EXERCISE TOLERANCE IN ADULT SICKLE CELL DISEASE PATIENTS

BY

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DECLARATION

I ISAAC NUAKO, author of this thesis do hereby declare that, with the exception of references to other people’s work which has been duly cited, this work has entirely resulted from my personal original research under the supervision of Rev. Dr. Charles Antwi-Boasiako and Dr. Alfred Doku and has not been presented for another degree elsewhere.

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(Co-Supervisor)
DEDICATION

I dedicate this thesis to the Lord Jesus Christ and to Rev. Dr. Charles Antwi-Boasako.
ABSTRACT

Background

Many adults with sickle cell disease (SCD) complain of significant exercise intolerance despite the health benefits in exercise. Most children with SCD also miss out on the important benefits of exercise because of unsubstantiated fears that it might be harmful in their condition. Several factors could contribute to exercise limitation in these patients. The six-minute walk test (6MWT) is a standardized test use to measure a person’s exercise tolerance. It is being increasingly used as a measure of overall functional ability in patients. However little information exists regarding the safety or the limit of exercise SCD patients can tolerate. The purpose of the present study is to examine these issues.

General Aim

To determine the exercise tolerance limit of SCD patients by using the six-minute walk test.

Method

A case control study was performed on 36 adult SCD patients (13 males and 23 females) and 36 healthy adult controls (13 males and 23 females) at the Tema General Hospital by the six minute walk test (6MWT). Anthropometric data of all participants comprising of height (cm) and weight (kg) were measured and body mass index (BMI) derived from this data were all recorded. The haemoglobin (Hb) level of all participants were measured. The following parameters were measured and recorded in all the participants prior to the 6MWT, 5 and 10 minutes after the test respectively: blood pressure (SBP and DBP), HR, SpO₂, PEFR, chest pain (angina scale), dyspnoea, and leg fatigue (modified Borg scale) The total distance walked was also recorded in metres. The 6MWD was used to estimate the VO₂ and the MET. Factors associated with the 6MWD were evaluated using multivariate analysis and used to derive an equation which aimed to estimate the likely 6MWD from the variables. The level of significance was set at p < 0.05. SPSS version 23 software was used for statistical analysis.
Results

The mean age of the SCD patients was 28.44 ± 6.29 years and the healthy controls was 28.44 ± 6.29 years. The mean Hb for SCD patients’ males and females were 8.60 ± 1.27 g/dl and 9.84 ± 1.75 g/dl respectively: (p = 0.002). The mean Hb for healthy control males and females were 14.11 ± 0.56 g/dl and 12.82 ± 0.69 g/dl respectively (p < 0.001). There was however no significant difference in the mean height (m) ((1.68 ± 0.08 m) vs. (1.70 ± 0.070 m) (p = 0.137)) and mean BMI ((20.09 ± 3.19 kg/m²) vs. (21.4 ± 2.80 kg/m²) (p = 0.060)) between cases and controls respectively. There was a significant difference in the mean weight between cases and controls ((56.64 ± 10.67 kg) vs. (62.51 ± 10.51 kg): (p = 0.021)). There was an increase in the SBP, DBP, HR at the end of the 6MWD and decreased subsequently at 5 minutes and 10 minutes after the test for the cases and as well as the controls. The SPO2 however, decreased at the end of the 6MWD and increased at 5 minutes and 10 minutes after the test both cases and controls. The PEFR increased at the end of the 6MWD up to 10 minutes after the test in both cases and controls. There was also significant difference (p < 0.001) in the mean distance walked in six minutes between SCD patients (551.03 ± 63.32 m) and healthy controls (666.72 ± 80.06 m).

Conclusion

This study provides the first preliminary data on exercise tolerance for healthy Ghanaian adults and SCD patients between the ages of 20 years and 45 years. The maximum HR achieved, minimum SPO2, VO2, MET and blood pressures in adult SCD patients and healthy controls were within normal range in this study. Therefore SCD patients may take the 6MWD test safely. There was an improvement in PEFR in both SCD patients and healthy controls after the test. Even though SCD patients achieved lower values than the healthy controls. The maximum distance walked by SCD patients was significantly shorter than that of the healthy controls. Therefore SCD patients have reduced tolerance to exercise than healthy controls.
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LIST OF ABBREVIATIONS

6MWD - Six Minute Walk Distance
6MWT - Six Minute Walk Test
ACS – Acute chest Syndrome
COPD – Chronic Obstructive Pulmonary Disease
DBP - Diastolic Blood pressure
ECG – Electrocardiogram
ERSD - Exercise-Related Sudden Cardiac Death
FC - Functional Capacity
GLTEQ - Godin Leisure-Time Exercise Questionnaire
Hb – Haemoglobin
HR – Heart Rate
MET - Metabolic Equivalents
NHANES III - National Health and Nutrition Examination Survey III
PEFR - Peak Expiratory Flow Rate
PEFR – Peak Expiratory Flow Rate
RBCs - Red Blood Cells
RPE - Rating of Perceived Exertion
SBP – Systolic Blood Pressure
SCD - Sickle Cell Disease
SPO2 – Peripheral Oxygen Saturation
VO2 - Oxygen Consumption
VO2 max - Maximum Oxygen Consumption
VOC – Vaso-occlusive Crisis
CHAPTER ONE

1.0 INTRODUCTION

1.1 Background

Sickle cell disease (SCD) is an inherited, autosomal recessive, condition caused by a gene mutation in the β-globin gene (Adekile, 2013). It is a global disease that has gained much public health concern because it can lead to severe complications in those affected especially in the long term. It is estimated that 275,000 babies are born with SCD each year globally (Modell & Darlison, 2008) and this figure is expected to rise to 400,000 births annually by 2050 (Piel et al., 2013). Sickle cell disease is a major cause of death for young children in Africa, which the World Health Organization has declared a public health priority (Elguero et al., 2015). The Sub-Saharan Africa accounts for two-thirds of SCD births worldwide, making it the most burdened region. It is estimated that 75–85% of children born with SCD are born in Africa, where mortality rates for those under age 5 range from 50% to 80% (Makani et al., 2011) (Aygun & Odame, 2012). In a great part of Central Africa, the Sickle Cell Trait (SCT) prevalence is more than 15% (Grosse et al., 2011). In Ghana, 30% of the population are known to carry the Sickle Cell Trait. It is also known that 2% of new-borns have the Sickle Cell Disease (SCD) (Ohene-Frempong & Oduro, 2008; Konotey-Ahulu, 2011) and this makes up about 14,000 babies born with the disease each year of which only 350 to 400 of these children are diagnosed as new-borns because of lack of support for new born screening (Kwei, 2014).

The mutation that occurred in the haemoglobin gene cause the sixth amino acid to be changed from glutamic acid to valine. The resultant haemoglobin (called HbS) is prone to polymerization with other haemoglobin molecules under conditions of low oxygen tension (Mubeen et al., 2016). Sickle cell disease therefore occurs when an individual inherits two HbS
(the commonest and most severe form) or HbS with another abnormal variants such as C, D or β-thalasaemia from both parents (Torres et al., 2015).

The abnormal rheology of the sickled red cells contributes to tissue hypoxia, vaso-occlusive crisis and ultimately organ damage (Edwin et al., 2011). Classic manifestations in persons with SCD crises include arthralgia, anorexia, fatigue, splenomegaly as well as destructive and painful bone and joint problems. Complications in SCD occur due to ischaemic tissue injury and could result in organ impairment or life-threatening conditions and even premature death (Beers et al., 2008). Even though there are several health benefits associated with exercise and physical activities, many adults SCD patients complain of significant exercise intolerance (Badawy et al., 2017). Most SCD children also miss out on the important benefits of exercise because of unsubstantiated fears that it might be harmful in their condition (Zeigler & Payne, 2010).

Supervised regular physical exercise has a positive effect on SCD individuals in their ability to efficiently perform daily activities (Martin et al., 2018). A person’s ability to effectively perform physical activities or exercises within a specified period is known as the functional capacity or ‘functional ability’ of the individual to exercise (functional exercise capacity) (Bocalini et al., 2008). One of the effective methods of evaluating the functional capacity (FC) is to use the six minute walk test (6MWT) which provides information about exercise tolerance, physiological status (cardiopulmonary) and the patient survival according to test performance (American Thoracic Society, 2002) (Bittner & Singh, 2016). Studies concerning the use of 6MWT in SCD population usually involved children and adolescents; these studies showed reduced capacity to exercise in SCD children and this was attributed to factors such as low haemoglobin levels (Connes et al., 2011). In addition, decreased exercise capacity in SCD
patients could result from systemic involvement such as dyspnoea, fatigue, general muscle weakness and pain especially in the hip and lower limb (Ohara et al., 2014). Pain has been shown to significantly influence one’s exercise capacity and hence affect the performance of daily activities in SCD patients (Botelho et al., 2017; dos Santos & Gomes Neto, 2013). Thus complications or damages caused by SCD can significantly impact on exercise capacity (Ohara et al., 2014).

The 6MWT measures the following parameters: blood pressure (systolic and diastolic), heart rate (HR), peripheral pulse oxygen saturation (SpO2), peak expiratory flow rate (PEFR), chest pain (angina scale), dyspnoea, and leg fatigue (modified Borg scale) at rest, at the end of the test (Gontijo et al., 2011) and up to 10 minutes after the 6MWT. Other parameters include; the total distance walked, the estimated oxygen consumption (VO2) and the metabolic equivalents (MET) (Khuangsirikul et al., 2014). During this test we look for complains like, dyspnoea, dizziness, fainting and Palpitations which are indications of cardiovascular complications (Venkatesh et al., 2011). Although the burden of (SCD) on affected individuals is significant, few studies have examined the exercise tolerance of these patients (Thomas & Lipps, 2011). Moreover, the physiologic basis of poor physical functioning in SCD patients is unknown and has not been studied extensively. Furthermore, outcome measures such as how far SCD patients can walk within 6 minutes (exercise capacity), whether they develop cardiovascular complications during exercise and the normal reference value of 6MWT in healthy Ghanaians is unknown.

The purpose of this study is therefore to determine the exercise capacity and the factors associated with it in SCD patients through the 6MWT.
1.2 Problem statement

Even though physical exercise comes with several health benefits, most adults with SCD complain of significant exercise intolerance (Badawy et al., 2017). This may be due to the fact that, increased the metabolic changes associated with exercise could initiate sickling and vaso-occlusive events which is the hallmark of SCD (Botelho et al., 2017).

However, some social barriers like discriminatory and discouraging practices by some members of the society against SCD patients in their engagement in most physical activities impose some psychological stress on them (Orish et al., 2014) and may also contribute to their fear in engaging in some exercises because they know they could elicit crisis and worsen their pain.

Additionally, exercise limitation in patients with SCD may be related to anaemia or chronic complications such as pulmonary vascular disease, chronic parenchymal lung disease, avascular necrosis and heart related conditions such as congestive heart failure, ischaemic heart diseases, cardiomyopathy (Ballas et al., 2012; Miller & Gladwin, 2012; Ohara et al., 2014). These barriers and complications could cause SCD patients to lead more sedentary life style which in turn result in an overall loss of muscle strength and a consequent reduction in their exercise tolerance (Gladwin & Sachdev, 2012). The reduction in muscular strength and tolerance to exercise is associated with reduced physical fitness and hence increased risk of injuries and reduced daily task performance (Hillegass, 2016).

However, these factors notwithstanding, some form of physical exercise is still useful and necessary for SCD patients to improve on their physical fitness (Ohara et al., 2014). There is however no evidence-based, exercise prescription programmes in Ghana aimed at improving
physical fitness, physical functioning and overall quality of life in SCD patients. There is also lack of data in the area of exercise capacity, including the physiologic contributors to exercise limitation in SCD patients. There is therefore the need to collate data.

1.3 Justification

Sickle cell disease is a major public health problem in Ghana. Currently, it is known that approximately 2% of new-borns have the SCD in Ghana (Ohene-Frempong et al., 2008; Konotey-Ahulu, 2011) and this makes up about 14,000 babies born with the disease each year of which only 350 to 400 of these children are diagnosed as new-borns because of lack of support for new born screening (Kwei, 2014). It is also known that 30% of the Ghanaian population are known to carry the Sickle Cell Trait.

The management of sickle cell disease in Ghana like most developing countries is still not adequate due to limited access to health care facilities, late screening and lack of current treatment protocols (Ansong et al., 2013). It is now known that more children with SCD survive into adulthood (Asare et al., 2018), hence the need to focus on current management practices in order to reduce the incidence of complications as well as reductions in hospital admissions and healthcare costs (Piel et al., 2017). This would also ensure survival in their adult stage of life.

Exercise is an important component for daily living which is necessary for improving the general health and wellbeing of every individual. Different people respond to the same exercise differently and this also depends on their tolerance level. Thus a knowledge in the level of tolerance is necessary in order to also know the intensity of the exercise (Carlier et al., 2017). Therefore specific exercises would be suitable for individual populations in order to achieve
their desired goal. The 6MWT is a standardized and an objective test to determine a person’s exercise tolerance and provides important information about exercise tolerance limit of SCD patients. There is therefore the need to use the 6MWT to investigate and institute measures to improve the care of SCD patients such as a scientific exercise prescription activity for these patients aimed at improving physical fitness, physical functioning and overall quality of life in SCD patients. Improvement in the physical activity of patients will reduce the high rate of morbidity and mortality associated with the SCD in Ghana where the prevalence of SCD is high.

1.4 Aim
To determine the exercise tolerance limit of adults SCD patients by using the six-minute walk test.

1.5 Objectives
To determine:

1. the achieved Maximum heart rate, minimum Oxygen saturation achieved, VO\textsubscript{2} and MET in SCD patients and healthy controls.

2. the cardiopulmonary response to exercise through the 6MWT in adults with SCD and healthy controls.

3. the maximum distance SCD patients can walk within 6 minutes (exercise capacity) in SCD patients and healthy controls.

4. the preliminary reference values in healthy Ghanaians during 6MWT.
CHAPTER TWO

2.0 LITERATURE REVIEW

2.1.0 Sickle Cell Anaemia and Pathophysiologic Mechanisms

Sickle cell anaemia (SCA) is a haemoglobinopathy arising from the replacement of a glutamic acid by a valine at the sixth position of the beta globin, giving rise to haemoglobin S (HbS) (Mansour et al., 2015). The resultant haemoglobin (HbS) has abnormal physiological characteristics which makes it susceptible to polymerization with other haemoglobin molecules when oxygen tension is reduced (Alayash, 2017). Vaso-occlusive crises which occur as a result of obstruction of the microcirculation of the ‘sickled’ red blood cells are frequent hence causing pain in bones, muscles, and joints (Stettler et al., 2015). The pathophysiological mechanism of the disease can cause several acute and chronic clinical manifestations, such as acute chest syndrome, pulmonary hypertension, heart failure and stroke (Thein et al., 2017).

The defective form of haemoglobin, haemoglobin S (HbS) in SCD undergoes some physiological changes that affect the normal structure and function of the RBCs (Alayash, 2017). In HbS, there is substitution of the charged hydrophilic glutamic acid that exists at the exterior surface of haemoglobin at sixth (6th) position in the β-globin chain with the hydrophobic valine residue which exists within the core of the protein (Adekile, 2013). This results in formation of hydrophobic pockets and begin hydrophobic interactions with other hydrophobic residues on the β-globin chain of another deoxy-HbS molecule. During deoxygenation of haemoglobin in the capillaries, the hydrophobic pocket causes the polymerization of haemoglobin S molecules into a polymer, forming complex helical fibres within the RBC (Odiève et al., 2011). Thus polymerization of Hb S molecules is triggered by hydrophobic interactions between the Val-β6 amino acid of an Hb S molecule and the Phe-β85.
and Leu-β88 amino acids of adjacent haemoglobin molecules (Odièvre et al., 2011; Torres et al., 2015).

The red blood cells (RBCs) undergo morphological changes from the flexible disc shape to the rigid sickle shape as a result of the polymerization process (Adekile, 2013; Yesudasan et al., 2018). The polymers are made up of 14-strand fibres that alter the shape of the erythrocyte membrane, changing its normal biconcave disc shape to the classic sickle shape and a number of other shapes such as granular and holly-leaf. This phenomenon is to some extent reversible after the cells become oxygenated; that is the sickled HbS RBC resume the normal shape.

The replacement of a glutamic acid by a valine residue at position 6 in the β-globin polypeptide chain characterizes the abnormal haemoglobin of SCD (HbS). Valine interacts with other hydrophobic amino acids (Leucine-β88 and Phenylalanine-β85) at low oxygen pressure and gets organised in long polymer fibres that deform and stiffen. This process represents the basic mechanisms leading to haemolytic anaemia and to vaso-occlusive events in the microcirculation.

Figure 2. 1: Pathophysiology of SCD (Odièvre et al., 2011)

The replacement of a glutamic acid by a valine residue at position 6 in the β-globin polypeptide chain characterizes the abnormal haemoglobin of SCD (HbS). Valine interacts with other hydrophobic amino acids (Leucine-β88 and Phenylalanine-β85) at low oxygen pressure and gets organised in long polymer fibres that deform and stiffen. This process represents the basic mechanisms leading to haemolytic anaemia and to vaso-occlusive events in the microcirculation.
The repeated RBCs oxygenated and de-oxygenated configuration cycles ultimately result in irreversible distortion of the RBCs into sickled cells which could be destroyed or haemolysed (Kato *et al.*, 2017). This haemolysis shortens the lifespan of the sickled RBCs to between 10 and 20 days; as the normal RBC lifespan is about 120 days (Maakaron, 2019).

### 2.1.1 Abnormal Haemoglobins

Sickle cell disease result from inheriting haemoglobin S (HbS) in addition to another abnormal haemoglobin. Thus haemoglobin SS (HbSS) is the most common and severe form of the disease (Ohene-Frempong *et al.*, 2008; Saraf *et al.*, 2014; Wild & Bain, 2017; Asare *et al.*, 2018).

Haemoglobinopathies result from either the production of an abnormal haemoglobin chain, such as when there is a single substitution of one amino acid as seen with sickling disorders, or the underproduction of a given chain resulting in the thalassaemias (Wilson *et al.*, 2010).

