absorption and excessive loss of electrolytes in urine. Serum electrolytes that are measured for this purpose are: [32-34]
  - Serum Sodium levels (Na+) : 135 to 145 mmols/liter
  - Serum Pottasium level (K+) : 3.5 to 5 mmols/liter
  - Serum Chloride level (Cl-) : 95 to 105 mmols/liter

2.6 Renal functions tests findings among patients with sickle cell anaemia

Ahmed Hussein etal conducted an Assessment of Renal Profile (Urea and Creatinine) with Renal Impairment among Sickle Cell Anemia Patients Attended into Kosti and Rabak Teaching Hospitals, in Sudan. [35] This study was case control study done in seventy five patients with sickle cell anemia and fifty healthy controls (adults and children). About 3ml of venous blood were collected using sterile disposable syringes and poured into lithium heparin containers then centrifuge at 3000 round per minute for five minute to obtained plasma which use to measure urea and creatinine using
colorimeter AP101. This study showed that normal levels of urea in child (25.8±10.5 mg/dl) and creatinine(0.5±0.2 mg/dl) and the urea of adult (31.4 ±7.8 mg/dl) and creatinine is (0.9 ± 0.2 mg/dl) in patient with sickle cell anemia as compared with healthy controls(child urea (17.5±3.5) mg/dl , creatinine (0.4±0.2 mg/dl) and adult control (urea 25.5 ± 7.2 mg/dl creatinine (0.7 ± 0.1mg/dl).[35]

In Iraq al-Naama LM et al assessed that levels of uric acid, urea and creatinine in Iraqi children with sickle cell disease. The uric acid level was elevated in sickle cell patients as compared with the normal control group. The 95% confidence intervals for differences in the mean of the two groups: HbAAvsHbAS was 4.22 (0.3), while for HbAA for HbSS was 3.4 (0.06), both being statistically highly significant [p < 0.0001]. Urea and creatinine levels were considerably lower in the sickle cell disease patients. The difference in the patient's mean for urea compared to the mean in the normal group (Hb AA) was 9.64 (1.95) and 8.55 (1.76) for HbSS and HbAS, respectively. Like wise, the difference in the mean for creatinine in HbSS group was 0.71 (0.12) and in HbAS was 0.76 (0.12), which was statistically significant [p < 0.0001].They concluded that raised serum urea levels were found in Iraqi children with sickle cell disease, creatinine clearance studies will be valuable to assess renal function.[36]

AamerAleem studied renal Abnormalities in Patients with Sickle Cell Disease: A Single Center Report from Saudi Arabia. They found that the patient population consisted of 34 males (46.5%) and 39 females (53.5%) with a median age of 23 years (range 14-40). Proteinuria was present in 30
patients (41%). Creatinine clearance was low in 12 patients (22.5%) and seven of these patients had low or low-normal serum creatinine despite reduced creatinine clearance. Low serum creatinine was common and present in 28 patients (38%). Two patients had chronic renal failure and one of them is on regular dialysis. Other abnormalities detected include hematuria in seven patients (8.5%) and hemoglobinuria in 12 patients (14.5%). In conclusion, renal abnormalities are present in a significant number of Saudi patients with SCD and proteinuria is the most common abnormality. Serum creatinine may remain low or within low-normal range in SCD patients despite reduced creatinine clearance.[37]

