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Alternative therapy for sickle cell disease

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Alternative therapy for sickle cell disease

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Abstract

Sickle cell disease can lead to serious complications, such as stroke, acute chest syndrome, pulmonary hypertension, organ damage, blindness, skin ulcers, gallstones and priapism. Additionally, patients with sickle cell disease usually have several pain crises during the year, which means they have to be admitted to the hospital a couple days or weeks in order to treat these crises by pain relievers through IV line or veins. This necessitates quite often that the patient would be absent from their jobs or schools. Frequent absences may cause people with sickle cell disease to experience stress which in turn leads to a higher incidence of pain crises. Therefore, people with sickle cell disease should have awareness about possible supplements that can decrease the numbers of pain crises during the year, so they can live their lives like their peers with less pain and complications. The purpose of this study is to review the options for pain relief available for people with sickle cell disease. Specifically, this paper will review and summarize the literature related to the relationship between both nutrition supplements and phytomedicine and their potential to alter the number and severity of crises events that occur in a year.

Note

Per an email message from the University of Maryland Medical System, the URL links in the following references on **Page 72** are no longer active and the material cited is no longer available through the UMM website:

- University of Maryland Medical Center (2013, June 27). Sickle cell disease | University of Maryland Medical Center. Retrieved November 15, 2013, from <http://umm.edu/health/medical/reports/articles/sickle-cell-disease>
- University of Maryland Medical Center (2013, May 7). Herbal medicine. Retrieved February 18, 2014, from <https://umm.edu/health/medical/altmed/treatment/herbalmedicine>
- University of Maryland Medical center (2014, May 7). Magnesium | University of Maryland Medical Center. Retrieved April 21, 2014, from <http://umm.edu/health/medical/altmed/supplement/magnesium>

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ALTERNATIVE THERAPY FOR SICKLE CELL DISEASE

Submitted in Partial fulfillment of the Requirement for the
Degree Master of Arts

HUDA ALSULTAN
UNIVERSITY OF NORTHERN IOWA
May 2015

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This Study by: Huda Alsultan

Entitled: ALTERNATIVE THERAPY FOR SICKLE CELL DISEASE

has been approved as meeting the research paper requirement for the

Degree of Master of Arts.

6/6/14
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Dr. Alison Beharka, Chair

6/4/14
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Table of Contents

Chapter 1. Introduction.....	4
Purpose if the study.....	9
Significance of the study.....	9
Delimitation.....	10
Limitation.....	11
Assumptions.....	11
Definition of terms.....	12
Chapter 2. Review of Related Literature.....	15
History.....	15
Epidemiology.....	17
Physiology of sickle cell disease.....	21
Episodes of pain.....	25
Psychosocial support.....	25
Therapeutics treatment.....	28
Blood transfusion.....	29
Hydroxyurea.....	31
Bone marrow transplant.....	34
Non-therapeutic treatment.....	37
Nutritional alternative.....	37
Phytomedicines.....	48
Chapter 3. Summary and Recommendation.....	51
Brief summary and Evaluation of Existing Literature.....	51
Individual level recommendation.....	55
Organizational level recommendation.....	56
Suggestion for future research.....	57

Chapter 1

Background:

My interest in the topic of this paper goes back to when I worked as a dietitian at a hospital in my hometown (Alhasa) in Saudi Arabia for two years. My job was to educate patients about their health conditions, particularly the role diet plays in promoting or harming health. The majority of those patients had sickle cell disease, a condition where alterations in the hemoglobin protein results in abnormal red blood cells. These patients were frequently admitted to the hospital for days or weeks at a time because of pain crises. During the crises periods, patients were unable to work, go to school or live their lives as normal. Some of these patients came to the emergency room almost every month because of severe pain crises. This experience has inspired me, as a dietitian, to investigate various food dietary supplements that could reduce the number of pain crises a sickle cell anemia victim endures annually.

Sickle-cell anemia is widespread in the coastal region of Saudi Arabia where I come from. In my city of Alhasa in Saudi Arabia, there is at least one child afflicted with either sickle cell disease or sickle cell trait in every family. The disease also affects me personally as two of my siblings and I have it. Almost every month, one of us would visit the emergency room due after suffering yet another pain episode triggered by the sickle cell anemia. The condition does not get any better with age. In fact, as a person with sickle cell disease ages, the condition worsens. For example, at first my older sister had pain crises between 3-5 times a year. As she got older, new health problems associated with sickle cell disease occurred. First, she had a problem with her vision, resulting in the inability to see and read clearly. The vision problem was followed by heart problems, and

finally kidney failure and death at age 49. Unfortunately, my brother developed the same complications as those my sister had. He developed fluid in his body and brain, which required surgery. After the surgery, he stayed in bed almost one year because his body did not respond to the treatment due to his sickle cell condition. All of these experiences in my life lead me to study the possible role of diet, especially food supplements, in decreasing the potential complication risks and severe pain crises associated with sickle cell disease.