The degree of anaemia which is the primary characteristic of the disease also depends on the type of sickle cell disease (Quinn, 2016). Chronic anaemia in SCD patients is also known to cause reduced tolerance during exercise (Badireddy & Baradhi, 2019). Table 2.1 summarises the haemoglobin mutations and the type of sickle cell disease associated with it; and table 2.2 shows the severity of sickle cell disease and its haemoglobin levels. The reference values for Ghanaians is also shown in table 2.3.
Table 2. 1: Haemoglobin mutations and associated syndromes (Wilson et al., 2010)

<table>
<thead>
<tr>
<th>Hb</th>
<th>Related condition</th>
<th>Molecular structure</th>
<th>Chromosome mutation</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>α thalassaemia, asymptomatic or fatal</td>
<td>Decreased/absent synthesis of α chain</td>
<td>16</td>
</tr>
<tr>
<td>A</td>
<td>β thalassaemia, wide spectrum of disease</td>
<td>Decreased/absent synthesis of β chain</td>
<td>11</td>
</tr>
<tr>
<td>S</td>
<td>Sickle cell disease/trait</td>
<td>Valine substituted for glutamic acid at position 6 of β chain</td>
<td>11</td>
</tr>
<tr>
<td>H</td>
<td>Formed in severe α thalassaemia</td>
<td>β_4</td>
<td>16</td>
</tr>
<tr>
<td>C</td>
<td>Decreased red cell survival, mild anaemia, vaso-occlusive disease rare</td>
<td>Lysine substituted for glutamic acid at position 6 of β chain</td>
<td>11</td>
</tr>
<tr>
<td>D</td>
<td>Asymptomatic, unless inherited with HbS</td>
<td>Glutamate substituted at position 121 of the β chain</td>
<td>11</td>
</tr>
<tr>
<td>E</td>
<td>Microcytosis, anaemia is rare</td>
<td>Lysine substitution in position 26 of the β chain</td>
<td>11</td>
</tr>
</tbody>
</table>

Table 2.2: Typical haematologic features of the common genotypes of SCD (Quinn, 2016)

<table>
<thead>
<tr>
<th>Genotype</th>
<th>Abbreviation</th>
<th>Name</th>
<th>Typical peripheral blood findings in untreated patients</th>
<th>Overall disease severity</th>
</tr>
</thead>
<tbody>
<tr>
<td>β^S^/β^S^</td>
<td>Hb SS</td>
<td>Sickle cell anaemia</td>
<td>Main Hbs: S; Hb (g/dL): 6–9</td>
<td>+++</td>
</tr>
<tr>
<td>β^S/^β^0^</td>
<td>Hb Sβ^0^</td>
<td>Sickle-β^0^- thalassemia</td>
<td>Main Hbs: S; Hb (g/dL): 6–9</td>
<td>+++</td>
</tr>
<tr>
<td>β^S/^β^C^</td>
<td>Hb SC</td>
<td>Sickle-Hb C disease</td>
<td>Main Hbs: S = C; Hb (g/dL): 9–12</td>
<td>++</td>
</tr>
<tr>
<td>β^S/^β^+^</td>
<td>Hb Sβ^+^</td>
<td>Sickle-β^+^- thalassemia</td>
<td>Main Hbs: S &gt; A; Hb (g/dL): 10–13</td>
<td>+</td>
</tr>
</tbody>
</table>
Table 2.3: Haemoglobin levels in g/dl of Ghanaians with SCD and healthy controls (Antwi-Boasiako et al., 2018)

<table>
<thead>
<tr>
<th>Group</th>
<th>Males</th>
<th>Females</th>
</tr>
</thead>
<tbody>
<tr>
<td>HbSS</td>
<td>8.53±1.61</td>
<td>8.31±1.57</td>
</tr>
<tr>
<td>HbSC</td>
<td>12.51±1.33</td>
<td>10.74±1.73</td>
</tr>
<tr>
<td>Healthy Controls</td>
<td>15.38±3.68</td>
<td>13.19±3.32</td>
</tr>
</tbody>
</table>

2.1.2 Sickle Cell Crisis

Sickle cell crisis or sickling crisis describes several independent acute conditions occurring in patients with SCD such as the vaso-occlusive crisis (acute painful crisis), aplastic crisis, splenic sequestration crisis, hyperhaemolytic crisis, hepatic crisis, dactylitis, and acute chest syndrome (Borhade & Kondamudi, 2019). These crises may lead to complications such as stroke (DeBaun & Kirkham, 2016), organ failure (Nath & Hebbel, 2015), priapism (Chinegwundoh et al., 2017), avascular necrosis (Ballas et al., 2012), leg ulcers (Minniti & Kato, 2016) and chronic pain (Brandow et al., 2017).

Vaso-occlusive crisis (VOC) is the commonest type of crisis in SCD and it is characterised by sudden onset of excruciating pain in any part of the body although gradual onset sometimes occur (Ahmed & Ibrahim, 2017; Lentz & Kautz, 2017). Almost SCD patients experience VOC at some point, but the frequency is usually variable and unpredictable (Lentz & Kautz, 2017). It is common among adolescents and adults with SCD and results from tissue ischaemia from vascular occlusion.

Acute chest syndrome (ACS) is a common cause of lung complications and death in patients with SCD; with most of cases occurring after VOC (Farooq et al., 2018). ACS is a frequent
cause of acute lung disease in children with SCD, whereas adults usually present as chest pain (Jain et al., 2017).

Haemolysis which simply means RBC breakdown is a fundamental feature of sickle cell anaemia that contributes to its pathophysiology and phenotypic variability (Kato et al., 2017). The number of RBCs being broken down far exceeds that which is being produced in the bone marrow. In this type of crisis, Hb levels can drop rapidly to about 3 g/dl within a short period because the red cells with precipitated abnormal haemoglobin are rapidly destroyed; and jaundice is a common feature of haemolytic crisis (Taher et al., 2013).

Frequency of crisis in SCD patients depends on the severity of the illness. Crisis is more common in HbSS individuals than those with HbSC (Adewoyin, 2015). Most episodes of sickle cell crises last between 5 and 7 days (Bölke & Scherer, 2012). The frequency of crisis also have a negative impact on the quality of life of SCD patients in terms of education (Brandow et al., 2017; Idowu et al., 2014a) and professional career (Idowu et al., 2014b; Matthie et al., 2015).

2.1.3 Management of sickle cell disease

Proper management of SCD with establishing diagnosis in early life, ideally during the newborn period before the onset of signs and symptoms of the disease (McGann et al., 2013). If patients do not manage SCD properly, severe complications usually occur. Patients’ adherence to medication is therefore important in the effective management of the disease. Compliant to routine drugs was 87% according to a study in Nigeria (Otaigbe, 2013) and as high as 63.3% in Saudi Arabia (Alkanhal et al., 2014).
In Ghana, the management in SCD patients usually are based on the therapeutic effect and the common drugs used fall under five major groups; analgesics/narcotics, anti-inflammatory, anti-malarials, antibiotics, vitamins/mineral supplements and supportive therapy such as blood transfusion, given to severely anaemic patients who were admitted to the hospital (Nsiah et al., 2014).

Analgesics are one of the most prescribed drugs among SCD patients since pain is a very common complaint by these patients (Jimoh et al., 2014). The type of analgesics to be given depends on the severity of the pain. The analgesic treatments for the management of pain in SCD patients consist of non-opioid based (NSAIDs, aspirin, paracetamol, and combination of two of these), opioid based – codeine, morphine, pethidine, tramadol and others (opioid or opioid combined with one or two non-opioids analgesics) (Boyd et al., 2014).

Transfusion therapy is an important intervention in decreasing morbidity and mortality in patients with SCD (Chou, 2013). Chronic RBC transfusion has been proven to be effective in prevention and management of strokes, silent cerebral infarcts, acute chest syndrome, in pregnancy and recurrent priapism (Master et al., 2016). Transfusion is usually recommended when Hb falls below 5-6g/dl or about 2-3g/dl and it is aimed at correcting anaemia and also to improve the oxygen carrying capacity of blood (Howard et al., 2013). Blood transfusion rate was 44% in some parts of Nigeria (Otaigbe, 2013) and 63.5% of SCD patients in central India had history of blood transfusion (Yadav et al., 2016).

Hydroxyurea is an important drug used in the treatment of SCD that targets the underlying pathology (Bykersma, 2018) and it is the gold standard of treatment for patients with sickle cell disease (Matte et al., 2019). Most of the beneficial effects of hydroxyurea are attributed to
the foetal Hb induction; and this foetal Hb also improves anaemia, reduces transfusion
frequencies, pain severity and reduces the number and duration of hospital admissions
(McGann et al., 2016). Despite the enormous benefits to SCD patients, hydroxyurea use is
limited in low-resource settings, particularly in sub-Saharan Africa, where the burden of SCD
is highest due to lack of data, absence of evidence-based guidelines, cost of treatment, drug
availability and inexperience among healthcare providers (Obaro, 2015). They are usually
prescribed for patients with frequent crisis or anaemia in this setting (McGann et al., 2016). In
Ghana this drug is not widely used by SCD patients (Asare et al., 2018).

2.1.4 Anthropometric indices in SCD
Hypoxaemia and tissue hypoperfusion which occur in SCA can cause impairment of tissue
resulting in retardation of growth and development which is observed in various
anthropometric measurements such as height, weight, body fat and skeletal maturation and also
in delayed puberty (Kamdi, 2013). Low socio-economic status and poor nutrition have also
been linked to delayed development in this population (Hyacinth et al., 2013). By early
adulthood, they attain normal height as with their healthy peers; however, their weight typically
remains below average (Adewoyin, 2015). There is a hypothesis that underweight in SCD is
caused by hypermetabolic state of the body due to the disease, which increases energy demand
and can lead to an undernourished state if not offset by increased nutrient consumption
(Kaufman et al., 2018). However, Kaufman et al., (2018) in their studies among some African
Americans with SCD found that 44% of their sample were overweight. Ajayi et al., (2017),
also assessed the BMIs of young adult Nigerians with SCD and reported that 5.6% of the total
study population were underweight, 57.2% were normal weight, 26.5% were overweight and
10.7% were obese. The standard classification of BMI has been summarized in table 2.4.
Table 2.4: Classification of Weight Status by Body Mass Index (BMI) (Dwyer et al., 2015)

<table>
<thead>
<tr>
<th>Classification</th>
<th>BMI (kg/m²)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Underweight</td>
<td>&lt;18.5</td>
</tr>
<tr>
<td>Normal weight</td>
<td>18.5-24.9</td>
</tr>
<tr>
<td>Overweight</td>
<td>25-29.9</td>
</tr>
<tr>
<td>Obesity Class 1</td>
<td>30-34.9</td>
</tr>
<tr>
<td>Obesity Class 2</td>
<td>35-39.9</td>
</tr>
<tr>
<td>Extreme Obesity Class 3</td>
<td>&gt;40</td>
</tr>
</tbody>
</table>

2.2.0 Exercise and its Effect on the Cardiopulmonary System

Exercise is a form of physical activity that is planned, structured, repetitive, and purposefully focused on improvement or maintenance of one or more components of physical fitness (Dasso, 2019). Exercise can be classified as either dynamic or static depending on the type of muscular contraction and has a significant effect on the cardiovascular system (Sandhu et al., 2013). Exercise can also be classified based on the type of metabolism involved that is, either aerobic or anaerobic (Turksoy et al., 2015). Aerobic exercise requires large amount of oxygen to produce the needed energy for continuous exercise. Examples of aerobic exercise include brisk walking, swimming, jogging, running and cycling. In anaerobic exercise, energy is produced without oxygen by burning stored glycogen in muscles. This results in lactic acid production which accumulates in the blood and muscles. Examples of anaerobic exercise are weight lifting, pull and push ups and sprinting.
2.2.1 Types of Exercise

2.2.1.1 Dynamic Exercise

Dynamic exercise is any exercise that comprises of isotonic muscular contractions or joint movement against low resistance (Awtry & Balady, 2010). Examples include walking, running, swimming and cycling. It involves external work, which is the shortening of muscle fibres against load. There is also increased blood flow to the skeletal muscles to meet the high metabolic demand during this type of exercise (Roseguini & Laughlin, 2019; Wang et al., 2019). Dynamic exercise is however ideal for testing because it puts a volume stress rather than a pressure load on the heart.

There are two types of skeletal muscle actions that occur during dynamic exercise which are concentric and eccentric contraction (Dale, 2012). In concentric contractions, there is shortening of muscle fibres which results in a decrease in the angle of the associated joint (Tan Dy, 2018). It is also known as positive work since it generally functions to accelerate a limb. On the other hand, eccentric contraction occurs when the muscle resists lengthening so that the joint angle increases during the action (Ombregt, 2013). It is therefore known as negative work and functions to decelerate a limb and provide shock absorption. It is also important to employ both muscle actions maximize the benefits associated with strength training (Hody et al., 2019).

During dynamic exercises, the heart rate, systolic blood pressure, myocardial contractility and cardiac output increase (Kaur & Mann, 2016). However, the diastolic blood pressure is unchanged or decreased since there is no change in peripheral resistance or it is decreased depending on the severity of exercise.
2.2.1.2 Static Exercise

Static or isometric exercise comprises of muscular contractions without the movement of joints (Nazmi et al., 2016). A typical example is pushing a heavy object. Isometric exercise does not include external work. During this exercise, there is increase in heart rate, myocardial contractility, cardiac output, systolic blood pressure, as well as diastolic blood pressure (Kaur & Mann, 2016). As a result increased in blood pressure, even light static exercise put much on the heart than dynamic exercise (Rosendorff, 2013; Crisafulli et al., 2015). The heart responds to the increased afterload by increasing contractility and heart rate and thus improving cardiac output. The increase in diastolic pressure in static exercise is due to increase in peripheral resistance during static exercise (Muthusamy et al., 2015).

2.2.2 Effects of Exercise on Cardiopulmonary System

Exercise can be one of the most stressful physiological responses that the body undertakes since it results increase in metabolic rate, heart rate, blood flow (hyperaemia), respiration, and heat production (Xiang & Hester, 2011). Apart from these, there are also cardiac structural adaptation which occurs with chronic exercise and this varies with the type of exercise (Nystoriak & Bhatnagar, 2018). For example isotonic exercise is associated left ventricular hypertrophy (LVH) and eccentric remodelling with chamber dilatation whiles isometric exercise is associated with hypertrophy and concentric remodelling with only slight chamber dilation (Tsioufis, 2018).

However, cardiovascular diseases or abnormalities may vary in the usual physiologic response to exercise. The heart rate, myocardial contractility and left ventricular wall thickness determine myocardial oxygen demand (Boyette & Manna, 2019). Nevertheless, in ischaemic heart disease and myocardial infarction this demand cannot be met due to damaged tissues
resulting in decrease in contractility, preload, afterload and heart rate (Sedehi & Cigarroa, 2018). Furthermore, an increase in heart rate, systolic blood pressure, and myocardial contractility induced by exercise is balanced by an increase in myocardial blood flow (Nystoriak & Bhatnagar, 2018). In contrast, coronary atherosclerosis affects the dilatory capacity of the coronary arteries and therefore restricts blood supply to myocardial tissues (Balla et al., 2018).

2.2.2.1 Heart Rate, Stroke Volume and Cardiac Output in exercise

Heart rate increase during exercise is primarily as a result of vagal withdrawal and activation of sympathetic nerves innervating the sinoatrial node (Klabunde, 2016). The heart rate increases to about 180 beats per minute in moderate exercises; in maximal exercise, it reaches about 200 beats per minute (Joyner & Casey, 2015). The thought of exercise or preparation for exercise can increase heart rate due to nerve impulses from cerebral cortex to medullary centres, which decreases vagal tone. Other factors that could increase heart rate during exercise include the following:

- Increase in body temperature acts on cardiac centres through the hypothalamus; increased temperature directly stimulates sinoatrial node (Jensen & Brabrand, 2015).
- Circulating catecholamines, which are secreted in large quantities during exercise (Manfredini et al., 2017).

The cardiac output increases due to increased stroke volume and heart rate; the stroke volume increases as a result of increased force of myocardial contraction (Vieira et al., 2016). However, as the intensity of exercise increases, the contribution of the stroke volume to cardiac output reaches a plateau which is about 40-50% of maximal VO₂ (Rivera-Brown & Frontera, 2012; Vieira et al., 2016), and the increase in cardiac output becomes primarily dependent on the ability to increase the heart rate further (Figure 2.2). However, at maximal
exercise, cardiac output varies greatly, from about 20 L/min in apparently healthy untrained individuals to about 40 L/min in trained athletes (Lavie et al., 2015); this wide variability in cardiac output in part explains the wide range in maximal VO$_2$, with normal values ranging from ~35 to 85 mlO$_2$•kg$^{-1}$•min$^{-1}$ (Fletcher et al., 2013).

![Heart rate and stroke volume response to exercise](http://ugspace.ug.edu.gh)

**Figure 2.2: Heart rate and stroke volume response to exercise (Guyton & Hall, 2016)**

As exercise intensity increases, the heart rate becomes the determinant of cardiac output since stroke volume plateaus or remains steady and heart rate continues to increase.

It is known that SCD patients have increased cardiac output and minimal increase in HR, all of which are abnormal (Gladwin & Sachdev, 2012; Voskaridou et al., 2012). This abnormality in heart rate is has been attributed to chronic anaemia (Tuncer et al., 2009) which is the cardinal feature of the disease.
2.2.2.2 Oxygen Saturation (SPO$_2$) in exercise

The increased metabolic demands of exercise tend to increase oxygen extraction from the blood, giving rise to a fall in oxygen saturation in the capillary bed that may predispose to sickling and vascular occlusion in SCA (Ramos, 2017). Desaturation is SCD patients have also been associated with increased risk factors for conditions such as stroke (Quinn & Sargent, 2008). However in most SCD patients, the decrease in oxygen saturation are usually within suitable ranges as have been demonstrated in some studies (Hostyn et al., 2013) (Dedeken et al., 2014).

Oxygen saturation is known to decrease more during exercise in SCD patients (Ramos, 2017) and a further decrease may be seen in patients with lung diseases (Moreira et al., 2014). This decrease in SPO$_2$ in SCD patients is due to anaemia (Waltz et al., 2013). Jenkins and Cecins (2011) stated that an SPO$_2$ of $<$80% meant severe desaturation and a reason to stop a patient from undertaking the 6MWT in patients with chronic obstructive pulmonary disease. The American Thoracic Society (2003) have also indicated that severe desaturation of SPO$_2$ $\leq$ 80% when accompanied by signs and symptoms of severe hypoxemia is a reason to terminate exercise.

However, Liberto et al (2016) in their 6MWT involving adult SCD patients recommended SPO$_2$ $<$ 88% as an indication of the physiological impact of exertion. This could be a useful guide to prevent extreme desaturation as a result of exercise; since desaturation in this population can lead to sickling of RBCs and hence vaso-occlusion (crisis) (Borhade & Kondamudi, 2019).
2.2.2.3 Blood Pressure changes in exercise

Increased blood pressure (BP) during dynamic exercise is based on the intensity of the exercise (Sabbahi et al., 2018). The, systolic blood pressure (SBP) increases whereas diastolic blood pressure (DBP) remains relatively constant or decrease thereby widening the pulse pressure (Schultz & Sharman, 2013). The DBP changes is because of the decrease in total peripheral resistance; and vasodilatation caused by metabolites decreases the peripheral resistance. Systolic blood pressure (SBP) increases markedly in line with an increase in stroke volume and the inotropic state of the heart. However, in exercises involving isometric contraction, the peripheral resistance increases which causes both systolic and diastolic pressure to also increase.

Exercise hypertension or a 'hypertensive response to exercise' (HRE) occurs in individuals whose BP increase excessively during exercise (that is, SBP≥ 210 mm Hg in men or ≥ 190 mm Hg in women or DBP≥ 110 mm Hg in men or women) despite their normal resting BP (Schultz & Sharman, 2013). This could predict future development of hypertension, cardiovascular events and mortality, independent of resting BP. In addition, a threshold of systolic BP ≥175 mm Hg during light-moderate intensity exercise increases the tendency of having hypertension (Figure 2.3). The American Thoracic Society (2002) has also stated that a person with, a resting heart rate of more than 120bpm, a SBP > 180 mmHg, and a DBP >100 mmHg should not undertake the 6MWT. A lack of increase or even a decrease in BP during exercise may also be related to cardiac dysfunction, although a reduction can also occur in healthy children (Massin, 2014). However, high prevalence of baseline relative systemic hypertension has been reported among SCD patients in Ghana which has been defined as SBP of 120 - 139mmHg and diastolic pressure of 70 - 89mmHg (Benneh-Akwasi Kuma et al., 2018).
Large quantities of metabolic end products accumulates in the tissues during exercise, especially in the skeletal muscle. These end products cause vasodilatation, hence, the BP may fall slightly below resting levels after exercise and return to baseline level when metabolic end products are removed (Joyner & Casey, 2015).

Figure 2.3: Blood pressure and exercise intensity (Schultz & Sharman, 2013)

The above illustration depicts the normotensive and hypertensive response to dynamic physical exercise. The normotensive response (solid arrows) shows systolic BP gradually increasing in a curvilinear fashion with exercise intensity, whereas diastolic BP remains largely unchanged or slightly decreased. The hypertensive response is represented by broken arrows and it shows how both systolic and diastolic BP could increase to a greater extent than a normotensive response, crossing respective BP thresholds that denote exercise hypertension in both males and females.
2.2.2.4 Blood Flow to skeletal muscles during exercise

During rest, the blood flow to the skeletal muscles is 3 to 4 mL/100g of the muscle per minute; this can increase up to about 60 to 80 mL in moderate exercise and 90 to 120 mL in severe exercise (Sembulingam & Sembulingam, 2012). Compression of blood vessels during muscle contraction causes blood flow to stop and in between the contractions, the blood flow increases (Joyner & Casey, 2015).