In Cameroon, Francois Folefack Kaze et al. studied the kidney function, urinalysis abnormalities and correlates in equatorial Africans with sickle cell disease. They found that the mean serum creatinine increased with increasing age, translating into a decreasing estimated glomerular filtration rate (eGFR) with age (P < 0.001). One patient (1.4%) had an eGFR of <60 mL/min and nine others (12.5%) had 60 ≤ eGFR ≤ 90 mL/min. The eGFR was lower in women and decreased with increasing systolic blood pressure. The prevalence of proteinuria (>200 mg/g) was 93% and the main urinalysis abnormalities were leukocyturia (77.8%), albuminuria (40.3%), hematuria (13.9%) and crystalluria (9.7%). None of the predictive clinical, hematological and urinary factors studied was associated with proteinuria or albuminuria, while hematuria and leukocyturia were associated with increasing age and male gender. They concluded that Cameroonians homozygous for SCD present a high prevalence of proteinuria and urinalysis abnormalities, and a slight renal impairment. Age, blood pressure variables
and gender seem to be the main determinants. Urinalysis abnormalities and kidney function assessment should be an active pursuit in cases with SCD\textsuperscript{[38]}

**In Congo**, Michel NtetaniAloni et al studied renal Function in Children Suffering from Sickle Cell Disease: Challenge of Early Detection in Highly Resource-Scarce Settings. They found that in Hb-SS group, blood pressure level tended to be lower than Hb-AA groups but there was no statistically significant difference (p>0.05) between the two groups. The absolute values for GFR corrected for BSA were significantly higher in Hb-SS group compared to Hb-AA group (130.5±34.1 ml/min/1.73 m\textsuperscript{2} vs 113.7±24.5 ml/min/1.73 m\textsuperscript{2}; p=0.004). Children with Hb-SS were more likely to hyperfiltrate (30.8\% of subjects) than children with Hb-AA (6.1\% of subjects). Proteinuria was found in 4 (6.2\%) children with Hb-SS. Uric acid level was significantly increased in children with Hb-SS compared to corresponding values in control group (4.4±1.3 mg/dl vs 3.5±1.1 mg/dl; p<0.001). Urea level was significantly decreased compared to corresponding values in Hb-AA group (15.3±8.3 mg/dl vs 22.9±10.1 mg/dl; p<0.001). They concluded that Hyperfiltration, low creatinine, lower urea and high uric acid are more common in children with sickle cell disease than in normal controls\textsuperscript{[39]}

**Rasheed Yusuf et al** conducted an assessment of kidney function in sickle cell anemia patients in Zaria, Nigeria. They found that Serum potassium, phosphate, and uric acid were statistically significantly higher while sodium, chloride, bicarbonate, calcium, and eGFR were significantly lower in SCA patient than in controls (P < 0.05). eGFR of <90 ml/min was found in 50
(67.6%) of SCA patients out of which 7 (9.5%) had Stage 3 chronic kidney disease (CKD) (<60 ml/min) and one patient with Stage 4 CKD who also had shrunken kidneys with elevated serum creatinine (203 μmol/L) and urea (11.7 mmol/L) concentration. Renal ultrasonography revealed reduced renal size in 20 (27.1%) of the patients while 2 (2.7%) had a renal enlargement. There was no correlation between renal length and serum electrolytes, urea, creatinine, and eGFR. They concluded that the majority of steady state SCA patients in Zaria have reduced eGFR and dyselectrolytemia. However, there was no association between the kidney length and the biochemical parameters. We, thus, recommend renal function tests to be routinely requested for proper management of these patients\textsuperscript{[40]}

**Other study** from Turkey, Renal function in children with sickle cell anemia by Bayazit AK1, etal. this study found that mean serum creatinine, sodium, phosphorus and calcium levels were not statistically different between patients and controls. Mean serum potassium and uric acid levels were significantly higher in patients than in controls. Mean tubular phosphate reabsorption (p < 0.001) and fractional excretion of potassium (p < 0.05) were lower in patients than in the control. There were no significant differences in fractional excretion of sodium and uric acid between patients and controls. Patients had significantly higher urine pH and significantly lower specific gravity and osmolality than controls. Also, there were no significant differences in urinary protein/ creatinine, urinary N-acetyl-beta-D-glucosaminidase/creatinine and urinary malondialdehyde/creatinine between patients and controls. They concluded that a significant proximal tubular dysfunction is not a common feature but distal tubular abnormality is the
most consistent renal functional derangement of patients with SCA in childhood.\cite{41}
Chapter Three

Materials and Methods
3. MATERIALS AND METHODS

3.1 Study design

This is a descriptive cross sectional hospital study conducted in the Jaafer Ibn Ouf pediatrics teaching hospital in Khartoum in period between March and August 2018 to evaluate the renal functions in patients with SCD.

3.2 Study area

The study will be conducted in Jaafer Ibn Ouf teaching hospital. The hospital located in Khartoum locality, Khartoum state, Sudan. It is considered one of main tertiary paediatrics referral teaching hospital. This hospital had laboratory, X ray department, blood bank, pharmacy, PICU, NICU, Renal unit, referred clinic, private rooms, and medical director office. Totally, it has buildings that contain not less than 10 wards for long admissions. Teaching and training opportunity offered for students. The hospital provided services basically who referred from Khartoum and from all areas in Sudan.

3.3 Study population

This study involved patients diagnosed with sickle cell disease admitted to Jaafer Ibn Ouf teaching hospital with in the duration of the study. Study group was selected randomly of 80 subjects from people 50 of cases (patients diagnosed with sickle cell disease) and 30 as control (healthy children not sickle cell disease).
Creatinine

Supplies and Equipment

1. Spectrophotometer(s) capable of measuring transmitted light at 500 nm
2. Appropriate cuvets, test tubes and rack
3. Pipetting devices for the accurate delivery of volumes of 0.1, 0.5, 1.0, and 5.0 mL

Reagents

1. Sodium Hydroxide Solution C Store at room temperature.
2. Acid Reagent C prepared mixture of sulfuric and acetic acid. Store at room temperature.
3. Creatinine Color Reagent C Picric acid. Store at room temperature. If reagent becomes cold, turbidity may develop. Warm reagent to clear, mix before use.

Specimens

1. Serum or plasma, stored at refrigerator temperature or frozen (up to several months) is suitable.

BUN/Urea Nitrogen

Supplies and Equipment

1. Appropriate cuvets, test tubes and rack
2. Spectrophotometer(s) capable of measuring transmitted light at 570 nm

3. Pipetting devices for the accurate delivery of volumes of 10 μL, 500 μL, 1 mL, and 5.0 mL

Reagents

Store all reagents refrigerated.

1. Phenol Nitroprusside Solution

2. Alkaline Hypochlorite Solution

3. Urease Buffer Reagent B (Jack Bean meal) When reconstituted, this dry reagent will be stable for one month.

4. Urea Nitrogen Standard Solution

Specimens

1. Serum separated from clot is suitable. Refrigerate or store frozen.

2. Plasma is suitable provided fluoride was not part of the anticoagulant. Also ammonium salts of anticoagulants must be avoided, due to the sensitivity of the reaction.

Serum electrolytes

Principle

An Ion-Selective Electrode (ISE) makes use of the unique properties of certain membrane materials to develop an electrical potential (electromotive force, EMF) for the measurements of ions in solution. The electrode has a selective membrane in contact with both the test solution and an internal filling solution. The internal filling solution contains the test ion at a fixed concentration. Because of the
particular nature of the membrane, the test ions will closely associate with the membrane on each side. The membrane EMF is determined by the difference in concentration of the test ion in the test solution and the internal filling solution. The complete measurement system for a particular ion includes the ISE, a reference electrode and electronic circuits to measure and process the EMF to give the test ion concentration. The sodium and potassium electrodes are based on neutral carriers is based on an ion exchanger.

Clinical significance

Electrolytes are involved in most major metabolic functions in the body. Sodium, potassium are amongst the most important physiological ions and the most often assayed electrolytes. They are supplied primarily through diet, absorbed in the gastrointestinal tract, and excreted by the kidneys.