Sympathetic activity (sympathetic cholinergic fibres) causes vasodilation which increases blood flow to muscles even during exercise preparation (Matsukawa et al., 2013). In addition, skeletal muscle production of lactic acid and adenosine as well as increased concentrations of potassium ions, hypercapnoea and increased body temperature during exercise causes dilation of the arteriolar resistance vessels, thus reducing the systemic vascular resistance and thereby increasing cardiac output and blood flow to the exercising skeletal muscle (Hong & Kim, 2017). Blood flow to exercising muscle is therefore a major determinant of cardiovascular responses during dynamic exercise at higher than moderate intensity (Ichinose et al., 2015).
2.2.2.5 Respiratory system in exercise

The respiratory system response becomes greater as exercise increases in duration and intensity and the demand for oxygen becomes more prevalent (European Respiratory Society, 2016). As exercise begins pulmonary ventilation (breathing) increases in direct proportion to the intensity and metabolic needs of the exercise (Bruce, 2017). The abrupt increase in ventilation is influenced by centre activity and afferent impulses from proprioceptors of the limbs, joints and muscles (Jardins, 2012). This increase in ventilation is also divided into three phases (Bruce, 2017) (Figure 2.4); phase I is characterized by an abrupt rise in ventilation at the start of exercise with a constant time of a few seconds. A gradual exponential rise in ventilation, with a time constant of ~1 minute is observed in phase II and then in phase III, ventilation reaches a steady state by the 3 minutes of exercise.

![Phases of ventilation during exercise](image)

**Figure 2.4: Phases of ventilation during exercise (Bruce, 2017)**

The figure represents the ventilatory response to exercise (shaded area), beginning at 0 min.

The response is characterized by 3 phases: phase I is an abrupt increase in ventilation at the inception of exercise (fast component), phase II indicates an exponential increase in ventilation (slow component) until phase III, which is a steady state during exercise.
Oxygen uptake or consumption (VO₂) increases linearly with increase in exercise intensity due to an increasing dependence on oxygen to help provide energy as exercise continues (Hussein, 2018). As the intensity of exercise continues to increase, a person reaches a maximum point above which oxygen consumption (VO₂ max) will not increase any further (Figure 2.5). Increased duration of exercise results in an oxygen deficit or debt which determines the time that will be spent in recovery to resolve that deficit. Respiratory rate and depth remain elevated during recovery period in order to expel carbon dioxide (CO₂) and return the blood as well as ‘muscle’ pH to physiological limits.

Figure 2.5: Oxygen consumption (VO₂) during exercise (Tracey, 2016)
The increase in exercise intensity results in maximum oxygen consumption (VO₂ max) which is at a steady state. The oxygen deficit is the difference between the oxygen required during the exercise and the oxygen actually consumed during the exercise. EPOC is the excess oxygen consumed following exercise and it's needed to replace the lost energy and remove metabolic waste created during the exercise.
2.3 Benefits of exercise

In recent times, exercise has been regarded as ‘medicine’ since it is integral in the prevention and treatment (non-pharmacological) of many medical conditions as well as promotes optimal health. Physical inactivity is not encouraged in any population. Therefore, healthy individuals and those with chronic conditions can improve their performance and overall quality of life with exercise (Knight, 2012; Fleg et al., 2015). Significant evidence has been attained regarding the dangers of sedentary lifestyles and the importance of regular exercise (Knight, 2012). Sedentary lifestyle is known to be a major risk factor for cardiovascular disease, cancers, type 2 diabetes, and osteoporosis and all-cause mortality.

Studies have indicated that, mortality rates in cardiovascular disease are much lower in physically active than inactive people (Lachman et al., 2018). Coronary artery disease which is a major cause of death in adults is higher in sedentary people than active people (Hajduk & Chaudhry, 2016). Therefore, regular exercise in early adulthood can help prevent these diseases in later life (Gallanagh et al., 2011). One of the important explanations to this is a mechanism that causes a decrease in the formation of atherosclerotic plaques by altering essential risk factors such as blood pressure and lipids (Hajduk & Chaudhry, 2016). High Density Lipoprotein (HDL) which protects against atherosclerosis by removing cholesterol from blood is known to be 20% to 30% higher in individuals who exercise regularly than those who are sedentary (Jan et al., 2017). Exercise has also been found to reduce triglycerides and very-low density lipoprotein levels.

Few studies have investigated the positive effects of exercise in patients with sickle cell disease (Faes et al., 2014). That is, regular exercises at moderate intensity may decrease the risk of inflammatory reaction related to exercise and may increase vasodilatory reserve (Botelho et
al., 2017; Romero et al., 2017) which is an increased blood flow above normal resting volumes. Hence, increased vasodilatory reserve could reduce the risk of vaso-occlusive crisis. In addition, post-exercise improvement in red cell disaggregation indices which enhance microcirculatory blood flow and reduce the occurrence of vaso-occlusive crisis in SCD patients who engage in moderate exercises have been reported (Waltz et al., 2012). In another study, SCD mice model also showed that regular physical activity could decrease oxidative stress and inflammation, limit blood rheology alterations and increase nitric oxide metabolism (Martin et al., 2015). Increased nitric oxide levels is also associated with vasodilatation (Donald, 2016) which could also reduce the probability of vaso-occlusion. A significant improvement was also seen in the respiratory muscle strength, functional exercise capacity, pain, fatigue, dyspnoea and quality of life in patients with recurrent acute chest syndrome after a period of inspiratory muscle training (Camcıoğlu et al., 2015). These studies therefore suggest that, exercise therapy may contribute to reduced length of hospital stay in children with vaso-occlusive crisis.

Type 2 diabetes accounts for 90% to 95% of all diabetes patients (Karalliedde & Gnudi, 2016); and at the time of diagnosis, 60% to 90% of these patients are physically inactive and obese (Harris et al., 2017). Regular exercise is known to account for increased insulin sensitivity, improved glucose metabolism and weight reduction, thereby reducing the risk of developing type 2 diabetes (Clamp et al., 2017; Bird & Hawley, 2017). It also prevents or delays the complications of diabetes, especially, peripheral and coronary artery disease (Colberg et al., 2016).

An appropriate exercise programme that involves weight bearing is known to reduce the progression of bone loss and improve muscle strength, thus, reduce the overall risk of
osteoporosis and its associated complications (Sözen et al., 2017). Lower bone mass density and serum vitamin D3 is common among adult sickle cell disease patients and therefore are more predisposed to osteoporosis which could lead to complications such as pathological fractures (Vaishya et al., 2015; Rudy et al., 2018). The reasons for this have been linked to chronic inflammation present in the bone of individuals with SCD (Rudy et al., 2018), highly predominant bone resorption markers, lack of physical activity (Menaa, 2014).

Mental stress, anxiety and depression are known to be common among patients with chronic medical conditions including those with sickle cell disease. These psychological disorders are known to increase the levels of stress hormones such as catecholamines and corticosteroids which have the potential to increase the risk of sickle cell vaso-occlusive crisis (VOC) by adversely affecting blood cell count, plasma volume, and blood viscosity (Ahmed & Ibrahim, 2017). However, studies among healthy population have proven that, regular physical exercise could help reduce anxiety and depression by decreasing the levels of these stress hormones in the body (Anderson & Shivakumar, 2013) (Stonerock et al., 2015). The psychological benefits of moderate physical activity may also be important in improving perceived health status in patients with SCD. Regular moderate exercise is recommended during childhood in people with SCD to facilitate physical and psychological growth and development (LeMura & Duvillard, 2004).

Since physical activity decrease the risk diseases, it can be concluded that exercise is also economically beneficial or a cost-saving activity.
2.4 Risks of Exercise

Engaging in regular exercises though beneficial, comes with risks since there is no action without risk. However, the physiologic and psychological benefits outweighs the risks. Additionally, although there are risks associated with exercise in some patients, the benefits outweigh the risks in most patients (Warburton et al., 2016).

Intense exercises exert great impact on body systems, especially on cardiovascular, respiratory, skeletal muscles and autonomic nervous systems as well as electrolyte and hormonal homeostasis (Femminella et al., 2013). These disturbances need adaptations which can be insufficient in case of altered cardiovascular system. Exercises are also known to induce observable metabolic changes, including lactic acidosis, tissue hypoxia and dehydration, all of which can cause HbS polymerization and vaso-occlusion in SCD (Hedreville et al., 2014). Sudden death is a major risk associated with exercise in SCD patients (Goodman et al., 2013). The absolute number of deaths in people with sickle cell anaemia due to physical exercise occurred with practitioners of intense physical exercise (Harmon et al., 2012).

Vigorous exercises are known to confer risk for adverse cardiac remodelling, cardiac arrhythmias and sudden death among athletes and non-athletes, young adults with structural heart disease, and older adults with cardiovascular risk factors (Sharma et al., 2015). The risk of myocardial infarction is transiently increased during exercise (Eijsvogels et al., 2016; Warburton et al., 2016). Abnormalities such as myocarditis, hypertrophic, cardiomyopathy and congenital coronary artery anomalies are the common causes of exercise-related sudden cardiac death (ERSD) among healthy young adults under the age of 35 years (Albert & Stevenson, 2018). The commonest cause of ERSD in healthy adults above the age of 35 years is acquired atherosclerotic coronary artery disease.
Environmental factors like temperature (hot and cold) and high altitude can also increase the risk of exercise in SCD patients and healthy adults (Brocherie et al., 2015). These factors are known to increase the risk level of sudden cardiac death. Studies have indicated that patients with SCD have increased sensitivity to temperature changes (Brandow et al., 2013) and often report cooler weather or exposure to cold as the most important precipitating factor for vaso-occlusion (Mekontso Dessap et al., 2014). The SCD patient is also at risk of hyperthermia in hot weather conditions which could cause dehydration and increase the chances of vaso-occlusion as a result of polymerization of HbS (Tewari, et al., 2015). As such SCD patients are cautioned against undertaking physical activities during extreme weather temperatures in order not to elicit crisis.

Musculoskeletal injuries are also major problems associated with exercise which occur due to excessive physical activity or suddenly undertaking an activity for which the body is not familiar with (Eber & Midulla, 2013). The commonest sites of injury are the knee, ankle and foot; and usually present as muscle fatigue, overuse injuries, and joint/ligament damage (Callahan, 2019). The determining factors that increase the risk of injuries are the impact nature of activity, increased duration, frequency of exercise as well as age (Morrow et al., 2012).

It is believed that exercise leads to increases in the oxidation of lactic acid by muscles and more intense exercises cause an increase in anaerobic metabolism of the muscle because of the low levels of O₂ in its cells could result in an increase in the production of lactic acid (Wan et al., 2017). Therefore, the increase in the blood lactic acid concentration may occur as a result of both its production and the reduction in its removal (Foucher & Tubben, 2019). This build of lactic acid could worsen in the sickle cell disease patient during intense exercise due to the
already low oxygen carrying capacity and cause polymerization of red blood cells which leads to VOC (Waltz & Connes, 2014).

Exercise stress testing serves as the basis of the exercise prescription and it is the main method of assessing exercise tolerance (Fletcher et al., 2013). Pre-exercise screening is therefore recommended for young athletes and those with cardiovascular risk, and athletes with prodromal cardiac symptoms should be assessed for sudden cardiac death risk (Dhutia & MacLachlan, 2018). Although exercise testing is safe, the risk of myocardial infarction and related deaths occur at a rate of 1 per 2,500 tests (Akinpelu, 2019). This means that even exercise testing could be dangerous if patients care not carefully monitored and standard protocols are not adhered to.

### 2.5.0 Physical Fitness

Physical fitness is defined by the American College of Sports Medicine (ACSM) as a set of attributes that people have or achieve that relates to the ability to perform physical activity (Wilder et al., 2006). Therefore a physical fitness assessment must be integrated into all activities of daily living. Physical fitness is therefore a combination of physical and psychological qualities characterized by “a physiologic state of well-being that enables an individual to meet the demands of daily living or that provides the basis for sport performance, or both” (Warburton et al., 2016).

A physical fitness assessment is made up of eleven components (Angel, 2013) but five are commonly used in assessment; they are cardiorespiratory endurance, muscular strength, muscular endurance, musculoskeletal flexibility and body composition (Knapik, 2015).
Cardiorespiratory endurance is the ability to perform large muscle, dynamic, moderate-to-vigorous intensity exercise for prolonged periods of time (Pate et al., 2012a). It therefore involves, the circulatory and respiratory systems' ability to supply the muscles with enough oxygen and necessary nutrients and eliminate waste products from cells to during long periods of physical activity. Aerobic exercises such as brisk walking, jogging and swimming can be used to build cardiorespiratory endurance. The conventional standard for measuring cardiorespiratory endurance is the maximal oxygen uptake (VO$_2$max) (Smirmaul, Bertucci, & Teixeira, 2013). Example the 6MWT can be used to estimate cardiorespiratory endurance or fitness in both healthy (Ubuane et al., 2018) and individuals with chronic conditions such as sickle cell disease (Waltz et al., 2013), diabetes (Lee, 2018) and cardiopulmonary related diseases (Mossberg & Fortini, 2012).

Muscular strength and muscular endurance are collectively assessed as muscular fitness (Ramírez-Vélez et al., 2016). While muscular strength refers to the muscle’s ability to exert force, muscular endurance on the other hand refers to the muscle’s ability to continue to perform successive exertions of many repetitions under sub-maximal load. Muscular strength comes before muscular endurance. Resistance training or activities that place additional force against a muscle group is an important way of improving muscular strength and endurance (Hong et al., 2014). Since resistance training increases muscle mass (fat-free mass), it helps to also improve body composition (Souza et al., 2014).

Flexibility is the ability to move a joint through its complete range of motion (Pate et al., 2012b). Flexibility is an essential component of musculoskeletal health, especially in terms of lower back functionality, balance and susceptibility to falls (El-Khoury et al., 2013). Methods
of assessing or measuring flexibility include sit and reach, back scratch/shoulder flexibility, and trunk flexion (Pate et al., 2012b).

Body composition which is usually referred to as percentage of body fat is described as the distribution of body fat and lean body mass (Borga et al., 2018). Percentage body fat of an individual is affected by the amount of calories consumed (energy in) and the amount of physical activity performed and calories used (energy out). A fat mass of >25% total body weight for men and >35% of total body weight for women has been defined as obesity (Woolcott & Bergman, 2018). It is therefore important to improve and maintain body compositions at healthy levels in order to reduce the risk of chronic conditions such as obesity, type 2 diabetes, heart diseases, stroke and some type of cancers (Roger et al., 2012).

A number of clinical, laboratory, and field tests are used to evaluate body composition. Clinical and laboratory techniques of measuring body composition include densitometry techniques such as hydrostatic (underwater) weighing and air displacement Plethysmography (BodPod) (Beestone, 2017). Densitometry techniques are considered as the reference standards to assessing body composition (Pupim et al., 2013).

Common field tests to estimate body composition include body mass index (BMI= weight in kg/height in m²), circumference and skinfold measurements, and bioelectrical impedance analysis (BIA) (Ojo & Adetola, 2017). Body Mass Index (BMI) is commonly used to estimate body composition and a predictor hypertension, cardiovascular diseases, type 2 diabetes, certain types of cancer, and mortality (Must & McKeown, 2012; Kyrou et al., 2018). Calculations are however limited because of its inability to distinguish between adipose tissue, muscle mass, or bone mass (Weber et al., 2014).
2.5.1 Physical Activity/Daily Practice

Physical activity is defined as bodily movement produced by the contraction of skeletal muscle that increases energy expenditure above the basal (resting) level (Thygerson & Thygerson, 2018). Baseline physical activity refers to the light-intensity activities of daily life, such as standing, walking slowly, and lifting lightweight objects; therefore people who do only baseline activity are considered to be inactive (Lee & Shiroma, 2014). So, although all exercise is physical activity, not all physical activity is exercise. Being inactive or sedentary would therefore imply a decrease in energy expenditure by either the absence or reduction of physical activity, which can reduce functional capacity and is associated with substantial health consequences (Guimarães & Ciolac, 2014).

Physical inactivity has been linked to mortality risk in adults and also increased risk of cardiovascular disease, type 2 diabetes mellitus, osteoporosis, depression, obesity, breast cancer, colon cancer, falls in the elderly, among others (Ciolac, 2013). It has also been identified as the fourth leading risk factor for global mortality (6% of deaths globally) (WHO, 2019). It is also known that only 32% of adults and 66% of children and adolescents, practice leisure-time physical activity (Guimarães & Ciolac, 2014). Physical activity which takes the form of a controlled exercise programme or the accumulation of activities of daily living or leisure exercise is part of a healthy lifestyle and its practice is associated with health benefits. Its long-term effects especially involving a higher percentage of the population could have significant impact on health and economy (Guimarães & Ciolac, 2014). People with chronic diseases are also encouraged to undertake some form of physical activity since being sedentary is known to further complicate their condition. Studies indicate that aspects related to complications of sickle cell anaemia may be related to the low physical activity levels among those with the disease (Melo et al., 2017). Physical activity is therefore an important example
of how lifestyle choices have a profound effect on health. Whatever form it takes, a health promotion intervention focusing on physical activity would help reduce inactivity as a way of decreasing the incidence of non-communicable diseases or their consequences (Abaraogu et al., 2016)

The benefits of physical activity and the negative consequences of sedentary behaviour for physical and mental wellbeing has been well documented. Hence, the need for approved methods of measuring physical activity in order to determine whether there is the need for intervention based on lifestyle modifications involving movement activities (Silfee et al., 2018). The methods of measuring physical activity include the use of self-reported questionnaires which are cost effective and easy to administer (Sylvia et al., 2014). Examples of these questionnaires are Modifiable Activity Questionnaire (MAQ), Previous Week Modifiable Activity Questionnaire (PWMAQ), Recent Physical Activity Questionnaire (RPAQ), International Physical Activity Questionnaires (IPAQ), Previous Day Physical Activity Recall (PDPAR), 7-day Physical Activity Recall (PAR) and the use Godin Leisure-Time Exercise Questionnaire(GLTEQ) (Amireault & Godin, 2015). This GLTEQ is widely used to measure a person’s physical activity based on which type exercises an individual has been involved, the intensity and how many times those exercises were undertaken within a week. The weekly leisure-time activity score obtained is then used to classify one as sedentary, moderately active or active.

Physical activity can also be assessed using devices such as accelerometers, heart rate monitors, armbands and pedometers which are placed on specific parts of the body to measure energy expenditure and step counts (Hills et al., 2014). Other methods of measuring physical activity
are the Direct Observation method and the use of Self-Report Activity Diaries (Sylvia et al., 2014).

2.5.2 Exercise as a Functional and Physical Fitness Assessment Tool

Physical fitness assessment involve the use non-invasive standardised tools which are specific physical activities to assess the various components of physical fitness. For example, the six minute walk test (6MWT), multistage fitness test, Bruce protocol, Astrand treadmill test, the 2.4 km run test, the multistage bleep test and Cooper 1.5-mile walk-run test can be used to measure the cardiorespiratory endurance of a person (Luo, 2017). Cardiopulmonary Exercise Testing (CPET) which employs the use of treadmill or cycle ergometer is the standard in assessing a person’s fitness (Forman et al., 2019). Burr and his colleagues (2011) also suggested that since the 6MWT is of moderate-to-vigorous intensity, it may be useful in the classification of aerobic fitness or cardiorespiratory fitness (Lee, 2018), which is associated with health outcomes.

Variables such as blood pressure, heart rate, amount of oxygen inhaled and exhaled, oxygen saturation, speed, time and distance covered can be obtained from exercise testing (Palange et al., 2007) and used to assess physical fitness. The maximum oxygen uptake (VO₂max) and the metabolic equivalents (METs) which estimates ones energy expenditure can also be derived using the variables from the tests and the outcome can then be used to assess a person’s functional and physical fitness level (Sanghvi, 2013; Wicks & Oldridge, 2016).