Sodium is the major extracellular cation and functions to maintain fluid distribution and osmotic pressure. Some causes of decreased levels of sodium include prolonged vomiting or diarrhea, diminished reabsorption in the kidney and excessive fluid retention. Common causes of increased sodium include excessive fluid loss, high salt intake, and increased kidney reabsorption. Potassium is the major intracellular cation and is critical to neural and muscle cell activity. Some causes of decreased potassium levels include reduced intake of dietary potassium or excessive loss of potassium from the body by prolonged vomiting, diarrhea, or increased kidney excretion. Increased

Potassium levels may be caused by dehydration or shock, severe burns, diabetic ketoacidosis, and retention of potassium by the kidney.
Specimen

Serum or heparinized plasma collected using standard sampling tubes or tubes containing separating gel. Samples should be separated from the clot or cells promptly after collection. Specimens to be tested for potassium must be centrifuged within one hour of collection. Grossly lipemic specimens should be cleared by ultracentrifugation. Universal precautions apply. Stability: 8 hours at 2-8°C in primary tube, 3 days at 2-8°C if removed from gel tube.

Equipment / instrumentation:

Roche c501 analyzer - Refer to the Operator’s Manual for operating instructions, maintenance, and troubleshooting.

3.5 Sampling

3.5.1 Sample size

Due to the relative high cost of the required investigation for each recruited study participants sample, a convenient sampling technique had been adopted to estimate the sample size for this study to be more suitable with the budget limits. The study covered 80 study participants, 50 cases (patients diagnosed with sickle cell disease) and 30 controls (healthy).

3.5.2 Sampling technique

Simple random sampling technique was used to select the study participants to be enrolled in this study who fitted with the study criteria.
3.6 Data collection tools/techniques

Data had been collected using comprehensive, close ended, structured data collection form covered the relevant variables and laboratory results. Please see appendix 1.

3.7 Data analysis

- Data was entered, cleaned, and analyzed using SPSS version 25.0
- Descriptive statistics in term of frequency tables with percentages and graphs. Means and standard deviations presented with relevant graphical representation for quantitative data.
- Bi-variable analysis (or comparison between the two study groups) was done to determine the associations between the main outcome variable (the level renal function parameters) and the main factors (presence of sickle cell disease) with t statistical test (between two means) and ANOVA test - analysis of variance - (between more than two means).
- P value of 0.05 or less is considered statistically significant.
- Data will be represented after analysis in form of uni-variable tables, cross tabulation (bi variable tables), figures and narrative illustration.

3.8 Ethical considerations

- Written ethical clearance and approval for conducting this research will be obtained from Shendi University ethical Committee.
- Formal permission will be obtained from the Administrative authority of Jaafer Ibn Ouf teaching hospital.
- Study data/information will be used for the research purposes only. The privacy issues will be intentionally considered.
- Verbal consent will be obtained before stating the data collection from the patients or their care givers
- The participation is voluntary. Any participants has his/her own right to withdraw at any stage.
Chapter Four

Results
4. RESULTS

Table (1) the distribution of the study participants according to their study groups (n = 80, 50 Cases + 30 Controls)

<table>
<thead>
<tr>
<th>Study groups</th>
<th>Frequency</th>
<th>Percent</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cases (patients with SCD)</td>
<td>50</td>
<td>62.5</td>
</tr>
<tr>
<td>Control (Healthy)</td>
<td>30</td>
<td>37.5</td>
</tr>
<tr>
<td>Total</td>
<td>80</td>
<td>100.0</td>
</tr>
</tbody>
</table>

Figure (1) the distribution of the study participants according to their study groups (n = 80, 50 Cases + 30 Controls)
Table (2) the distribution of the study participants according to their age (n = 80, 50 Cases + 30 Controls)

<table>
<thead>
<tr>
<th>Age - years</th>
<th>Study groups</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Cases</td>
<td>Controls</td>
</tr>
<tr>
<td></td>
<td>Freq.</td>
<td>%</td>
</tr>
<tr>
<td>&lt; 1</td>
<td>9</td>
<td>18.0</td>
</tr>
<tr>
<td>1 - 5</td>
<td>11</td>
<td>22.0</td>
</tr>
<tr>
<td>6 - 10</td>
<td>16</td>
<td>32.0</td>
</tr>
<tr>
<td>10 - 18</td>
<td>14</td>
<td>28.0</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>50</td>
<td>100.0</td>
</tr>
</tbody>
</table>

Figure (2) the distribution of the study participants according to their age (n = 80, 50 Cases + 30 Controls)
Table (3) the distribution of the study participants according to their gender (n = 80, 50 Cases + 30 Controls)

<table>
<thead>
<tr>
<th>Gender</th>
<th>Study groups</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Cases</td>
<td>Controls</td>
</tr>
<tr>
<td></td>
<td>Freq.</td>
<td>%</td>
</tr>
<tr>
<td>Male</td>
<td>21</td>
<td>42.0</td>
</tr>
<tr>
<td>Female</td>
<td>29</td>
<td>58.0</td>
</tr>
<tr>
<td>Total</td>
<td>50</td>
<td>100.0</td>
</tr>
</tbody>
</table>

Figure (3) the distribution of the study participants according to their gender (n = 80, 50 Cases + 30 Controls)
Table (4) the distribution of the study participants according to History of recurrent urinary tract infection (n = 80, 50 Cases + 30 Controls)

<table>
<thead>
<tr>
<th>History of recurrent urinary tract infection</th>
<th>Study groups</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Cases</td>
<td>Controls</td>
</tr>
<tr>
<td></td>
<td>Freq.</td>
<td>%</td>
</tr>
<tr>
<td>Yes</td>
<td>37</td>
<td>74.0</td>
</tr>
<tr>
<td>No</td>
<td>13</td>
<td>26.0</td>
</tr>
<tr>
<td>Total</td>
<td>50</td>
<td>100.0</td>
</tr>
</tbody>
</table>

Figure (4) the distribution of the study participants according to History of recurrent urinary tract infection (n = 80, 50 Cases + 30 Controls)
Table (5) the distribution of the study participants according to other medical conditions (n = 80, 50 Cases + 30 Controls)

<table>
<thead>
<tr>
<th>Other medical conditions</th>
<th>Study groups</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Cases</td>
<td>Controls</td>
</tr>
<tr>
<td></td>
<td>Freq.</td>
<td>%</td>
</tr>
<tr>
<td>Dehydration</td>
<td>0</td>
<td>0.0</td>
</tr>
<tr>
<td>Bleeding</td>
<td>0</td>
<td>0.0</td>
</tr>
<tr>
<td>Liver disease</td>
<td>0</td>
<td>0.0</td>
</tr>
<tr>
<td>Congestive heart disease</td>
<td>0</td>
<td>0.0</td>
</tr>
<tr>
<td>Hypothyroidism</td>
<td>0</td>
<td>0.0</td>
</tr>
<tr>
<td>Leukemia</td>
<td>0</td>
<td>0.0</td>
</tr>
<tr>
<td>Adrenal gland disease</td>
<td>0</td>
<td>0.0</td>
</tr>
<tr>
<td>None</td>
<td>50</td>
<td>100.0</td>
</tr>
<tr>
<td>Total</td>
<td>50</td>
<td>100.0</td>
</tr>
</tbody>
</table>

Notes

- The cause of bleeding was cut wound before 6 years prior to the study.
- No remembered history of dehydration among study participants
- One control had a history of hepatitis A before 3 years prior to the study.