Maximum oxygen consumption (VO₂max), also known as maximal oxygen uptake, is the maximum capacity to transport and utilize oxygen during exercise done at increasing intensity (Shete et al., 2014) or the maximum amount of oxygen a person can utilize during intense
exercise. Some of these exercise tests are indirect tests that estimates VO$_{2\text{max}}$ using a formula whiles some use direct measurements to determine the maximum amount oxygen an individual is using and require the collection and measurement of the volume and oxygen concentration of inhaled and exhaled air using gas exchange analyser (Beltz et al., 2016). Oxygen consumption (VO$_2$) is however, a measure of the volume of oxygen that is used by the body to form ATP at the cellular level. Increased exercise intensity ultimately corresponds to an increased VO$_2$. Oxygen consumption is measured in mL of O$_2$ per kg of body weight per minute (ml.kg$^{-1}$.min$^{-1}$).

METs is the working metabolic rate relative to the resting metabolic rate (WHO, 2018). That is, metabolic equivalent (MET) relates to the rate of the body's oxygen uptake for a given activity as a multiple of resting oxygen consumption (VO$_2$) (Sanghvi, 2013). METs are often used synonymously to describe the exercise intensity and energy expenditure/metabolic cost of physical activity (Woolf-May & Meadows, 2017). Therefore on average, an individual utilises 3.5ml.kg$^{-1}$.min$^{-1}$; 1 MET equals a VO$_2$ of 3.5 ml.kg$^{-1}$.min$^{-1}$ (Sanghvi, 2013; Shahpar et al., 2018). Hence, to attain a MET value for a particular activity, one needs to measure the VO$_2$ for that activity. According to the World Health Organization, moderate-intensity physical activity (e.g. brisk walking) is equivalent to 3-6METs and vigorous-intensity physical activity (e.g. running) is equivalent to ≥6METs (WHO, 2018).

2.6.0 Exercise as a tool for Screening and Identifying Clinical Complications

There are different modalities of exercise testing that can provide valuable information to health care providers about a patient’s fitness and cardiopulmonary status (Nelson & Asplund, 2016). These modalities include six minute walk test (6MWT), stair climbing, shuttle-walk test, cardiac stress test (e.g. Bruce protocol), and cardiopulmonary exercise test (Bittner &
Singh, 2016; Mezzani, 2017). The indications for these methods are functional capacity assessment, prognostic stratification, training prescription, treatment efficacy evaluation, diagnosis of causes of unexplained reduced exercise tolerance, and exercise pathophysiology evaluation in an extremely wide spectrum of clinical conditions (Guazzi et al., 2016). Therefore exercise testing is important in providing vital information about a patient’s condition, which may not be apparent in the resting state of the patient (Motonaga & Dubin, 2017)

2.6.1 Screening for Pulmonary Complications

Cardiopulmonary exercise testing (CPET) can be used in assessing and diagnosing chronic obstructive pulmonary diseases and heart failure (Weatherald, Farina, Bruno, & Laveneziana, 2017). Impaired or Reduction in ventilation and gas exchange and maximum oxygen uptake (VO2max) with respect to predicted values is an indicator of a pulmonary complication or diseases as well as other clinical conditions (Mezzani, 2017). The dyspnoea (using the Borg scale) in relation to the distance covered and pulmonary function tests in the 6MWT may suggest the presence or absence of a pulmonary vascular disease (Ijiri et al., 2014). In addition, the use of the 6MWT is known to be practically safer than CPET in screening patients with serious complications such as SCD patients with pulmonary hypertension although the CPET may provide more information.

2.6.2 Screening for Heart Disease

Screening for heart diseases employs the use of exercise testing protocols. The commonest method is the cardiac stress test or the exercise ECG which involves the use of treadmill or cycle ergometer together with electrocardiogram or echocardiogram to assess the cardiac electrical activity during physical exertion (American Thoracic Society, 2003). The goal of these exercise tests is to assess markers of previous myocardial infarction, myocardial
ischemia, and other cardiac abnormalities (such as left ventricular hypertrophy, bundle branch block, or arrhythmia) that may be associated with cardiovascular disease or predict future cardiovascular disease events (Curry et al., 2018). Incremental exercise cycle ergometer tests with electrocardiographic assessment studied in patients with SCA revealed various cardiac abnormalities but ECG studies among the same population in the resting state did not reveal any ischaemic changes (Connes et al., 2011). A study, which involved the use of the 6MWT and transthoracic echocardiography among patients with SCD showed a raised pulmonary artery systolic pressure (Marouf et al., 2014) whilst another study with 12 minute walk test with ECG among SCD patients showed non-specific ECG findings. Connes and colleagues therefore suggested that intense exercise test such as the cardiopulmonary exercise tests is appropriated in revealing silent cardiac diseases than walking tests (Connes et al., 2011).

2.7 Exercise Prescription and Practice

Exercise is a form of physical activity that is planned, structured, repetitive, and purposefully focused on improvement or maintenance of one or more components of physical fitness (Dasso, 2019).

Exercise prescription can be defined as specific plan of fitness-related activities that are designed for a specified purpose, which is often developed by a fitness or rehabilitation specialist for a client or patient (Suleman, 2016). Exercise prescription can be very challenging since for most people regardless of their health status, would not want to engage in exercise as a means of treatment or improving health (Bezner, 2015). Besides, many health practitioners are also known to live sedentary lifestyles (Mackenzie et al., 2017; Kunene & Taukobong, 2015), making it even more difficult to introduce the idea of habit changing to someone. Studies have shown that a health practitioner’s exercise habits have a major influence on exercise
prescription and that the more one exercises the higher probability of prescribing exercise to patients (Teferi, 2017). Successful prescription of exercise for a patient should include asking the patient about exercise, assess readiness, consider risks and need for exercise stress testing or other screening, choose an appropriate exercise prescription, and plan for re-evaluation at follow-up (Crookham, 2013). Evaluating a patient’s willingness for exercise prescription is vital in order to ensure that he or she would adhere to the programme. Patients are much more likely to be adherent with exercise if they agree to a plan that they are more confident they can complete an exercise programme (Lemstra et al., 2016). Once it has been established that the patient is willing to start an exercise program, the Physical Activity Readiness Questionnaire form (PAR-Q) can then be used as a guide to know who will need to be categorised as low or high risk of health complications before exercise prescription (Crookham, 2013). This would determine whether there would be need for pre-participation exercise testing, and the need for professional or clinical supervision during exercise.

The “FITT Principle” is used as a guide to the components of an exercise prescription. Thus, an exercise prescription will include frequency, intensity, time (or duration), and type of exercise (FITT) (Jonas & Phillips, 2012). Determining the exercise intensity by using the targeted heart rate or the calculated VO$_2$max is the most important task in exercise prescription (Lee, 2018). Thus, if the exercise intensity is too low, the effect of the exercise cannot be expected and if it is too high, patients will not be able to exercise continuously. Therefore, to obtain the effects of an exercise programme, it should be performed for a certain amount of time with appropriate exercise intensity. It is therefore important to consider the target heart rate of a patient in an exercise programme which is the widely accepted measure of moderate-intensity physical activity or exercise. Moderate intensity of exercise leads to a heart rate of 64% to 75% of maximal heart rate (Crookham, 2013).
Although the Karvonen formula may overestimate or underestimate the exercise intensity in certain patients, it provides general rule-of-thumb for estimating the target heart rates (Ignaszewski et al., 2017). The Target Heart Rate = (Heart Rate Reserve) x Training Intensity (%) + Resting Heart Rate. The heart rate reserve is also calculated = Maximum Heart Rate – Resting Heart Rate. The maximum heart rate for women is calculated as 220 minus the age whilst that for men is calculated as 220 minus ½age.

The ideal exercise programme should consist of periods of warm-up, endurance exercise, flexibility exercise, resistance training, and cooling down. When choosing an exercise prescription, the goal is to work to meet the American College of Sports Medicine (ACSM) guidelines of 150 to 300 minutes of moderate-intensity exercise per week or 75 minutes to 150 minutes a week of vigorous-intensity aerobic physical activity, or an equivalent combination of moderate- and vigorous-intensity aerobic activity (Piercy et al., 2018). Children and adolescents are encouraged to perform 60 minutes or more of physical activity daily, including aerobic, muscle-strengthening and bone-strengthening activities and to create a plan that the patient can complete regularly. Thus by using the FIIT principle exercise can be tailored for each individual patient to suit his or her lifestyle and health requirements.

Adults with chronic conditions such as sickle cell disease, heart diseases, type 2 diabetes and pulmonary diseases would need clinical supervision an exercise prescription programme. Each condition has a specific set of indicators that must be monitored for the safety of the individual. Physiological markers such as blood pressure, heart rates, peripheral oxygen saturation, respiratory rates and blood glucose levels are key indicators in such patients during an exercise prescription programme (Derek Bellemore, 2015). According to Kato (2018) clinicians taking
care of patients with sickle-cell anaemia perhaps need to issue the same prescription issued to those with cardiovascular disease. However, exercise prescription among health professionals for SCD patients is limited due to fear of eliciting crisis and complications associated with the condition (Connes et al., 2011). Patients with SCD are therefore advised to begin exercise progressively, avoid vigorous exercise and stop exercising in case they start experiencing fatigue. They should also avoid exercising for more than 20 minutes without resting in order to prevent dehydration and lactic acid build-up. In addition, to the prevention of dehydration, SCD patients must drink water during and after exercise (Botelho et al., 2017). SCA patients with spleen enlargement should avoid contact sports (Brousse et al., 2014).

2.8 Peak Expiratory Flow Rate (PEFR)

Peak expiratory flow rate (PEFR) is a measure of the maximal flow rate that can be achieved during forceful expiration following full inspiration (DeVrieze & Bhimji, 2018). PEFR is conventionally measured in litres per minute (L/min). Pulmonary functions are usually determined by respiratory muscle strength, compliance of the thoracic cavity, airway resistance, and elastic recoil of the lungs. PEFR thus, provide an idea about bronchial tone (Jena et al., 2017). It measures airflow through the bronchial tree especially in large airways (proximal airways, with diameter >2 mm) compared with other spirometric measurements (Dobra & Equi, 2018). Thus, peak flow may not fully assess the full extent of airway obstruction in the bronchial tree.

Measurement of PEFR is widely used in clinical practice for the assessment of patients with obstructive and restrictive airway diseases (Manjunath et al., 2013). However, it is more useful in evaluating obstructive lung diseases especially bronchial asthma by monitoring the disease progression and response to treatment. Apart from the age, sex, weight and height
(Anthropometry), obesity, posture and geographical, socioeconomic, nutritional and climatic conditions that are associated with the PEFR, attitude is also a factor that influences PEFR (Gupta et al., 2013).

Peak expiratory flow rate, by itself, has limitations that makes it inferior to FEV$_1$ in clinical value. However, traditionally FEV$_1$ measurement at home was not practical or technologically feasible (DeVrieze & Bhimji, 2018). Hence the need for a convenient tool such as the peak flow meter to measure lung functions (PEFR) (Gold & Koth, 2016).

The peak flow meter is a simple, inexpensive hand-held device and not time consuming (Thorat et al., 2017). The device is equipped with gauge markers indicating three “zones” that can be set by the patient or health professional to aid in interpreting the peak flow rates or scores. In order to interpret the results, a comparison is done between the measured values and the predicted values which are taken from reference value tables or formula published in literature (Singh, 2013) (Fawibe et al., 2017).

The peak flow variability which is expressed as a percentage is calculated as:

$$\text{Peak flow variability (\%) = \left( \frac{\text{actual peak flow rate}}{\text{predicted peak flow rate}} \right) \times 100}$$

The steps in using the peak flow metre are provided by America Lung Association and its interpretation to these variability scores are given by the follows (American Lung Association, 2019);

- Green zone (safe zone): 80 to 100%; as long as no symptoms are present, the patient is considered at steady state.
- Yellow zone (zone of alert) : <80% to >50%; the airways are narrowing and patient may require extra treatment.
- Red zone (zone of emergency): <50%; Severe airway narrowing may be occurring. Immediate treatment required.

Peak flow measurement is also useful in guiding the management approach in the clinical setting. A patient with a peak flow of ≤ 50% without improvement despite aggressive treatment should be on admission for ongoing care and close monitoring for signs of impending respiratory failure (DeVrieze & Bhimji, 2018).

2.9 The 6MWT as a Standardized Test for Exercise Tolerance Test in SCD Patients

Exercise tolerance has become an important outcome measure in patients with chronic obstructive pulmonary disease and congestive heart failure, as well as other chronic diseases (Nelson & Asplund, 2016). Walk tests have been used to measure the state or the functional capacity of patients since walking is one of the main activities of daily living (Morales-Blanhir et al., 2011). In 2002, the American Thoracic Society (ATS) published guidelines on how to perform the 6 MWT (American Thoracic Society, 2002). This guideline stressed the need for a standardized protocol to perform the 6 MWT to minimize variation in results. The 6MWT was initially developed to measure the functional capacity of patients with cardiopulmonary diseases for preoperative and postoperative evaluation and for measuring the response to therapeutic interventions. The 6MWT has proven to be reproducible and is well tolerated by patients with different conditions such as stroke, heart diseases, chronic lung diseases, and sickle cell disease (Morales-Blanhir et al., 2011) and even healthy individuals (Tables 2.5 and Table 2.6). When performed appropriately, the complication rate with the 6 MWT is very low as patients determine their own pace during the test (Bittner & Singh, 2016).
Table 2. 5: Six minute walk distance (6MWD) by SCD patients and healthy individuals

<table>
<thead>
<tr>
<th>Distance walked by Healthy adults</th>
<th>Distance walked by Adult SCD patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nigerians - 517.6 ± 72.2 m (Ajiboye, Anigbogu, Ajuluchukwu, &amp; Jaja, 2014) and 619.41±125.76m (Mbada et al., 2015)</td>
<td>USA - 463.6 meters ± 99.2m (males- 488 ± 14.4; females- 427.4 ± 25.1 meters) (Castro et al., 2008)</td>
</tr>
<tr>
<td>Koreans - (598.5±57.92 m) (Kim et al., 2014)</td>
<td>Brazil - 447±62 vs. 405±71 meters (Ohara et al., 2014)</td>
</tr>
<tr>
<td>African Americans - (males: 709 ± 68 m and females: 627±55 m) (Alqahtani, 2017)</td>
<td></td>
</tr>
<tr>
<td>North Africans - 680 ± 70m (Bourahli et al., 2016)</td>
<td></td>
</tr>
</tbody>
</table>

Table 2. 6: Six minute walk distance (6MWD) by adults with chronic conditions

<table>
<thead>
<tr>
<th>CONDITIONS</th>
<th>6MWD (m)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Obese (Gontijo et al., 2011)</td>
<td>531.5 ± 57.2</td>
</tr>
<tr>
<td>Type 2 diabetes mellitus (Lee, 2018)</td>
<td>538.2 ± 54.0</td>
</tr>
<tr>
<td>Neuromuscular conditions (Prahm et al. 2014)</td>
<td>532.6 ± 173.0</td>
</tr>
<tr>
<td>COPD (Ijiri et al., 2014)</td>
<td>370</td>
</tr>
<tr>
<td>COPD (Tornatore et al. 2017)</td>
<td>306 ± 69.6</td>
</tr>
</tbody>
</table>

The 6MWT is a practical test that requires a 20 or 30 metre flat, hard surface/ walkway but no special exercise equipment. The test measures the distance that a patient can quickly walk in a period of 6 minutes (the 6MWD). The self-paced 6MWT assesses the submaximal level of functional capacity. That is, patients choose their own intensity of exercise and are allowed to stop and rest during the test.
In the six minute walk test, the patients’ blood pressure, heart rate and the peripheral oxygen saturation are measured before the test is taken and after the test. The changes in these physiological parameters determine the cardiopulmonary response of an individual to this submaximal test.

The Borg dyspnoea scale is an eleven point scale (0 to 10) used during the 6 minute walk test to assess the level of breathlessness of a patient (Crisafulli & Clini, 2010). Participants are made to grade their level of shortness of breath both at the beginning and the end of the test. The scale is also used when a participant stops or is unable to complete the time range for the exercise. The Borg Rating of Perceived Exertion (RPE) Scale is a widely used and reliable indicator to monitor and guide exercise intensity (Williams, 2017). A scale of 11 to 14 is considered moderate intensity whilst 17 to 19 is considered vigorous intensity. The scale allows individuals to subjectively rate their level of exertion or fatigue during exercise testing (Pianosi et al., 2016). Its use is similar to the dyspnoea scale and the original form is a point scale (6 to 20). The rate of perceived exertion (RPE) can also be used in different tests such as the cycle ergometer test and treadmill tests to subjectively measure the exertion or fatigue level of an individual (Scherr et al., 2013). The validity of the scale in regulating exercise intensity has been established (Ohara et al., 2014).

Studies have examined the physical activity level and exercise capacity of different age groups in patients with sickle cell disease using the 6MWT (Ohara et al., 2014; Melo et al., 2017). Although SCD patients exhibited low capacity for exercise in these studies, they were able to complete the 6MWT without any complications or adverse effects. The distance covered in these tests were also lower than predicted values. Patients who were compared with healthy controls also showed reduced exercise capacity when compared with their healthy counterparts.
In recent years, studies have shown that the distance covered (6MWD) in the 6MWT test can also be used to predict the metabolic equivalents (METs) and oxygen consumption which are measures of exercise intensity (Venkatesh et al., 2011; Khuangsirikul et al., 2014). These measures further enhance the validity and reliability of the 6MWT as a measure of once tolerance to exercise or functional exercise capacity. These studies concluded that the METs acquired was associated with the moderate intensity exercises. Spirometry have also been employed as an additive tool in combination with other physiological parameters in the 6MWT to assess the lung function of patients with chronic pulmonary disease (Agrawal & Awad, 2015). Lung function test has also been assessed in SCD patients with the 6MWT since the respiratory system is one of the most affected systems in this population (Ohara et al., 2014) (Vieira et al., 2016) and has a significant effect on one’s exercise tolerance. Apart from spirometry to assess lung function, the Peak Flow Meter is also a simple device that is normally used to assess peak expiratory flow rate (PEFR) in asthma patients and people with chronic obstructive pulmonary disease (Thorat et al., 2017). However, some studies have used the peak flow meter in the 6MWT to assess lung function among sickle cell disease patients (Hostyn et al., 2013). Although spirometry is more accurate and the preferred tool to measure lung function, the peak flow meter is a simple, hand-held, less expensive and easily accessible tool that can be used as a quick measure of lung function.

In conclusion, since most activities of daily living are performed at submaximal levels of exertion, the 6MWT could better reveal the functional exercise capacity for daily physical activities.
CHAPTER THREE

3.0 MATERIALS AND METHODS

3.1 Study area

The adult patients with SCD were recruited from the Tema General Hospital Sickle Cell Clinic. The hospital serves as a referral centre for all government hospitals, private hospitals and clinics in and around the Tema metropolis. It also serves the people of Tema and all other surrounding communities/towns such as Ashaiman, Nungua, Tema Newtown, Ningo, Prampram, Kpone, Ada as well as those outside the region such as Akosombo and Akuse. There are fourteen (14) wards and a bed capacity of about three hundred (300) with an occupancy rate of 80%. It also provides a 24 hour specialist and general services both on out-patient and in-patient basis and has a daily average out-patient attendance of 650. The sickle cell clinic is one of the specialist clinics has a monthly client attendance of one hundred and twenty (120) with a male to female ratio of 1:2. The adults make up about 40% of the total client attendance. They healthy control adults were also recruited from same the hospital.

3.2 Study design

The study was a case control study which involved adults with SCD and healthy controls.

3.3.0 Study population

This consisted of all adults laboratory diagnosed SCD patients who attended the between the Tema General Hospital for their routine check-up between the period of 1st March 2019 to 17th May 2019.
3.3.1 Healthy controls
The control group consisted of apparently normal healthy adults between 20 and 45 years working at the Tema General Hospital or caregivers of patients who visit the hospital as well as students on rotation.

3.4 Sample size
The minimum sample size for the study was determined by the use of software from: http://samplesize.sourceforge.net/iface/s3
With the following values:
Minimum Odds Ratio to detect = 24
Percentage exposed among controls = 40%
Power = 80%
Alpha risk = 5%
1:1 matched study design
The minimum sample size for the participants in the study was 72. This is made up of 36 sickle cell disease patients and 36 healthy adults.

3.5 Sampling Procedure
Systematic (simple random sampling) sampling technique was used to select sickle cell patients who visit the Sickle Cell clinic. Only the first participant was randomly selected.
N/n = kth where N = total population, n = sample size, k = sampling interval
Using the total population of 120 (sample frame) and a sample size of 36. Therefore the rest of the participant were selected by every 3rd patient who attended the clinic during the period of study. The sampling interval was 3.
The healthy control group were selected by simple random sampling and then matched with SCD patients by age and gender.

3.6 Eligibility

All patients in a steady state between the ages of 20 – 45 years who attend the SCD clinic with no history of blood transfusions in the previous three months and with no acute symptoms for at least one month prior to the study.

3.7 Inclusion criteria

1. Adults with SCD who attend the sickle cell clinic.
2. Adult SCD patients who are in their steady state with Hb not less than 6g/dl.
3. Adults who have not been diagnosed of any abnormality apart from the SCD.

3.8 Exclusion criteria

1. Sickle cell disease patients with a history of neurological impairments such as stroke.
2. Sickle cell disease patients with a history of orthopaedic impairments such as avascular necrosis.
3. Adult SCD patients who are in their steady state with Hb less than 6g/dl.

3.9.0 Study procedures

3.9.1 Materials/ equipment used in the study

1) A flat walking surface, with a length not less than 20 meters, without obstacles, and marked at intervals of 1m.
2) Chairs for rest.
3) Cones to be placed at both ends (20 metres apart)
4) Acosson Mercury Sphygmomanometer (Accoson Ltd, UK)

5) 3MTM Littmann Classic III Stethoscope (3M Medical Solutions Division, USA)

6) Pulse Oximeter Model: M-60 (Mindray Bio-Medical Electrical Co. Ltd. Hamburg Germany)

7) Round dial Column Scale with Height rod (ADE Germany)

8) Philips Respironics PersonalBest universal Peak Flow Meter (60 – 800L/min), (Respironics Respiratory Drug Delivery (UK) Ltd.)

9) Haemoglobinometer – HemoCue 301 Hb System (HemocueAB, Sweden)

10) Digital Stopwatch Timer: Model HS-3V-1R (Casio, China)

11) Fibreglass measuring tape - 50m (Tolsen Tools Co. Ltd., China)

12) Cylinder with oxygen

3.9.2 Participant enrolment

All Participants who agreed to take part in the study were then taken through a detailed description of the study. They were then given an appointment and reminded through phone call a day prior to the study in order to ensure that they came to the study site in the right clothing and footwear and met the standards needed for the study. On the day of the study, the description of the study as well as demonstrations were re-emphasised. They were then made to sign a consent form before proceeding with other procedures in the study.

Adult SCD participants who consented to take part in the study were screened by interviewing them to obtain any relevant information that may not be in their medical records. Their medical history were obtained from medical records/ folders.
3.9.3 Questionnaire administration

A structured questionnaire was used to collect the data from the participants prior to the 6MWT. The questionnaire covered areas concerning demographic information their exercising status for both sickle cell patients and healthy controls. In addition, the SCD patients provided information on crisis, last blood transfusion, medication and other information concerning their condition. (Appendix 2)

The level of physical activity of each participant was also assessed using the Godin Leisure-Time Exercise Questionnaire (Amireault & Godin, 2015). This questionnaire aims to provide the type of activities that the participant had been performing during the previous seven days. (Appendix 3). The sum of scores was calculated to determine the final score in order to categorise each participant as sedentary, moderately active and active.

3.9.4 Measurement of haemoglobin level (Hb)

Participants’ haemoglobin (Hb) level was measured with HemoCue® 301 Hb analyser and by capillary blood collection method; values were then recorded on form (Appendix 1).

3.9.5 Anthropometric Measurements

The height and weight were measured using the ADE® Round dial column scale with Height rod which can be used to measure both height and weight. The scale was placed on a flat horizontal surface. Weight was measured with participants on barefoot and with light clothing and was recorded to the nearest 0.1kg. Height was also measured at the same time that the weight was taken, with shoulders in normal alignment. The height in centimetres was then converted to meters. Body mass index (BMI in kg/m²) was calculated for each participant as
the individual's body weight (in kilogrammes) divided by the square of his or her height (in meters) (Nuttall, 2015). They were then recorded on a form (Appendix 1)

3.9.6 **Measurement of blood pressure, heart rate and oxygen saturation**

The Blood pressure (BP) was measured using the Acosson® Mercury Sphygmomanometer and 3M Littmann Classic III® Stethoscope. The measurement was taken with participant in sitting position and on the left arm. Heart Rate (HR) and peripheral oxygen saturation (SPO₂) were measured using the Mindray Pulse Oximeter® Model: M-60 by placing the probe on the index finger of the participant and the readings on the display screen recorded on a form.

3.9.7 **Peak expiratory flow rate (PEFR) measurement**

The peak expiratory flow rate (PEFR) was measured with the Philips Respironics®, Peak Flow metre in accordance with the American Lung Association standard procedures (American Lung Association, 2019). The measurements were taken in standing position to ensure good expiratory effort. The procedure was explained and demonstrated to them before the actual recording was made. Participant was asked to take in a deep breath (as deep as he or she could) and put the mouthpiece of the peak flow meter into his mouth with the lips tightly sealed around the mouthpiece. The peak flow meter was horizontally held and in one breath, blow out as hard and as quickly as possible into the peak flow metre until participant has emptied out nearly all the air from the lungs. The force of the air coming out of the lungs causes the marker to move along the numbered scale and the number was noted. The marker was returned to zero after every measurement. The entire routine was repeated three times and the highest of the three ratings was recorded. Disposable mouthpieces was used for each participant.
All cardiovascular indices and PEFR measurements were taken before the test, at the end and five and ten minutes after the test and recorded on form (appendix 4).

3.9.8 Measurement of dyspnoea, fatigue and Chest pain

Measurements concerning dyspnoea, fatigue level and chest pain were assessed subjectively using standard scales. These scales were explained to participants and made available to them prior to the 6MWT, at the end and five and ten minutes after the test in order for participants to grade themselves at each stage of the test to score themselves based on their state.

The modified Borg Scale dyspnoea scale was used in assessing participants’ level of breathlessness. The scale was in a score of 0 to 10 with 0 being no breathlessness and 10 being maximal breathlessness (Appendix 5). The Borg rating of perceived exertion scale for rating fatigue level was also in a scale of 6 to 20 with 6 being no exertion at all and 20 being maximal exertion (Appendix 6). Participants’ chest pain were graded using the Canadian Cardiovascular Society grading of Angina Pectoris (Campeau, 2002). The grade was I to IV and participant were asked to categorise their level of chest pain if it was present (Appendix 7).

3.9.9 Precautions taken during the 6MWT

The following precautions were ensured;

- The adult emergency department was informed prior to the test so that they can take care of to any adverse event that may ensue during the test.
- A cylinder with oxygen was always on site throughout the study.
- Participants were well hydrated before and after the test.
- No warm-up was done prior to the test.
- No heavy meal was allowed at least two hours to the test.
- The test also was carried out indoors in a well-ventilated environment.
• Participants were not having pain in any part of the body prior to test.

• Participants were required to wear appropriate footwear and clothing for the study.

• All participants were called on phone (SCD patients and control group) at 24 hours and every 72 hours for 1 week following the test to document any adverse events that could ensue.

• The age predicted maximum heart rate was determined ((maximum HR = 220 – age) – females and 220 - ½age- males) to ensure that participants were within range when performing the exercise test.

3.9.10 Six Minute walk Test (6MWT)

The test was conducted using the American Thoracic Society (ATS) published guidelines on how to perform the 6 MWT. Participants were made to sit at rest in a chair, located near the starting position (for the 6MWT), for at least 10 minutes before the test starts.

In the 6MWT, participants were asked to walk for six (6) minutes in their own maximum pace along a flat level floor, turning around cones placed at 20 metres distances apart. During the test, participants were informed of the time remaining each minute like ’you have 5 minutes more, 4 minutes more until the last 15 seconds when participants were prompted to get ready to stop. The BP, HR, and SPO2 was obtained again in the same position that was taken prior to the test and then every five (5) minutes during recovery for ten (10) minutes. Participants were allowed to stop for a period if they wanted to but were encouraged to continue once they recovered. However, participants were also informed that if they felt exhausted or could not continue for any appropriate reason (such as chest pain, intolerable dyspnoea, leg cramps, pale appearance, staggering etc.), he/ she should give a signal and would be asked to stop and the required parameters would be measured including the distance covered. All parameters including the distance covered within the 6 minutes (6MWD) were recorded in a table. Each
participant was also asked to subjectively grade their level of breathing/dyspnoea, level of exertion and chest pain using the modified Borg Scale, the Borg rating of perceived exertion (RPE) scale and the angina scale respectively at the end of the test. All values obtained were recorded in a data sheet (Appendix 4)

3.9.11 Estimation of oxygen consumption (VO$_2$), metabolic equivalent (MET) and predicted PEFR

- The oxygen consumption (VO$_2$) and metabolic equivalents (MET) were estimated after the 6MWD using the standard formula (Pescatello, 2014);

$$\text{VO}_2 = [0.1 \times \text{speed (m·min}^{-1} \text{)} + 3.5\text{mLO}_2\text{·kg·min}^{-1}]$$

$$\text{MET} = \frac{[0.1 \times \text{speed (m·min}^{-1} \text{)} + 3.5\text{mLO}_2\text{·kg·min}^{-1}]}{3.5\text{mLO}_2\text{·kg·min}^{-1}}$$

The speed (m·min$^{-1}$) was calculated by dividing the total 6MWD (metres) by 6 (minutes)

- The predicted values for PEFR was calculated using the reference equation for a West African population (Fawibe et al., 2017)

Male = -4.199 + (-0.054)Age + 0.091Height(cm)

Female = -4.986 + (-0.045)Age + 0.082Height(cm)

The Peak flow variability was also calculated as, \(\% = \frac{\text{actual peak flow rate}}{\text{estimated peak flow rate}} \times 100\) in order to be able to interpret the PEFR values.

3.10 Data Handling

Records were kept throughout the period of the study and would be kept for at least three years after the study. The hard copies were put in a file and kept in a locker box. The soft copies of
the data collected were blocked (password protected) in a folder to prevent any unauthorized person from having access to the soft copies. Participants were asked to fill questionnaires and deliver it to the research investigators or research assistants and were not permitted to take the questionnaire away and submit it at a later date. Research assistants (physiotherapists) were trained to help in the collection of the data.

3.11 Statistical Analysis

Data collected were entered into a database software (Statistical Package for the Social Sciences- SPSS version 23) after which the appropriate results using the desired method were generated. Continuous variables was expressed as means ± standard deviation and ranges, and categorical variable was expressed as percentages. Parametric variables was analysed by independent Student’s t-test and continuous measurements by ANOVA for repeated measures. Factors associated with the 6MWD were evaluated using multivariate analysis and used to derive an equation which aimed to estimate the likely 6MWD from the variables. Data from another independent group of four patients were used to assess the reliability of the equation using linear regression to test for the evidence of any proportional bias. The level of significance threshold was set at p < 0.05. Tables and graphs were obtained using Microsoft excel spreadsheet and outcomes generated from SPSS.

3.12 Ethical issues

The data obtained were used for the purposes of the study only. Each participant was made to sign/thumbprint a written, informed consent form after reading a detailed explanation and/or receiving a verbal description of the procedures and protocols of the study. For participants who could not read, the study was explained to them in the language that they understood. The names of the participants were not used in the study for confidentiality reasons; instead codes
numbers were used. Ethical clearance was sort from the Ethical and Protocol Review Committee of the College of Health Sciences, University of Ghana.
CHAPTER FOUR

4.0 RESULTS

4.1 Demographic and Anthropometric data of participants

This study involved 72 participants comprising 36 SCD patients (13 males and 23 females) and 36 healthy controls (13 males and 23 females). The mean age of the SCD patients was 28.44 ± 6.29 years and that of the healthy controls was 28.44 ± 6.29 years. The SCD patients were made up of 89% homozygous SS and 13.9% heterozygous SC phenotype. In terms of educational level, 25% of the cases had achieved tertiary level education, 61.2% senior high school (SHS) education and 13.9% Junior high school (JHS) education. In the control group, 80.6% had achieved tertiary level education and 19.4% senior high school (SHS) education. (Table 4.1 and Table 4.2).

The mean difference in height between cases and controls respectively was not significant (1.68 ± 0.08m vs. 1.70 ± 0.07m; p = 0.137). However, there was significant difference in mean weight between cases and controls (56.64 ± 10.67kg vs. 62.51 ± 10.5kg; p = 0.021). The mean BMI (20.09 ± 3.19kg/m² vs. 21.4 ± 2.80kg/m²) was also not statistically significant between cases and controls (p = 0.060) (Table 4.2). In addition, 30.6% and 11.1% of cases and controls respectively were underweight. The percentage of cases (63.9%) with normal weight were the same as that of the controls (63.9%). The percentage of cases who were overweight and in class 1 obesity category were 2.8% and 2.8% respectively. In the control group, 25% were overweight and none was classified as obese (Table 4.3).
Table 4.1: Demographic data of Cases and Controls

<table>
<thead>
<tr>
<th>Demographics</th>
<th>Case n (%)</th>
<th>Control</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>13(36.1%)</td>
<td>13(36.1%)</td>
</tr>
<tr>
<td>Female</td>
<td>23(63.9%)</td>
<td>23(63.9%)</td>
</tr>
<tr>
<td>Type of SCD (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>HbSS</td>
<td>31(86.19%)</td>
<td></td>
</tr>
<tr>
<td>HbSC</td>
<td>5(13.9%)</td>
<td></td>
</tr>
<tr>
<td>Educational level (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tertiary</td>
<td>9(25%)</td>
<td>29(80.6%)</td>
</tr>
<tr>
<td>SHS</td>
<td>22(61.2%)</td>
<td>7(19.4%)</td>
</tr>
<tr>
<td>JHS</td>
<td>5(13.9%)</td>
<td>0(0%)</td>
</tr>
</tbody>
</table>

Data presented as percentages

Table 4.2: Demographic and Anthropometric data of Cases and Controls

<table>
<thead>
<tr>
<th>Demographics/anthropometric</th>
<th>Case</th>
<th>Control</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>28.44 ± 6.29</td>
<td>28.44±6.29</td>
<td>1.00</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>56.64 ± 10.67</td>
<td>62.51± 10.51</td>
<td>0.021*</td>
</tr>
<tr>
<td>Height (m)</td>
<td>1.68 ± 0.08</td>
<td>1.70 ± 0.07</td>
<td>0.137</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>20.09 ± 3.19</td>
<td>21.4 ± 2.80</td>
<td>0.060</td>
</tr>
</tbody>
</table>

Quantitative values are expressed as mean ± standard deviation

* Significance at p < 0.05
Table 4.3: Classification of participants by BMI

<table>
<thead>
<tr>
<th>BMI Classification</th>
<th>Case n (%)</th>
<th>Control n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Underweight</td>
<td>11 (30.6)</td>
<td>4 (11.1)</td>
</tr>
<tr>
<td>Normal weight</td>
<td>23 (63.9)</td>
<td>23 (63.9)</td>
</tr>
<tr>
<td>Overweight</td>
<td>1 (2.8)</td>
<td>9 (25)</td>
</tr>
<tr>
<td>Obesity Class 1</td>
<td>1 (2.8)</td>
<td>0 (0)</td>
</tr>
</tbody>
</table>

Data presented as percentages

4.2 Clinical history of SCD patients

Most SCD patients had history of crisis (91.7%), whiles 8.3% had no known history of crisis.

The type of crisis encountered by the SCD patients in this study were bone pain, chest pain, back pain (vaso-occlusive crisis) and anaemia with Hb < 5g/dl (haemolytic crisis). Moreover, 38.9% of SCD patients had no history of blood transfusion. For those who had history of blood transfusion, the period ranged from 1 to 6 months (16.7%), 1 to 5 years (22.2%), 6 to 10 years (11.1%) and 11 to 20 years or greater (11.1%). These are summarised in Table 4.4.

Majority of the SCD patients (69.4%) also confirmed that, they have had crisis within the last 12 months. The mean number of crisis that required did not require emergency or hospital admission was 2.9 ± 1.97 and that which required admission was 1.74 ± 1.20. In addition, days off from school or work due to crisis was 7.33 ± 4.56 days (Table 4.5).

Regarding medication, all SCD patients were taking folic acid. Drugs taken by the patients in addition to the folic acid were multivitamins (47.2%), analgesics (11.1%), hydroxyurea (5.6%), food supplements (5.6%) and herbal preparations (11.1%). However, 75% took their medication regularly (compliant) whiles 25% of SCD patients were either not regularly taking their medication or had stopped entirely (noncompliant) (Table 4.6).
Table 4.4: SCD patients’ history on crisis and blood transfusion

<table>
<thead>
<tr>
<th>Last Crisis</th>
<th>n (%)</th>
<th>Type of Crisis</th>
<th>Last Blood Transfusion</th>
<th>n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1-3months</td>
<td>13 (36.1%)</td>
<td>Joint pain</td>
<td>No transfusion</td>
<td>14 (38.9%)</td>
</tr>
<tr>
<td>4-8months</td>
<td>9 (25%)</td>
<td>Chest pain</td>
<td>1-6months</td>
<td>6 (16.7%)</td>
</tr>
<tr>
<td>1-2yrs</td>
<td>8 (22.2%)</td>
<td>Back pain</td>
<td>1-5yrs</td>
<td>8 (22.2%)</td>
</tr>
<tr>
<td>3-5yrs</td>
<td>3 (8.3%)</td>
<td>Haemolytic</td>
<td>6-10yrs</td>
<td>4 (11.1%)</td>
</tr>
<tr>
<td>No crisis</td>
<td>3 (8.3%)</td>
<td></td>
<td>11-20yrs or ≥</td>
<td>4 (11.1%)</td>
</tr>
</tbody>
</table>

Data presented as percentages

Table 4.5: Outcome of crisis in SCD patients

<table>
<thead>
<tr>
<th>Variables</th>
<th>Number of respondents</th>
<th>Percentage (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Have you had crisis in the last 12 months?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(n = 36)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>– Yes</td>
<td>25</td>
<td>69.4</td>
</tr>
<tr>
<td>– No</td>
<td>11</td>
<td>30.6</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Variables</th>
<th>Mean ± SD</th>
<th>Min – Max</th>
</tr>
</thead>
<tbody>
<tr>
<td>How many crisis that did NOT require hospital or emergency room admission?</td>
<td>2.90 ± 1.97</td>
<td>1 – 7</td>
</tr>
<tr>
<td>How many crisis that DID require hospital or emergency room admission?</td>
<td>1.74 ± 1.20</td>
<td>1 – 5</td>
</tr>
<tr>
<td>How many days crisis made you miss school/work?</td>
<td>7.33 ± 4.56</td>
<td>2 – 15</td>
</tr>
</tbody>
</table>

Data presented as frequencies, percentages, mean ± standard deviation and maximum and minimum values.
Table 4.6: SCD patients’ medication and its compliance

<table>
<thead>
<tr>
<th>Taking Medication</th>
<th>n (%)</th>
<th>Type of Medication</th>
<th>n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Compliant</td>
<td>27(75%)</td>
<td>Folic acid</td>
<td>36(100%)</td>
</tr>
<tr>
<td>Noncompliant</td>
<td>9(25%)</td>
<td>Multivitamins</td>
<td>17(47.2%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Analgesics</td>
<td>4(11.1%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Hydroxyurea</td>
<td>2(5.6%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Food supplement</td>
<td>2(5.6%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Herbal medication</td>
<td>4(11.1%)</td>
</tr>
</tbody>
</table>

Data presented as percentages

4.3 Haemoglobin levels (Hb) of cases and controls

The haemoglobin levels (Hb) for SCD patients’ males and females were (8.60 ± 1.27)g/dl and 9.84 ± 1.75g/dl respectively and this was significant (p = 0.002). Moreover, in the healthy control males and females, their Hb were 12.82 ± 0.69g/dl and 14.11 ± 0.56g/dl respectively and was also statistically significant (p < 0.001) (Table 4.7). The haemoglobin levels (Hb) was significantly lower in the cases (9.05 ± 1.56g/dl) than the controls (13.28 ± 0.89g/dl) (p = 0.05) as shown in table 4.8.