Table (6) the summary statistics for renal function tests among the study participants (n = 80, 50 cases + 30 controls)

<table>
<thead>
<tr>
<th>RFTs</th>
<th>Observations</th>
<th>Mean</th>
<th>Std. deviation</th>
<th>Minimum</th>
<th>Maximum</th>
</tr>
</thead>
<tbody>
<tr>
<td>Urea (mmol/L)</td>
<td>80</td>
<td>4.83</td>
<td>1.35</td>
<td>2.57</td>
<td>7.04</td>
</tr>
<tr>
<td>Creatinine (mg/dL)</td>
<td>80</td>
<td>0.89</td>
<td>0.12</td>
<td>0.70</td>
<td>1.11</td>
</tr>
<tr>
<td>Sodium (mmol/L)</td>
<td>80</td>
<td>141.29</td>
<td>3.82</td>
<td>135.30</td>
<td>148.10</td>
</tr>
<tr>
<td>Potassium (mEq/L)</td>
<td>80</td>
<td>5.99</td>
<td>0.40</td>
<td>5.10</td>
<td>6.70</td>
</tr>
<tr>
<td>Chloride (mEq/L)</td>
<td>80</td>
<td>102.04</td>
<td>3.05</td>
<td>96.30</td>
<td>108.10</td>
</tr>
</tbody>
</table>
Table (7) the difference between the two study groups in renal function tests results (n = 80, 50 cases + 30 controls)

<table>
<thead>
<tr>
<th>RFTs</th>
<th>Study group</th>
<th>Difference</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Cases</td>
<td>Controls</td>
<td></td>
</tr>
<tr>
<td>Urea (mmol/L)</td>
<td>4.81</td>
<td>4.52</td>
<td>0.29</td>
</tr>
<tr>
<td>Creatinine (mg/dL)</td>
<td>0.89</td>
<td>0.92</td>
<td>-0.03</td>
</tr>
<tr>
<td>Sodium (mmol/L)</td>
<td>142.06</td>
<td>139.81</td>
<td>2.25</td>
</tr>
<tr>
<td>Potassium (mEq/L)</td>
<td>6.16</td>
<td>5.51</td>
<td>0.64</td>
</tr>
<tr>
<td>Chloride (mEq/L)</td>
<td>102.05</td>
<td>102.02</td>
<td>0.03</td>
</tr>
</tbody>
</table>

Figure (5) the difference between the two study groups in urea results (n = 80, 50 cases + 30 controls)

Figure (6) the difference between the two study groups in creatinine results (n = 80, 50 cases + 30 controls)
Figure (7) the difference between the two study groups in Sodium results (n = 80, 50 cases + 30 controls)

Figure (8) the difference between the two study groups in Potassium results (n = 80, 50 cases + 30 controls)
Chapter Five

Discussion, Conclusion and Recommendation
5.1 Discussion

This study aimed to investigate renal function abnormalities in sickle cell patients in Sudan, 2018. This study covered 80 study participants that divided into two comparison groups, Cases group that represented (62.5%) and Controls group that represented (37.5%).

Our study found that (62.5%) of the study participants were above 5 years in age. The age distribution were similar among both study groups (cases versus controls). Other studies stated that although hematologic changes indicative of the disorder are evident as early as the age of 10 weeks, clinical characteristics of SCD generally do not appear until the second half of the first year of life, when fetal Hb levels decline sufficiently for abnormalities caused by HbS to manifest. SCD then persists for the entire lifespan. After age 10 years, rates of painful crises decrease, but rates of complications increase. [8] The median age at the time of renal failure in patients with SCD is 23.1 years, the median survival time after the diagnosis of ESRD is about 4 years, and the median age of death is 27 years, despite dialysis treatment. [9]

Concerning the gender distribution, our study found that more than half of the study participants were females (56.3%) with male female ratio 0.7:1 among cases and 0.9:1 among controls. Other studies stated that he male-to-female ratio is 1:1. No sex predilection exists, since sickle cell anemia is not an X-linked disease. Although no particular gender predilection has been shown in most series, analysis of the data from the Renal Data System demonstrated marked male predominance of sickle cell nephropathy in affected patients. [10]