Table 4.7: Haemoglobin levels (Hb) of Cases and Controls by Gender in g/dl

<table>
<thead>
<tr>
<th>Gender</th>
<th>Female</th>
<th>Male</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Case</td>
<td>8.60 ± 1.27</td>
<td>9.84 ± 1.75</td>
<td>0.002*</td>
</tr>
<tr>
<td>Control</td>
<td>12.82 ± 0.69</td>
<td>14.11 ± 0.56</td>
<td>&lt; 0.001*</td>
</tr>
</tbody>
</table>

Data are expressed as mean ± standard deviation

*The level of significance was set at p < 0.05
Table 4.8: Haemoglobin levels (Hb) for case and control in g/dl

<table>
<thead>
<tr>
<th></th>
<th>Cases</th>
<th>Controls</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hb (g/dl)</td>
<td>9.05 ± 1.56</td>
<td>13.28 ± 0.89</td>
<td>&lt;0.001*</td>
</tr>
</tbody>
</table>

Data are expressed as mean ± standard deviation

*The level of significance was set at p < 0.05

4.4 Exercise practices and barriers in SCD patients and healthy controls

Although 52.8% said they undertake physical exercise, 36.8% rarely did so and 31.6% exercise 1 to 2 times per week. For those who do not do any physical exercise (47.2%), 82.4% had no reason for not exercising whiles 17.6% stated fear of eliciting crisis as the reason for not doing any form of physical exercise. Additionally, 68.4% of the SCD patients who exercise complain of experiencing either pain in the leg, chest, bone or back whenever they exercise and they managed these pains with on the counter analgesics (81.8%) and rest (18.2%). The frequency of crisis and physical exercise habits are summarised in table 4.8.

Majority of the healthy controls (83.3%) stated that they undertake physical exercises, with 63.3% exercising one to three times or more per week. However, 26% rarely did any form of physical exercise. The physical exercises performed by these participants were jogging, fast walking, football, skipping, push-ups, swimming, squatting and weight lifting. The non-exercising group (16.7%) stated not getting enough time, feeling lazy, lack of interest and nothing as their reasons for not doing any physical exercise (Table 4.9).
Table 4.9: Exercise habits in SCD patients

<table>
<thead>
<tr>
<th>Variables</th>
<th>Number of respondents</th>
<th>Percentage (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Do you exercise? (n = 36)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Yes</td>
<td>19</td>
<td>52.8</td>
</tr>
<tr>
<td>- No</td>
<td>17</td>
<td>47.2</td>
</tr>
<tr>
<td>If yes, how often do you exercise?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>- 1 - 2x per week</td>
<td>6</td>
<td>31.6</td>
</tr>
<tr>
<td>- Once per month</td>
<td>6</td>
<td>31.6</td>
</tr>
<tr>
<td>- Rarely</td>
<td>7</td>
<td>36.8</td>
</tr>
<tr>
<td>If no, what prevents you from exercising?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Fear of crises</td>
<td>3</td>
<td>17.6</td>
</tr>
<tr>
<td>- Nothing</td>
<td>14</td>
<td>82.4</td>
</tr>
<tr>
<td>When you exercise do you feel pain or discomfort in any part of your body?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Yes</td>
<td>13</td>
<td>68.4</td>
</tr>
<tr>
<td>- No</td>
<td>6</td>
<td>31.6</td>
</tr>
<tr>
<td>If yes, which part of your body do you feel the pain? (n=13)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Bone pain</td>
<td>2</td>
<td>15.4</td>
</tr>
<tr>
<td>- Chest pain</td>
<td>3</td>
<td>23.1</td>
</tr>
<tr>
<td>- Leg pain</td>
<td>6</td>
<td>46.2</td>
</tr>
<tr>
<td>- Back pain</td>
<td>2</td>
<td>15.4</td>
</tr>
<tr>
<td>How do you manage the pain or discomfort?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Analgesics</td>
<td>9</td>
<td>81.8</td>
</tr>
<tr>
<td>- Rest</td>
<td>2</td>
<td>18.2</td>
</tr>
</tbody>
</table>

Data presented as frequencies and percentages.
Table 4.10: Exercise practices in healthy controls

<table>
<thead>
<tr>
<th>Variables</th>
<th>Number of respondents</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Do you exercise? (n=36)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>– Yes</td>
<td>30</td>
<td>83.3</td>
</tr>
<tr>
<td>– No</td>
<td>6</td>
<td>16.7</td>
</tr>
<tr>
<td>If yes, how often do you exercise? (n=30)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>– 3x or more per week</td>
<td>4</td>
<td>13.3</td>
</tr>
<tr>
<td>– 1 - 2x per week</td>
<td>15</td>
<td>50.0</td>
</tr>
<tr>
<td>– Once per month</td>
<td>3</td>
<td>10.0</td>
</tr>
<tr>
<td>– Rarely</td>
<td>8</td>
<td>26.7</td>
</tr>
</tbody>
</table>

Data presented in frequencies and percentages

4.5 Godin Leisure-Time Exercise Questionnaire interpretation for case and control

When participants were also assessed subjectively concerning their weekly activity level, it was found out that, majority of the SCD patients were either sedentary (33.3%) or moderately active (41.7%) with an average score of (16.75 ± 9.05) whiles the controls were in the moderately active (33.3%) or active (47.3%) category with an average score of (25.61 ± 14.80) Table 6a. Again concerning their activity level, 38.9% of SCD patients stated that they engage in activities within the week that make them sweat often, whiles 52.8% of healthy controls said they sweat often. However, 36.1% of patients claimed they sometimes engage in activities that make them sweat and 25% rarely sweat because they seldom engage in physical activities. It was also noted that the healthy controls who sometimes engage in physical activity to make them sweat within the week or rarely sweat were 33.3% and 19.4% respectively. The above are presented in Table 4.10 and Table 4.11 below.
Table 4.11: Godin weekly leisure-time activity for case and control

<table>
<thead>
<tr>
<th></th>
<th>Score (Mean ± SD)</th>
<th>Interpretation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Case</td>
<td>16.75 ±9.05</td>
<td>Moderate</td>
</tr>
<tr>
<td>Control</td>
<td>25.61 ± 14.80</td>
<td>Active</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Godin scale</th>
<th>Case n (%)</th>
<th>Control n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Active</td>
<td>9 (25%)</td>
<td>17 (47.2%)</td>
</tr>
<tr>
<td>Moderate</td>
<td>15 (41.7%)</td>
<td>12 (33.3%)</td>
</tr>
<tr>
<td>Sedentary</td>
<td>12 (33.3%)</td>
<td>7 (19.4%)</td>
</tr>
</tbody>
</table>

Data presented as frequencies and percentages; means ± standard deviation

Table 4.12: How often participants engage in any regular activity in their leisure time

<table>
<thead>
<tr>
<th></th>
<th>Case n (%)</th>
<th>Control n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Often</td>
<td>14 (38.9%)</td>
<td>19 (52.8%)</td>
</tr>
<tr>
<td>Sometimes</td>
<td>13 (36.1%)</td>
<td>9 (25%)</td>
</tr>
<tr>
<td>Never/ Rarely</td>
<td>9 (25%)</td>
<td>8 (22.2%)</td>
</tr>
</tbody>
</table>

Data presented as frequencies and percentages

4.6 Cardiopulmonary response for case and control during the 6MWT

4.6.1 Systolic blood pressure (SBP)

The mean baseline SBP for the cases was 104.17±10.94mmHg. This increased at the end of the 6MWD (126.44±13.85mmHg) and then decreased at 5minutes (108.33±9.13mmHg) and 10minutes (104.89±9.63mmHg) after the test. The control group also recorded a baseline SBP of 111.44±9.84mmHg and an increase at the end of the 6MWD (136.92±22.59mmHg). There was a subsequent decrease at 5minutes (111.83±8.73mmHg) and 10minutes (107.33±7.67mmHg) respectively (Figure 4.1).
4.6.2 Diastolic blood pressure (DBP)

The mean DBP also followed a similar trend as in the SBP in that, the baseline DBP for cases was 66.17±8.18mmHg and this increased at the end of the 6MWD (76.89±7.98mmHg) and further decreased at 5minutes (69.78±6.84mmHg) and 10minutes (67.00±6.89mmHg). The same applied to the controls (baseline - 68.44±7.60mmHg, end of 6MWD - 80.67±6.63mmHg, 5minutes - 80.67±6.63mmHg and 10minutes - 71.07±7.46mmHg) (Figure 4.2).
4.6.3 Heart rate (HR)

The mean HR for the cases at baseline was 80.44±9.79bpm and this increased to 109.78±11.87bpm at the end of the test; there was however a decrease at 5minutes (86.36±9.27bpm) and 10minutes (82.56±9.31bpm) after the test. The control group (baseline – 74.22±10.23bpm, end of test – 109.53±17.61bpm, 5minutes after test – 85.67±13.37bpm and 10minutes after test – 80.36±10.40bpm also followed the similar changes as in the cases (Figure 4.3).
### 4.6.4 Peripheral oxygen saturation (SPO$_2$)

The mean baseline SPO$_2$ for the cases and controls were 97.19±2.29% and 98.75±0.97% respectively. This however decreased at the end of the 6MWD for cases (95.11±3.70%) and controls (97.39±1.40%). This then increased at 5minutes (96.58±3.20%) and also at 10minutes (97.47±2.38%) for the cases. There was an increase in the SPO$_2$ at 5minutes (98.78±0.99%) after the 6MWD and a slight decrease at 10minutes (98.14±3.74%) for the control group (Figure 4.4).

*Figure 4.3: Line graph illustrating mean HR for cases and controls during the 6MWT. The mean Heart rate of participants increased at the end of the 6MWT. A continuous reduction in the HR was noted after the end of the test up to 5mins and 10mins after the test. Similar values were recorded at the end of the test to 10mins after the test in healthy adults control group and adult SCD patients.*
4.6.5 Peak expiratory flow rate (PEFR)

There was a decrease in the mean PEFR from baseline (344.44±73.71L/min) to the end of the test (340.47±81.58L/min) in the cases. This however, increased at 5 and 10 minutes after the test (353.47±71.25L/min and 358.06±74.47L/min) respectively. There was a continuous increase in the controls from baseline to up to 10 minutes after the test (455.56±90.88L/min, 456.94±93.89L/min, 467.22±94.03L/min and 481.11±92.21L/min respectively) (Figure 4.5).
Moreover, SCD patients with normal airways (green zone) walked longer distances 574.78 ± 59.14 m than those with narrowing airways (yellow zone) 543.11 ± 63.72 m; (p = 0.198). In the healthy controls also, those with normal airways walked longer distances (676.15 ± 73.36 m) than those with narrowing airways (638.44 ± 96.69 m) p = 0.226 as shown in Figure 4.6.

The healthy control group recorded higher values in PEFR than the SCD patients throughout the test. There was a continuous increase in the mean PEFR from the end of the test up to 10 mins after the test in both groups.

Moreover, SCD patients with normal airways (green zone) walked longer distances 574.78 ± 59.14 m than those with narrowing airways (yellow zone) 543.11 ± 63.72 m; (p = 0.198). In the healthy controls also, those with normal airways walked longer distances (676.15 ± 73.36 m) than those with narrowing airways (638.44 ± 96.69 m) p = 0.226 as shown in Figure 4.6.

Participants with PEFR indicating normal airways (green zone) walked longer distance than those with narrowed airways (yellow zone) in both cases and controls.
4.7 Modified Borg (Dyspnoea and Rate of perceived exertion (RPE) and Angina ratings in the 6MWT

Baseline values for both cases and controls in the dyspnoea and RPE were 0 and 6 respectively. However, there was a significant difference in the Borg scales at the end of the 6MWD between the cases and controls respectively (dyspnoea: 0.32±0.62 vs. 0.01±0.83; p = 0.005) and (RPE: 12.61±1.02 vs. 11.78±0.87; p < 0.001). They then returned to baseline values 5 and 10 minutes after the test. There was also no complain of chest pain (angina) before, during and after the test by both cases and controls (Table 4.12). In addition, none of the participants reported any adverse event as a result of the 6MWT during 24hours and 72hours up to one week after the test.

Table 4.13: Modified Borg and Angina scale for case and control SCD in the 6MWT

<table>
<thead>
<tr>
<th>Variables</th>
<th>Moment</th>
<th>Cases</th>
<th>Control</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Baseline</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Borg D</td>
<td>End of test (six minute)</td>
<td>0.32±0.62</td>
<td>0.01±0.83</td>
<td>0.005*</td>
</tr>
<tr>
<td></td>
<td>5mins after test</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td></td>
<td>10mins after test</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Borg</td>
<td>Baseline</td>
<td>6</td>
<td>6</td>
<td></td>
</tr>
<tr>
<td>(RPE)</td>
<td>End of test (six minute)</td>
<td>12.61±1.02</td>
<td>11.78±0.87</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td></td>
<td>5mins after test</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td></td>
<td>10mins after test</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Angina</td>
<td>Baseline</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td></td>
<td>End of test (six minute)</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td></td>
<td>5mins after test</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td></td>
<td>10mins after test</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
</tbody>
</table>

Abbrev: D: Dyspnoea, RPE: rate of perceived exertion  Data presented as mean ± standard deviations
*Significance at p < 0.05
4.8 Correlation between parameters in the 6MWT of SCD patients

The association between the various parameters showed that, there was a significant correlation between haemoglobin level and oxygen consumption, metabolic equivalent and peak expiratory flow rate at baseline to 5 minutes after the test, PEFR baseline and oxygen saturation at 10mins (r = 0.409, 0.400, 0.417, 0.317; p < 0.05 respectively). There was also a positive correlation between Hb and SPO₂ values, Hb and PEFR values, PEFR\textsubscript{END} and SPO₂ values, 6MWD and PEFR\textsubscript{BL, END, \text{10MIN}} and then RPE and dyspnoea but these were not significant (p > 0.05). However, a negative correlation was also seen between MET and RPE (r = -0.132), MET and BMI (r = -0.195), 6MWD and RPE (r = -0.138) and RPE and VO₂ (r = -0.135) but these were also not significant (p > 0.05). The correlation between the various parameter are summarised in Table 4.13 and Table 4.14.
Table 4. 14: Correlation between parameters in the 6MWT

<table>
<thead>
<tr>
<th>Variables</th>
<th>Correlation (r)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hb vs. VO$_2$</td>
<td>0.409</td>
<td>0.013*</td>
</tr>
<tr>
<td>MET vs PEFR$_{BL}$</td>
<td>0.400</td>
<td>0.016*</td>
</tr>
<tr>
<td>MET vs PEFR$_{END}$</td>
<td>0.417</td>
<td>0.012*</td>
</tr>
<tr>
<td>MET vs PEFR$_{5MIN}$</td>
<td>0.317</td>
<td>0.026*</td>
</tr>
<tr>
<td>MET vs. RPE</td>
<td>-0.132</td>
<td>0.455</td>
</tr>
<tr>
<td>MET vs. BMI</td>
<td>-0.195</td>
<td>0.254</td>
</tr>
<tr>
<td>PEFR$_{BL}$ vs. SPO$_2$(10MIN)</td>
<td>0.330</td>
<td>0.049*</td>
</tr>
<tr>
<td>6MWD vs. PEFR$_{BL}$</td>
<td>0.073</td>
<td>0.671</td>
</tr>
<tr>
<td>6MWD vs. PEFR$_{END}$</td>
<td>0.034</td>
<td>0.844</td>
</tr>
<tr>
<td>6MWD vs. PEFR$_{10MIN}$</td>
<td>0.130</td>
<td>0.452</td>
</tr>
<tr>
<td>6MWD vs. RPE</td>
<td>-0.138</td>
<td>0.422</td>
</tr>
<tr>
<td>RPE vs. VO$_2$</td>
<td>-0.135</td>
<td>0.432</td>
</tr>
<tr>
<td>RPE vs. Dyspnoea</td>
<td>0.253</td>
<td>0.136</td>
</tr>
</tbody>
</table>

Hb: haemoglobin level, VO$_2$: oxygen consumption, PEFR: peak expiratory flow rate, MET: metabolic equivalent, SPO$_2$: peripheral oxygen saturation, RPE: rate of perceived exertion, BMI: body mass index, 6MWD: six minute walk distance, BL: baseline, END: end of 6MWD, 5MIN: five minute after 6MWD, 10MIN: ten minutes after 6MWD

Pearson correlation coefficient (r)

*P value significant at < 0.05
Table 4.15: Correlation between parameters in the 6MWT

<table>
<thead>
<tr>
<th>Variables</th>
<th>Correlation (r)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hb vs. SPO&lt;sub&gt;2(BL-10MIN)&lt;/sub&gt;</td>
<td>0.268, 0.248, 0.250, 0.240</td>
<td>&gt; 0.05</td>
</tr>
<tr>
<td>Hb vs. PEFR&lt;sub&gt;(BL-10MIN)&lt;/sub&gt;</td>
<td>0.319, 0.320, 0.237, 0.321</td>
<td>&gt; 0.05</td>
</tr>
<tr>
<td>PEFR&lt;sub&gt;END&lt;/sub&gt; vs SPO&lt;sub&gt;2(BL-10MIN)&lt;/sub&gt;</td>
<td>0.137, 0.038, 0.009, 0.206</td>
<td>&gt; 0.05</td>
</tr>
</tbody>
</table>

Hb: haemoglobin level, PEFR: peak expiratory flow rate, SPO<sub>2</sub>: peripheral oxygen saturation, BL-10MIN: baseline up to ten minutes after 6MWD

Pearson correlation coefficient (r)

*P value significant at < 0.05

4.9 Prediction equation for the 6MWD for Sickle cell disease patients

By using multivariate analysis, the dyspnoea value at the end of the 6MWD (DE) (p = 0.001; β: - 0.659) and the body mass index (BMI - kg/m<sup>2</sup>) (p = 0.005; β: -0.492) were found to be factors that predicted the six minute walked distance (6MWD) but were negatively associated.

An equation was therefore derived using the stepwise method to estimate the distance walked by the SCD patients: 6MWD = 746.302 – (DE x 60.714) – (BMI x 8.451) expressed in metres.

The correlation between the actual 6MWD and estimated 6MWD according to the Pearson correlation was 0.544. The reliability of the equation was also assessed using data from another independent group of four SCD patients and this test showed that there was no proportional bias in the equation hence the equation was reliable (p = 0.143).