The study found that nearly three quarters of cases (74%) had positive history of urinary tract infections compared with controls (13.3). Many studies stated
that long-term transfusion therapy to prevent stroke in children with abnormal transcranial Doppler velocity (≥200 cm/s). In patients with sickle cell anemia, transfusion therapy should be used to increase hemoglobin levels to 10 g/dL [12]

Concerning the results of renal function tests, our study found that the overall means were urea 4.8 ± 1.35 mmol/L, Creatinine 0.89 ± 0.7 mg/dl, Serum Na 141.29 ± 3.82 mmol/L, Serum K 5.99 ± 0.4 mEq/L and Serum Chloride 102.04 ± 3.05 mEq/l. Our study found that there was a significant difference in the level of potassium (p value < 0.001) and in the creatininte even with in the normal ranges (p = 0.0422). The study did not found a significant difference in the levels of urea, Sodium and chloride. The study were almost similar to other study conducted in Kosti area in Sudan by Ahmed Hussein etal, [35] they showed that normal levels of urea in child (25.8±10.5 mg/dl) and creatinine(0.5±0.2 mg/dl) and the urea of adult (31.4 ± 7.8 mg/dl) and creatinine is (0.9 ± 0.2 mg/dl) in patient with sickle cell anemia as compared with healthy controls(child urea (17.5±3.5) mg/dl , creatinine (0.4±0.2 mg/dl) and adult control (urea 25.5 ± 7.2 mg/dl creatinine (0.7 ± 0.1mg/dl). [35]

Our results were differ from other Iraqi study by al-Nama LM etal, [36] Urea and creatinine levels were considerably higher in the sickle cell disease patients. They concluded that raised serum urea levels were found in Iraqi children with sickle cell disease, creatinine clearance studies will be valuable to assess renal function.[36] While in Saudi study, they found similar results regarding the creatinine level, and they stated Serum creatinine may remain low or within low-normal range in SCD patients
despite reduced creatinine clearance.[39] In other study by Michel et al from Congo, they found similar results that Hyper-filtration, low creatinine, lower urea and high uric acid are more common in children with sickle cell disease than in normal controls. But other study from Nigeria [40] by Rasheed Yusuf et al found an elevated serum creatinine (203 μmol/L) and urea (11.7 mmol/L) concentration. [40] Other study at Bayazit et al from Turkey, found that the Mean serum potassium and uric acid levels were significantly higher in patients than in controls. [41]

The study had some limitations. The relatively limited number of study participant (80 only) may affect negatively the probability of founding significant relationships between different renal function tests with the overall incidence of variant renal function tests among SCD patient in Sudanese hospitals and for that may be the researchers observed that the evidence on this topic is currently limited and weak. Future research should be based on this type of design, but with larger sample sizes.
5.2 Conclusion

- Concerning the results of renal function tests, our study found that the overall means were urea $4.8 \pm 1.35$ mmol/L, Creatinine $0.89 \pm 0.7$ mg/dl, Serum Na $141.29 \pm 3.82$ mmol/L, Serum K $5.99 \pm 0.4$ mEq/L and Serum Chloride $102.04 \pm 3.05$ mEq/l. Our study found that there was a significant difference in the level of potassium (p value < 0.001) and in the creatinine even within the normal ranges (p = 0.0422). The study did not found a significant difference in the levels of urea, Sodium and chloride.

- This study has explained renal profile (urea & creatinine) and their role in sickle cell anaemia which could be used in designing of the better management of sickle cell patients in Sudan.
5.3 Recommendation

1. Routine screening of sickle cell disease patients is recommended for timely intervention in order to prevent or delay renal damage.

2. As interruption RFTs results is a risk factor for developing renal impairment in future, these patients should be actively monitored and those who develop abnormal renal function, should be considered for early intervention in Sudan.