4.10 VO<sub>2</sub> and MET of cases and controls in the 6MWD

The mean estimated VO<sub>2</sub> 12.69±1.07ml.kg<sup>-1</sup>.min<sup>-1</sup> vs. 14.63±1.33ml.kg<sup>-1</sup>.min<sup>-1</sup> and MET 3.60±0.30METs vs. 4.18±0.38METs differed significantly (p <0.001 and <0.001 respectively) between cases and controls as shown in table 4.15.
Table 4.16: VO\textsubscript{2} and MET of cases and controls in the 6MWD

<table>
<thead>
<tr>
<th>Variables</th>
<th>Case</th>
<th>Control</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>VO\textsubscript{2} (ml.kg\textsuperscript{-1}.min\textsuperscript{-1})</td>
<td>12.69±1.07</td>
<td>14.63±1.33</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>MET (METs)</td>
<td>3.60±0.30</td>
<td>4.18±0.38</td>
<td>&lt;0.001*</td>
</tr>
</tbody>
</table>

Data presented as mean ± standard deviation

MET: metabolic equivalents, VO\textsubscript{2}: oxygen consumption

*Significance at p < 0.05

4.11 The Six minute walked distance (6MWD)

All 72 participants successfully completed the 6MWD without stopping for any reason. The difference in the mean 6MWD between cases (551.03±63.32)m and controls (666.72±80.06)m was statistically significant (p<0.001) (Table 4.16). There was a significant difference in the mean distance covered by males and females among SCD patients (611.69±33.17)m vs. (516.74±48.73)m: p<0.001). A significant difference was also noted between males and females in the healthy controls as well (722.67±69.05)m vs. (635.13±68.60)m: p = 0.001) (Table 4.17).

Table 4.17: Six minute walked distance (6MWD) for cases and controls

<table>
<thead>
<tr>
<th>Variables</th>
<th>Case</th>
<th>Control</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>6MWD (m)</td>
<td>551.03±63.32</td>
<td>666.72±80.06</td>
<td>&lt;0.001*</td>
</tr>
</tbody>
</table>

Data presented as mean ± standard deviation

*Significance at p < 0.05

Table 4.18: 6MWD (m) by gender for cases and controls

<table>
<thead>
<tr>
<th>Participants</th>
<th>Female</th>
<th>Male</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Case</td>
<td>516.74±48.73</td>
<td>611.69±33.17</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>Control</td>
<td>635.13±68.60</td>
<td>722.67±69.05</td>
<td>0.001*</td>
</tr>
</tbody>
</table>

Data presented as mean ± standard deviation

*Significance at p < 0.05
CHAPTER FIVE

5.0 DISCUSSION, CONCLUSIONS, LIMITATION AND RECOMMENDATIONS

5.1 DISCUSSION

5.1.1 Demographic and Anthropometric characteristics of SCD patients

This study evaluated exercise tolerance in sickle cell disease (SCD) patients. A higher proportion of the SCD patients were HbSS phenotype compared to HbSC individuals and also more females than males. Fewer SCD patients in this study have also achieved tertiary education compared to majority of the control group. Matthie et al. (2015) also stated that SCD patients are less likely to be educated because of complications associated with the condition.

The heights of SCD patients did not vary much with that of healthy controls. However, significant differences in the weight between cases and controls in this study confirms with literature (Adewoyin, 2015). In that, almost a third of the SCD patients were underweight compared to a small number of their healthy colleagues. However, one study in Nigeria reported a fewer proportion of adult SCD patients being underweight (Ajayi et al., 2017) with majority having normal weight, 26.5% overweight and 10.7% being obese. Compared to our study, where a higher proportion had normal weight and very few being overweight and obese, there is a possibility that geographical location had caused this wide differences.

5.1.2 Clinical History of Adult SCD patients.

A greater number of Adult SCD patients had history of crisis within twelve months prior to the study. Some did not go on admission and others were on hospital admission for some days due
to crisis. Again, some patients also missed school or work during their crisis period which is similar to the number of days reported by Bölke and Scherer (2012) and reported pain involving the bone and back (vaso-occlusive crisis) as the most common type of crisis followed by chest pain (acute chest syndrome) and haemolytic crisis (Bölke & Scherer, 2012; Ahmed & Ibrahim, 2017). Thus, frequent crisis in SCD patients could result in poor health and have significant impact on their education and could also result in job losses (Matthie et al., 2015).

Another study reported that, school absenteeism and poor academic achievement were profound for adult patients with SCD and there was a significant difference in the school absenteeism between SCD patients and their healthy siblings (Idowu et al., 2014a). The same authors in another study observed that, out of 80% of the SCD patients who previously had a job, only 25% were employed at the time of their study (Idowu et al., 2014b). The number of days-off could have also suggested the severity of the crisis.

In addition, SCD patients were aware that they should be on medication, but 25% were not taking their medication or had stopped. They gave reasons such as being that, they were not getting ‘sick’ often or were not getting sick at all. Another reason could have been that they forget to taken the medication and had also lost interest in taking the medication or ‘were tired of taking the medication’. Folic acid, which is the most widely known and prescribed drug for sickle patients because of anaemia and was being taken by all adult SCD patients. Moreover, some patients were also taking multivitamins in addition to the folic acid. With the exception of hydroxyurea, drugs taken by patients in this study (folic acid, multivitamins, analgesics) were among the top ten commonly prescribed drugs for SCD patients in Ghana (Nsiah et al., 2014). Hydroxyurea (hydroxcarbamide), which is now the gold standard of treatment for patients with sickle cell disease (Matte et al., 2019) was being used by only a small number of patients in this study. The possible reason for using this drug was that, these patients had
frequent crisis and recurrent severe anaemia which required blood transfusion and the same reason was given by McGann et al., (2016). This could confirm that, hydroxyurea is still not a popular treatment drug for patients with sickle cell disease in Ghana (Asare et al., 2018). Analgesics such as paracetamol and diclofenac tablets were usually taken by patients to manage pain which occurred due to crisis or after exercise. Furthermore, some patients were taking ‘food supplements’ and local herbal medicine in addition to their routine drugs prescribed by the doctor. The use of herbal medicine in the management of SCD in most West African countries has been established (Busari & Mufutau, 2017). This could give the clue that, traditional beliefs still play a role in the management of sickle cell disease.

5.1.3 Haemoglobin levels in SCD patients

The mean Hb level for adult SCD patients was consistent with the range of values for sickle cell patients provided by Quinn (2016). This is also within the normal range for SCD patients in Ghana (Antwi-Boasiako et al., 2018). In addition, Hb for healthy controls in this study was within the normal range for healthy Ghanaians (Table 2.3). Patients with SCD have lower basal Hb values due to abnormal haemoglobin with shorter lifespan and frequent haemolytic crisis (Hänggi et al., 2014; Maakaron, 2019). During exercise, the demand for oxygen for the use of metabolic activities to release energy is increased (Burtscher, 2013) but however, the oxygen carrying capacity of red blood cells (RBCs) is reduced during exercise in patients such as those with SCD due to reduced Hb levels or chronic anaemia which could lead to exercise intolerance (Badireddy & Baradhi, 2019) as was demonstrated in this study. In addition, chronic anaemia is known to cause increased cardiac demand and decreased oxygen saturation which result in reduced exercise capacity in SCD patients (Ramos, 2017). However, despite these explanations with Hb and SPO2, there was no significant correlation between Hb and SPO2 among SCD patients in this study.
5.1.4 Exercise practices and barriers in SCD patients

Majority of the SCD patients who undertook physical exercise complained of pain in the bone, leg and back whenever they did an exercise. Karlson et al., (2016) stated pain as a factor that limits SCD patients from engaging in physical activity. This might by linked to the reason why although majority claimed to exercise, a small proportion actually engage in physical exercise once or twice per week. Moreover, few of them complained of fear of eliciting crisis as the reason for not exercising. Interestingly, a higher percentage of adult SCD patients had no reason for not engaging in physical exercise. From the above statements the frequency of crisis, fear of eliciting crisis during exercises, pain after exercising and not exercising for no reason could suggest why most SCD patients in this study lived sedentary lifestyles or were moderately active according to subjective assessment from the Godin scale. On the contrary, one study that sought to investigate the relationship between pain and physical activity among children with SCD revealed that lower physical activity was associated with greater pain during the same day and the next day and less pain the next day was associated with patients who engaged in more physical activity (Karlson et al., 2016). Botelho et al., (2017) also indicated that combined physical activity in adult SCD patients could help reduce pain among this population. This means that, with the right approach to exercise, patients with SCD could benefit from the pain relieving aspect associated with exercise.

5.1.5 Cardiopulmonary response in the 6MWT

5.1.5.1 Systolic and diastolic pressure (SBP and DBP)

The rise in SBP and DBP at the end of 6MWD and their subsequent reduction during a resting period of 5 and 10 minutes is the usual expectation in the 6MWT as shown in literature. A study by Hostyn et al., (2013) in children and adolescents with sickle cell disease and
healthy children (Oliveira et al., 2013) showed that, the increase in SBP and DBP and their subsequent reduction 10 minutes after the test was not much compared to adult SCD patients and healthy controls in this study. Studies have also shown that, a SBP >175mmHg in a moderate intensity exercise increases the tendency of developing hypertension (Schultz & Sharman, 2013). The SBP in SCD patients at the end of the 6MWT was within the normal range, indicating that SCD patients in this study did not exhibit signs of pathology in terms of SBP. Benneh-Akwasi et al., (2018) have also reported a high prevalence of relative systemic hypertension in SCD patients in Ghana. However, in this study, normal baseline mean SBP and DBP were noted among the SCD patients. The healthy control group were also within the normal range. In addition, the DBP for SCD patients at the end of the test was far below the ≥ 110mmHg (Schultz & Sharman, 2013) to predict future pathology and mortality.

5.1.5.2 Heart rate (HR)

The HR followed a similar pattern of increase and decrease as in the blood pressures. Sickle cell disease patients were expected to have a HR of between 60% to 75% of the predicted maximum HR in a moderate intensity exercise (Crookham, 2013). The maximum HR in this study for SCD patients which was achieved at the end of the 6MWD was within safe range although there was a wide margin between the predicted and actual value. Moreover, the heart rates in SCD patients was also higher than that of the healthy controls although it was only significant at the baseline. Gladwin and Sachdev (2012) asserted that this increase in HR is expected in SCD patients since they usually have cardiovascular abnormalities. Tuncer et al., (2009) also observed a higher HR in SCD patients compared to healthy individuals during a limited physical activity when they were assessed with 24-hour ambulatory Holter and attributed it to chronic anaemia which was also noted in this study.
Studies have also shown that, adaptive mechanisms such as increased heart rate (HR) and decreased peripheral vascular resistance is known to occur in SCD patients to prevent further reduction in oxygen saturation during exercise (Melo et al., 2017). This could cause a decrease in resistance of sickled RBCs in capillary circulation and oxygen supply allowing close to normal saturation in the mixed venous blood (Hostyn et al., 2013). The decrease in HR ten minutes after the test in this study and hence a decrease in blood pressure (SBP and DBP) could have also resulted in the recovery of the SPO$_2$ to normal resting state in this study.

5.1.5.3 Peripheral oxygen saturation (SPO$_2$)

Liberto et al (2016) stated an SPO$_2$ < 88% could indicate the extent of exertion in SCD patients during the 6MWT. However, the decrease in SPO$_2$ in this study at the end of the 6MWD in SCD patients was not enough to induce any physiological abnormalities. The decrease in SPO$_2$ during exercise has been associated with the severity of anaemia and haemolysis in SCD patients (Waltz et al., 2013). Normal range of values have been reported among SCD children who undertook the 6MWT (Hostyn et al., 2013; Dedeken et al., 2014; Melo et al., 2017). Moreira et al (2014), reported about 4% decrease in SPO$_2$ among patients with chronic lung disease during a 6MWT. This study however found about 2% decrease in the SPO$_2$ which suggests a better outcome for SCD patients when compared with other population with chronic lung diseases. The minimum value attained in this study shows that, SPO$_2$ should be monitored in SCD patients in order to prevent desaturation.

5.1.5.4 Peak expiratory flow rate (PEFR)

The mean PEFR values in adult SCD patients was lower than that of the healthy controls in this study. Chest pain which also accounted for 22.2% of one of the types of crisis that affected SCD patients in this study could be an indication of ACS (Jain et al., 2017); together with
chronic lung diseases which is common among adult SCD patients (Miller & Gladwin, 2012) could have resulted in reduced lung function in the long term and hence might have contributed to the reduction in their PEFR. Previous studies involving teenagers (Adeniyi & Saminu, 2011) and children (Achigbu et al., 2015) were consistent with the above findings in our study with the conclusion that lung function parameters are impaired in SCD patients.

Hostyn et al., (2013) observed an increase in the PEFR values at the end of the test, up to 10 minutes after the 6MWD in children with SCD. Similar results were reproduced in our study among adult SCD patients and healthy controls. Some studies have also shown that, regular respiratory muscle training can increase a person’s tolerance or exercise capacity during aerobic exercises such as walking, running and cycling (Alibakhshi & Lores, 2015). Adeniyi and Saminu (2011) again found that SCD patients’ PEFR improved after breathing exercises. Our study also saw significant improvement in PEFR of SCD patients after the 6MWD. Therefore, exercise such as the 6MWT is beneficial in helping to improve PEFR in SCD patients. It can also be said that, effective expiration after inspiration (or ‘breath control’) forms an important part in one’s performance or tolerance to exercise.

Baseline PEFR variability interpretations (Mrindha et al., 2012) (American Lung Association, 2019) also showed that, SCD patients with normal variability (80% to 100%) walked longer distance than those with lower values (50% to 79%); thus, demonstrating the relationship between the PEFR values and the 6MWD but this was not statistically significant. Maji et al., (2015), also found a similar relationship in patients with COPD and was significant in their case. This significant association could be attributed to the fact that, obstruction in patients with COPD was more severe than SCD patients in our study.
Therefore, lower oxygen consumption, energy expenditure and PEFR during 6MWT contributed to the shorter distance walked by the SCD patients compared to the healthy control group in the study.

**5.1.6 Exertion and Dyspnoea perceptions in the 6MWD**

The score for the Borg rating of perceived exertion (RPE) which indicates fatigue level for case and control at the end of the 6MWT represent a moderate intensity score (normal range for moderate intensity is 11 to 14) (‘The Borg Scale of Perceived Exertion’, 2012; Williams, 2017). Moreover, SCD patients score for dyspnoea also implies moderate intensity on the Borg dyspnoea scale. The rate perceived exertion score in SCD patients and their health controls in an acute moderate exercise was 11 to 13, which is similar to our results (Hedreville et al., 2014).

Castro and colleagues (2008) reported a rather higher dyspnoea scale scores in adult SCD patients than in our study. This may be linked to the severity of lung impairments in SCD patients. In addition, high dyspnoea scores and low exertion perception was observed in obese individuals in a 6MWT (Gontijo et al., 2011) and this was contrary to what was seen in this study. Ijiri et al., (2014) and Maji et al., (2015) also found a correlation between dyspnoea rating and 6MWD in patients with COPD. In our study, dyspnoea scores predicted the distance walked by SCD patients. Thus, shorter distance walked in other populations could be associated with higher dyspnoea scores. This demonstrates an inverse relationship between dyspnoea and 6MWD.

All the moderate intensity values achieved in this study confirms that the six minute walk test is a moderate intensity exercise. Although SCD patients walked shorter distances compared to
their healthy counterparts, they were able to complete this test without any complications or adverse events. This suggests that, SCD patients can take part in moderate intensity exercise such as the 6MWT safely without any complications provided all protocols are observed appropriately.

5.1.7 Oxygen consumption and metabolic equivalents in the 6MWD

The amount of oxygen uptake (VO$_2$) during a physical activity determines the energy expenditure (MET) (Coelho-Ravagnani et al., 2013). The estimated oxygen consumption (VO$_2$) for the SCD patients was significantly lower than their healthy counterparts. Some studies have reported a decreased peak VO$_2$ in SCD patients compared with healthy individuals (Watson et al., 2015; Liem et al., 2015). In addition, Charlot et al., (2015) also reported a lower efficiency in oxygen consumption in adults with SCA compared with healthy controls in a submaximal incremental exercise and suggested that oxygen consumption is impaired in SCA patients during exercise. In another study Beers et al., (2014), reported a decrease in peak VO$_2$ which also significantly correlated with Hb levels in SCD patients in a cardiopulmonary exercise test. These findings are similar to what was achieved in this study. That is, there was a significant positive correlation between VO$_2$ and Hb in SCD patients in this study, suggesting that low Hb in SCD patients contributed in reduced VO$_2$ in SCD compared with their healthy controls. Lower VO$_2$ in SCD patients could have been due to lower PEFR as a result of possible lung impairments observed in this study.

Khuangsirikul et al., (2014) agrees with our use of the 6MWD in estimating the MET. The values obtained in this study is therefore an indication of a moderate intensity physical activity (normal range is 3 to 6MET) (Coelho-Ravagnani et al., 2013; WHO, 2018). There was a significant positive correlation between MET and PEFR$_{BL-5MIN}$ which could imply that,
impaired lung function seen in majority of SCD patients resulted in the moderate intensity MET values. This can be confirmed by a study conducted among patients with COPD whose MET value in a walking exercise was within a moderate intensity (Katajisto et al., 2012).

5.1.8 The Six Minute Walk Distance (6MWD)

The average total distance walked by SCD patients in this study was significantly shorter than that of the healthy controls (Table 4.12). The male SCD patients walked longer distance than the females. A study in the USA (Castro et al., 2008) among adult SCD patients also revealed that males walking longer distance than females. Another study in Brazil among SCD patients of African ethnicity (Ohara et al., 2014) also confirmed this distance comparison between males and females. These studies together with our study confirm that, gender play a role in the 6MWD and this does not only apply to healthy population but also in people with chronic illness such as SCD. In addition, the distance walked by SCD patients in Ghana in this study, was also higher than those in the USA and Brazil and also give the indication that geographical location may also play a role in the 6MWD. Adult Patients with other chronic conditions such as Obesity (Gontijo et al., 2011), neuromuscular conditions (Prahm et al., 2014), type 2 diabetes mellitus (Lee, 2018) and COPD (Ijiri et al., 2014; Tornatore et al., 2017) in other studies also covered shorter distances compared to SCD patients in this study. This may be attributed to the clinical severity in these conditions.

The shorter distance walked by adult SCD patients compared to healthy controls indicates their reduced tolerance to exercise. However, some studies have also reported reduced tolerance in the 6MWT in SCD patients compared to their healthy counterparts in children (Dedeken et al., 2014; Melo et al., 2017). This intolerance could be attributed to reduced lung function, low
haemoglobin levels, oxygen consumption and metabolic equivalents in SCD patients compared to healthy individuals.

Among the healthy adults, distances lower than that achieved in this study have been reported in different parts of Nigeria (Ajiboye et al., 2014; Mbada et al., 2015), Healthy Korean adults (Kim et al., 2014) and African Americans (Alqahtani, 2017). In contrast to these findings, studies in North Africa (Bourahli et al., 2016) have shown a higher walked distance than that in our study.

Most studies involving the 6MWT shown that, the 6MWD is usually influenced by age, gender, height, weight and BMI: it is directly related with age and height and inversely associated with weight and BMI. However, the factors that predicted the distance walked in the SCD patients in our study which also predicted the equation were the body mass index (BMI) and dyspnoea level at the end of the 6MWD. These variables were inversely related to the total walked distance and confirms the inverse relationship between 6MWD in other studies (Beekman et al., 2014; Melo et al., 2017). This could be attributed to the fact that weight was usually inversely related to the 6MWD and the BMI is proportional to the weight. Bourahli et al., (2016) however found that the BMI positively related to the 6MWD. Other variables that could possibly predict of the 6MWD among SCD patients in this study are Hb, PEFR, VO₂, and MET and these are positively related with the 6MWD.
## 5.2 CONCLUSIONS

<table>
<thead>
<tr>
<th>OBJECTIVES</th>
<th>FINDINGS</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>1. The achieved Maximum heart rate, minimum Oxygen saturation achieved,</strong></td>
<td>The achieved Maximum heart rate, minimum Oxygen saturation achieved, VO$_2$ and MET in SCD patients and healthy controls were within normal range. Therefore adult SCD patients may take the 6MWT safely without any complications.</td>
</tr>
<tr>
<td><strong>minimum Oxygen saturation achieved, VO$_2$ and MET in SCD patients and</strong></td>
<td></td>
</tr>
<tr>
<td>healthy controls.</td>
<td></td>
</tr>
<tr>
<td><strong>2. The cardiopulmonary response to exercise through the 6MWT in adults</strong></td>
<td>Blood pressures for the cases and controls were within normal ranges although healthy adults recorded higher values than SCD patients.</td>
</tr>
<tr>
<td><strong>with SCD and healthy controls.</strong></td>
<td>moreover, the PEFR for the cases was reduced at the end of the 6MWD but increased at 5 minutes and 10 minutes after the test.</td>
</tr>
<tr>
<td></td>
<td>In contrast to the healthy controls, the PEFR increased at the end of the 6MWD and also at 5 minutes and 10 minutes after the test.</td>
</tr>
<tr>
<td></td>
<td>There was an improvement in the PEFR during the 6MWT. This suggests that exercise may improve lung function in SCD patients and healthy adults.</td>
</tr>
<tr>
<td><strong>3. The maximum distance SCD patients can walk within 6 min (exercise</strong></td>
<td>There was a significant difference in the means distance walked in 6 minutes between SCD patients and health controls. This implies that SCD patients have reduced tolerance to exercise compared to their healthy counterparts.</td>
</tr>
<tr>
<td><strong>capacity) in SCD patients and healthy controls.</strong></td>
<td></td>
</tr>
<tr>
<td><strong>4. The preliminary reference values in healthy Ghanaians during 6MWT.</strong></td>
<td>The preliminary reference value in healthy Ghanaians between 20 years and 45 years in 6MWT is 666.72 ± 80.06 metres. In</td>
</tr>
</tbody>
</table>
addition, the reference values for healthy Ghanaian males and females are 722.67±69.05m and 635.13±68.60m respectively.

### 5.3 LIMITATION

Due to time and resources constraints, this study could not be carried out in other hospital settings.

### 5.4 RECOMMENDATIONS

1. Further studies are recommended to measure oxygen consumption using other equipment to determine more precisely the energy expenditure in SCD patients and healthy individuals during the 6MWT.

2. Studies to measure the effect of HbF in SCD patients in exercise tolerance with healthy controls could be of interest in research.

3. Studies should be carried out to compare the exercise tolerance level between SCD patients and patients with other conditions.
REFERENCES


McGann, P. T., Nero, A. C., & Ware, R. E. (2013). Current Management of Sickle Cell Anemia. *Cold Spring Harbor Perspectives in Medicine, 3*(8), a011817.


Menaa, F. (2014). Supplementation of Vitamin D in Patients with Sickle Cell Bone Disease: A Debate or a Combate? *Journal of Hematology & Thromboembolic Diseases, 02*(04).


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APPENDICES

APPENDIX 1

DATA EXTRACTION SHEET/ QUESTIONNAIRE

Demographics/ medical Information

Participant ID# ___________                           Date: _________________

1. Gender: Male / Female                                                Age (years): ____

2. Marital status (married/ single etc.) __________________________

3. Employment status: ______________

4. Highest educational level: ____________________

5. Sickle cell type (HbSS, SC etc.)__________________

6. a. Last time of crisis______________

       b. Type of crisis ______________

       c. Last blood transfusion (period) ______________

7. Current Hb: ______

8. Current medication: __________________________________________________

9. Medications taken before the test (dose and time): __________________________

10. Other information

___________________________________________________________________________

___________________________________________________________________________

Anthropometric Data

1. Height: ______cm    ____m    Weight: _____ kg    BMI_______ (kg/m²)
APPENDIX 2

Questionnaire to background information and Barriers to exercise in SCD

| Q1 | Do you take any medication apart from what the doctor has prescribed for you? YES / NO |
| Q2 | If yes, what kind of medication do you take? |
| Q3 | Have you had crisis in the last 12 months? YES / NO |
| Q4 | In the last 12 months, how many crisis that did NOT require hospital or emergency room admission have you had? You can give an estimation. __________ |
| Q5 | In the last 12 months, how many crisis that DID require hospital or emergency room admission have you had? You can give an estimation. __________ |
| Q6 | In the last 12 months, how many days crisis made you miss work or school? You can give an estimation. __________ |
| Q7 | Do you exercise? YES / NO |
| Q8 | If yes, how often do you exercise? (Once per week, 2x per week, once per month, rarely, never) |
| Q9 | If no, what prevents you from exercising? |
| Q10 | When you exercise do you feel pain or discomfort in any part of your body? YES / NO |
| Q11 | If yes, which part of your body do you feel the pain? |
| Q12 | How do you manage the pain or discomfort? (Take on the counter drugs, visit the doctor for treatment) |

Questionnaire to Assess Exercise practices - CONTROL

| Q1 | Do you exercise? YES / NO |
| Q2 | If yes what type of exercise do you do? |
| Q3 | If yes, how often do you exercise? (Once per week, 2x per week, once per month, rarely, never) |
| Q4 | If no, what prevents you from exercising? |
APPENDIX 3

Godin Leisure-Time Exercise Questionnaire

1. During a typical 7-Day period (a week), how many times on the average do you do the following kinds of exercise for more than 15 minutes during your free time (write on each line the appropriate number).

Weekly leisure activity score = (9 × Strenuous) + (5 × Moderate) + (3 × Light)

<table>
<thead>
<tr>
<th>Weekly leisure-time activity score</th>
<th>Time per week</th>
<th>Totals</th>
</tr>
</thead>
<tbody>
<tr>
<td>a) STRENUOUS EXERCISE (HEART BEATS RAPIDLY)</td>
<td>9</td>
<td>X9</td>
</tr>
<tr>
<td>(e.g., running, jogging, hockey, football, soccer, squash, basketball, cross country skiing, judo, roller skating, vigorous swimming, vigorous long distance bicycling)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>b) MODERATE EXERCISE (NOT EXHAUSTING)</td>
<td>5</td>
<td>X5</td>
</tr>
<tr>
<td>(e.g., fast walking, baseball, tennis, easy bicycling, volleyball, badminton, easy swimming, alpine skiing, popular and folk dancing)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>c) MILD/LIGHT EXERCISE (MINIMAL EFFORT)</td>
<td>3</td>
<td>X3</td>
</tr>
<tr>
<td>(e.g., yoga, archery, fishing from river bank, bowling, horseshoes, golf, snow-mobiling, easy walking)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

WEEKLY LEISURE-TIME ACTIVITY SCORE

<table>
<thead>
<tr>
<th>Godin Scale Score</th>
<th>Interpretation</th>
</tr>
</thead>
<tbody>
<tr>
<td>24 units or more</td>
<td>Active</td>
</tr>
<tr>
<td>14 – 23 units</td>
<td>Moderately Active</td>
</tr>
</tbody>
</table>
2. During a typical **7-Day period** (a week), in your leisure time, how often do you engage in any regular activity **long enough to work up a sweat** (heart beats rapidly)

   1. OFTEN □  
   2. SOMETIMES □  
   3. NEVER/RARELY □

**APPENDIX 4**

**Six Minute Walk Test (6MWT)**

Lap counter: __ __ __ __ __ __ __ __ __ __ __ __ __ __ __

Baseline                                                                 End of Test
Time ___:___                                                               ___:___

4. Test parameters

<table>
<thead>
<tr>
<th>VARIABLES</th>
<th>BASELINE</th>
<th>END OF TEST</th>
<th>5MINS</th>
<th>10MINS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blood Pressure (mmHg)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heart Rate (bpm)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SpO₂ (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PEF (L/min)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

5. Borg scale

<table>
<thead>
<tr>
<th>VARIABLES</th>
<th>BASELINE</th>
<th>END OF TEST</th>
<th>5MINS</th>
<th>10MINS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dyspnœa</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fatigue</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

6. Stopped or paused before 6 minutes? Yes / No

7. Reason (if yes): __________

Record response 1-5. (*1=desaturation, 2=foot, knee, hip or other orthopaedic pain, 3=muscle fatigue or pain, 4=breathlessness, 5=adverse event*)
8. If response to item 7 = 5, select all that apply. *(a=angina, b=light-headedness, c=intolerable dyspnoea, d=leg cramps, e=staggering, f=diaphoresis, g=pale or ashen appearance, h=mental confusion or headache, i=other).* If other is selected, please explain.

___________________________________________________________________________

9. Number of laps: _____ (x 30 meters) + final partial lap: _____ meters = total distance walked

10. Total distance walked in 6 minutes: _____ meters/ Predicted distance: _____ meters

11. Metabolic equivalents (MET) conversion

\[
MET = \left[0.1 \times \text{speed (m\cdot\text{min}^{-1})} + 3.5\text{mLO}_2\cdot\text{kg}\cdot\text{min}^{-1}\right] \div 3.5\text{mLO}_2\cdot\text{kg}\cdot\text{min}^{-1}
\]

\[
\text{VO}_2 = \text{(Estimated oxygen consumption)}
\]

\[
\text{VO}_2 = \text{________} \text{(ml/kg/min)}
\]

\[
\text{MET}=\text{________} \text{(METs)}
\]

12. Other comments:
APPENDIX 5

Modified Borg Dyspnoea Scale

<table>
<thead>
<tr>
<th>Rating</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>Nothing at all</td>
</tr>
<tr>
<td>0.5</td>
<td>Very, very slight (just noticeable)</td>
</tr>
<tr>
<td>1</td>
<td>Very slight</td>
</tr>
<tr>
<td>2</td>
<td>Slight</td>
</tr>
<tr>
<td>3</td>
<td>Moderate</td>
</tr>
<tr>
<td>4</td>
<td>Somewhat severe</td>
</tr>
<tr>
<td>5</td>
<td>Severe</td>
</tr>
<tr>
<td>6</td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>Very severe</td>
</tr>
<tr>
<td>8</td>
<td></td>
</tr>
<tr>
<td>9</td>
<td>Very, very severe (almost maximal)</td>
</tr>
<tr>
<td>10</td>
<td>Maximal</td>
</tr>
</tbody>
</table>

APPENDIX 6

Borg Rating of Perceived Exertion (RPE) Scale

<table>
<thead>
<tr>
<th>Rating</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>6</td>
<td>No exertion at all</td>
</tr>
<tr>
<td>7</td>
<td>Extremely light</td>
</tr>
<tr>
<td>8</td>
<td></td>
</tr>
<tr>
<td>9</td>
<td>Very light</td>
</tr>
<tr>
<td>10</td>
<td></td>
</tr>
<tr>
<td>11</td>
<td>Light</td>
</tr>
</tbody>
</table>
12
13 Somewhat hard
14
15 Hard (heavy)
16
19 Extremely hard
20 Maximal Exertion

**APPENDIX 7**

Angina (Chest pain) scale (Canadian Cardiovascular Society grading of angina pectoris)

<table>
<thead>
<tr>
<th>GRADE</th>
<th>DESCRIPTION</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade I</td>
<td>Ordinary physical activity does not cause angina, such as walking and climbing stairs. Angina with strenuous or rapid or prolonged exertion at work or recreation.</td>
</tr>
<tr>
<td>Grade II</td>
<td>Slight limitation of ordinary activity. Walking or climbing stairs rapidly, walking uphill, walking or stair climbing after meals, or in cold, or in wind, or under emotional stress, or only during the few hours after awakening. Walking more than two blocks on the level and climbing more than one flight of ordinary stairs at a normal pace and in normal conditions.</td>
</tr>
<tr>
<td>Grade III</td>
<td>Marked limitation of ordinary physical activity. Walking one or two blocks on the level and climbing one flight of stairs in normal conditions and at normal pace.</td>
</tr>
<tr>
<td>Grade IV</td>
<td>Inability to carry on any physical activity without discomfort, anginal syndrome may be present at rest.</td>
</tr>
</tbody>
</table>
INFORMED CONSENT TO PARTICIPATE IN A RESEARCH STUDY

Study Title: Exercise Tolerance in Adult Sickle Cell Disease Patients

Introduction

You are being invited to participate in a research study. This consent form will provide you with information on the research project, what you will need to do, and the associated risks and benefits of the research. Your participation is voluntary. Please read this form carefully. It is important that you ask questions and fully understand the research in order to make an informed decision. You will receive a copy of this document to take with you.

Who are the people in charge of this study?

1. MPhil Student: Isaac Nuako, Department of Physiology, School of Biomedical and Allied Health Sciences, Korle-Bu. Email: inuako001@st.ug.edu.gh
   Mobile: 0244518275

2. Principal Supervisor: Rev. Dr. Charles Antwi-Boasiako, Department of Physiology, School of Biomedical and Allied Health Sciences, Korle-Bu. Email: antwiboasiako@chs.edu.gh
   Mobile: 0244729026

3. Co-Supervisor: Dr. Alfred Doku, Department of Internal Medicine, School of Medicine and Dentistry University of Ghana Medical School. Email: dokukavin@gmail.com
   Mobile: 0244273573
What is the purpose of this study?

The purpose of this study is to find out how adult sickle cell patients are able to tolerate exercise tests such as the six minute walk test. This would give us an idea of which exercises or physical activity would be safe for people with sickle cell disease.

What is the purpose of taking the parameters for your data?

The data collected from participants – blood pressure, heart rate, oxygen saturation, and peak expiratory flow rate would give an indication of how the heart, blood and lungs respond to exercise.

Who is sponsoring this study?

This study is currently self-sponsored.

Who can be in this study?

Both Sickle cell patients and healthy individuals can be part of the study. Both groups should not have any physical impairment. Sickle cell patients may not have had recent history sickle cell crisis or stroke.

How many people would be participating in this study?

The study will involve fifty (36) sickle cell disease patients comprising both males and females with ages from 20 to 45 years who attend the sickle cell clinic at Tema General Hospital. There would also be 36 control group comprising healthy adults within the same age group of sickle cell disease patients involved in the study.
What is the procedure for the study?

Participants who consent to take part in the study would be screened by interviewing them and using the information in their medical records. Participants’ haemoglobin (Hb) will also be measured by capillary blood collection and by haemoglobinometer. Participants would then be taken through a detailed description of the study and as well as demonstrations. Participants would be required to answer some few questionnaires. Blood pressure, heart rate, oxygen saturation and peak expiratory flow rate would be measured.

Participants would be required to wear appropriate footwear and clothing for the study. All scales used would also be explained and made available to participants.

Participants would be asked to walk for six (6) minutes in their own maximum pace along a flat level floor, turning around cones placed at 30 metres distances apart. During the test, participants would be informed of the time remaining each minute like ‘you have 5 minutes more, 4 minutes more, and you are doing well’ until the last 15 seconds when participants would be prompted to get ready to stop. The BP, HR, RR and SPO$_2$ would be measured again in the same position that was taken prior to the test and then every two (2) minutes during recovery for six (6) minutes. Participants would be allowed to stop for a period if they want to but would be encouraged to continue once they are recover. However, if a participant become exhausted or cannot continue for any appropriate reason, he/ she would be asked to stop and the required parameters would be measured including the distance covered.
What are the potential risks or discomforts?

The risks of exercise in this study are similar to those side affects you may currently experience during your training regime. As you know, exercise may lead to muscle soreness and feelings of tiredness.

What are the potential benefits to me or others?

There are no direct benefits to you from participating in this study. You may find out information about your health with respect to parameters that would be measured during the study. The results from this study may further medical or scientific knowledge.

Is being in the study voluntary?

Your participation in this study is completely voluntary. By signing this form, you are agreeing to participate in the study. If you choose to participate, you can withdraw at any time without any effect on the care that you receive at Tema General Hospital.

What happens if I decide not participate or to withdraw from the study?

If you decide to withdraw, please notify the investigators on the front page of this form. If you withdraw or are withdrawn from the study, data collected by the study investigators up until your withdrawal may be included in the study results.

Under what conditions would I be asked to withdraw from the study?

The study investigators may discontinue your participation in the study for various reasons, including:

1. It is not in your best interest to continue in the study.
2. You need treatment which is not allowed in this study or do not meet eligibility for study participation.

3. You fail to follow study instructions.

4. The study is cancelled.

What are the costs for being in the study?

There would be no charge for participating. It is absolutely free of charge.

Will people be paid for being in this study?

You will not be paid for participating in the study. However, water and snacks would be provided after the study. Your transport fare will also be paid to you.

Compensation for Injury

If you suffer an injury as a direct result of the study, medical care was provided to you in the same manner as you would ordinarily obtain any other medical treatment. In no way does signing this form waive your legal rights nor release the investigator from legal and professional responsibilities.

Will I be told of any new findings while the study is in progress?

We may learn new things during the study that you may need to know. You would be informed of any new findings developed during the course of the study that may be of benefit to you in a timely manner.
How will the information collected from and about people in the study be protected?

All persons involved in the study, including the study investigators and study personnel (research assistants) are committed to respecting your privacy. No other persons will have access to your personal health information or identifying information without your consent, unless required by law. We will make every effort to keep your personal health information private and confidential. Any personal health information or personal information collected about you was ‘de-identified’ (coded) by replacing your personal identifying information with a ‘study number’.

All information that identifies you, both hard/paper copy and electronic information (password protected), was kept confidential and stored and locked in a secure place.

The results of this study may be presented at scientific meetings or in publications without disclosing your identity.

How else might these samples be used?

Data obtained in this study would be analysed and used for this study only and would be used only for the purposes of this study. It is possible we may wish to contact you for further study.

If you do not want to be re-contacted for further study, please indicate by ticking one of the boxes below;

I do not wish to be re-contacted

I want to be re-contacted

Who can I talk to about my rights as a study participant?
If you have any questions regarding the study or study procedures, you should contact Rev. Dr. Charles Antwi-Boasiako, Physiology Department of University of Ghana, School of Biomedical and Allied Health Sciences, Korle-Bu, principal supervisor, at 0244729026, or contact Isaac Nuako, student, Physiology Department of University of Ghana, School of Biomedical and Allied Health Sciences, Korle-Bu., at 0244518275 during business hours.

I ………………………………………………………………………………………………………………………………..
voluntarily agree to participate in this study by undertaking a six minute walk test. The research study has been explained to me, and my questions have been answered to my satisfaction. I have the right not to participate in this study and the right to withdraw without compromising the quality of medical care at Tema General Hospital for me. As well, the potential risk and benefits of participating in the study have been explained to me. I have been told that I have not waived my legal rights nor released the investigators or involved institutions from their legal and professional responsibilities. I am aware that every effort was made to ensure my confidentiality.

 ......................................................... Date....................... place......................
(Signature/thumbprint of participant)

 ......................................................... Date....................... place......................
(Signature of investigator; Isaac Nuako)

For Illiterate

I ………………………………………………………………………………………………………………………………..

Acknowledge that the above investigator signed this form in my presence.
..................................  Date..................  place............................

(Signature of witness)
University of Ghana
COLLEGE OF HEALTH SCIENCES

EPRC/FEB/2019

February 27, 2019

Ref. No.: ...........................................

Mr. Isaac Nuako
Department of Physiology
School of Biomedical and Allied Health Sciences
Korle-Bu

ETHICAL CLEARANCE

Protocol Identification Number: CHS-Et/M.6 – 5.15/2018-2019

FWA: 000185779  IORG: 0005170  IRB: 00006220

The College of Health Sciences Ethical and Protocol Review Committee (EPRC) at its February 08, 2019 full board meeting reviewed and approved your re-submitted research protocol.

Title of Protocol: “Exercise Tolerance in Adult sickle cell Disease Patients”

Principal Investigator: Mr. Isaac Nuako

This approval requires that you submit six-monthly review report(s) of the study to the Committee and a final full review report to the EPRC at the completion of the study. The Committee may observe, or cause to be observed, procedures and records of the study before, during and after implementation.

Please note that any significant modification(s) to this project/study must be submitted to the Committee for review and approval before its implementation.

You are required to report all serious adverse events related to this study to the EPRC within seven (7) days verbally and fourteen (14) days in writing.

As part of the review process, it is the Committee’s duty to review the ethical aspects of any manuscript that may be produced from this study. You will therefore be required to furnish the Committee with any manuscript for publication.

This ethical clearance is valid till February 10, 2020.

Please always quote the protocol identification number in all future correspondence in relation to this protocol.

Signed: ...........................................

Professor Andrew Anthony Adjei
Chair, Ethical and Protocol Review Committee

cc: Provost, CHS
Dean, SBAHS
Head, Department of Physiology

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