3. Requesting RFTs routinely can help to implement potential preventive strategies to reduce renal problems induced by the sickle cell disease pathology in these risky groups of patients.
APPENDIXES
REFERENCES


31. Sunderman FW. STUDIES OF SERUM ELECTROLYTES: VII. The Total Base and Protein Components of the Serum during Lobar


Shendi University

Evaluation of renal function in sickle cell disease patients in Jaafer Ibn Ouf Peadiatric teaching hospital, Khartoum state, Sudan, 2018

Questionnaire

Socio-demographical data

1. Age … years
2. Gender
   - Male
   - Female

Clinical data

3. History of recurrent urinary tract infection
   - Yes
   - No
4. Other medical condition(s)
   - Bleeding
   - Dehydration
   - Liver disease
   - Congestive heart disease
   - Hypothyroidism
   - Leukemia
   - Adrenal gland problems
   - Other, please specify …

Laboratory data

5. Serum urea …
6. Serum creatinine …
7. Serum potassium …
8. Serum Sodium …
9. Serum Chloride …
The ISE measures sodium, potassium, chloride, lithium, calcium and/or pH in biological fluids, using ion selective electrode technology. The flow-through sodium and pH electrodes contain gels that are specifically formulated to be sensitive to sodium ions. The flow-through potassium and calcium electrodes employ a plastic tube, incorporating neutral carrier ampholines. The flow-through chloride electrode and lithium electrode include a plastic tube, specifically formulated to be selective to chloride or lithium ions. The potential of each electrode is measured relative to a fixed, stable voltage established by the silver/silver chloride reference electrode. An ion selective electrode develops a voltage that varies with the concentration of the ion to which it responds. The relationship between the voltage developed and the concentration of the sensed ion is logarithmic, as expressed by the Nernst equation:

$$ E = E^0 + RT \log \left( \frac{a_i}{A} \right) $$

where:
- $E$ = The potential of the electrode in sample solution
- $E^0$ = The potential developed under standard conditions
- $RT$ = A temperature dependent constant, termed the slope
- $a_i$ = 1 for sodium, potassium, chloride, lithium and pH
- $A$ = 2 for calcium
- $\log$ = Base ten logarithm function
- $A$ = Activity coefficient of the measured ion in the solution
- $C$ = Concentration of the measured ion in the solution
7. Principles of Operation

ISE Theory

Electrolyte measurements in blood products were traditionally performed using flame photometry, in which a sample, diluted with a known concentration of a reference ion (usually lithium or cesium), is vaporized and passed through a flame which excites the cations. The ratio of the resulting light of different frequencies, the sum of which is proportional to the ion concentration in the sample. The development of sodium and pH-selective glass, and selective organic components for potassium, calcium, and chloride, has permitted the development of sensors capable of measuring biological fluid directly, throughout the physiological range. These sensors are known as ion-selective electrodes.

The Enzyme measures sodium, potassium, chloride, lithium, calcium, and/or pH in biological fluids, using ion-selective electrode technology. The flow-through sodium and pH electrodes contain glass tubing, specifically formulated to be sensitive to sodium ions. The flow-through potassium and calcium electrodes employ a plastic tube, incorporating neutral carrier ionophores. The flow-through chloride electrode and lithium electrode contain a plastic tube, specially formulated to be selective to chloride or lithium ions. The potential of each electrode is measured relative to a reference electrode established by the silver/silver chloride reference electrode. An ion selective electrode develops a voltage that varies with the concentration of the ion to which it responds. The relationship between the voltage developed and the concentration of the sensed ion is logarithmic, as expressed by the Nernst equation:

\[ E = E^0 + R T \ln \frac{a_i}{C} \]

where:
- \( E \) = The potential of the electrode in sample solution
- \( E^0 \) = The potential determined under standard conditions
- \( R \) = A temperature-dependent "constant", termed the slope
- \( T \) = Activity coefficient of the measured ion in the solution
- \( a_i \) = Concentration of the measured ion in the solution
- \( C \) = Concentration of the ion to which the electrode responds

3. De Blas, J., Simon, W., Cliness, W., Clines, W., Clines, W., 1974.