Sickle cell disease was unknown before 1910, but today it is a well known disease. The first case recognized as sickle cell disease was that of a patient named Walter Clement Noel. He was a dental student who suffered from what we now know is sickle cell anemia. He went to the hospital several times for pain crises, but the doctors were unable to help him because they had no idea what he was suffering from. Mr. Clement died in 1916 from pneumonia, which is often a major complication of sickle cell disease (Steensma, Kyle, Shampo, 2010). Dr. Ernest Irons had examined Noel's blood microscopically and found his red blood cells were abnormally shaped—sickle. Dr. Irons, however, did not know what caused the deformity (Steensma, Kyle, Shampo, 2010). In 1949, Dr. Pauling and colleagues were the first to indicate that sickle cell disease occurs as a result of an abnormality in the hemoglobin molecule (Steensma, Kyle, Shampo, 2010). This was the first time a genetic disease was linked to a mutation of a specific protein. The sickle cell mutation occurs when a single base change in the DNA, is the fundamental genetic material that determines the arrangement of the amino acid building blocks in all proteins. This protein has two subunits. The alpha subunit is normal in people with sickle cell disease. The beta subunit has the amino acid valine at position 6

rather than the glutamic acid that is normally present. The alteration is the basis of all the problems that occur in people with sickle cell disease.

It is now a known fact that Sickle cell disease (SCD) is an inherited disease which is passed down from parents to children. SCD is a serious disorder in which the body makes sickle-shaped red blood cells. Normal red blood cells are disc-shaped and look like doughnuts without holes in the center. They move easily through blood vessels. Red blood cells contain a protein called hemoglobin. Hemoglobin binds oxygen in the lungs and transport to the rest of the body.

Sickle cells contain abnormal hemoglobin called sickle hemoglobin or hemoglobin S. Sickle hemoglobin causes the red blood cells to develop a sickle shape. Sickle cells are stiff and sticky. They tend to block blood flow in the blood vessels, which can cause pain and organ damage. It can also raise the risk for infection (National Institutes of Health (NIH), 02-01-2104).

People with sickle cell disease usually have a lower quality of life due to the complications related to sickle cell disease. For example, pain episodes occur randomly, so the person lives constantly in a state of uncertainty. While not all episodes require hospitalization, those that do alter both the life of the patient, the patient's family and the institution (job/ school) connected to the patients.

Stress, pain and other complications of sickle cell disease result in a reduced lifespan for those affected. However, today people with sickle cell disease can live up to and beyond 50 years if they have access to quality health care and support (Claster & Vichinsky, 2003). Examples of quality health care include taking penicillin daily to

protect children from infections. People with sickle cell disease can also get vaccinations against *Streptococcus pneumoniae*, which causes pneumonia. Pneumonia is a major complication of the disease which can lead to death (Maryland University, 2012).

Sickle cell disease is an international health problem and a global challenge. This condition is more common among people whose families are originally from Africa, the Caribbean, Greece, India, Italy, Malta, Sardinia, Saudi Arabia, Turkey or South or Central America. Although the sickle cell disease is fatal and chronic disease, there are no widely acceptable treatments. The only solution currently available is to protect the new generation from this genetic disease by screening before marriage.

Many babies are born with this condition each year. In the United States, approximately 1000 babies are born with sickle cell disease each year. In Nigeria, approximately 45,000-90,000 babies are born with sickle cell disease each year (Sickle Cell Disease American Association SCDA, 03-11-2014). In addition, it estimated that in sub-Saharan Africa more than 250,000 babies with sickle cell disease are born each year (Serjeant, 2013). Furthermore, in England, about 1 in every 2,400 babies is born with sickle cell disease (Patient.co.uk, 2012). Indeed, it is estimated that more than 300,000 babies are born worldwide each year with hemoglobin disorder, including sickle cell anemia, the majority in low and middle-income countries (World Health Organization WHO, 2011).

Although approximately 300,000,000 people in the world have one copy of the gene (sickle cell trait) (Tsaras, Ansah, Boateng, & Adjepong, 2009) and about 2,000,000 people live with sickle cell disease worldwide (Barton, 2007), there is no widely

acceptable or effective cure. Early diagnosis and extensive care may increase the quality of life, decrease the number of pain crises and decrease the complication risks.

Even though there are many options to treat sickle cell pain crises, none is 100% effective and not all work for every patient. Additionally, some treatments have negative side effects that can be significant. These options include pain reliever medicine, blood transfusion and hydroxyurea. All these options treat just the pain crises not the disease itself. An option that can treat the disease is a bone marrow transplant. This option does offer a possible cure from the disease, but this procedure costs a lot of money and opens the patient to multiple side effects including infections, graft-versus-host disease, graft failure, veno-occlusive disease, infertility and death.

Besides these treatment options, some researchers have moved toward treating this condition with nutritional supplements and phytochemistry in order to prolong the severity of and time between pain crises episodes. Research has shown that nutritional supplements have less side effects, are cheaper and more easily obtained than some of the more traditional treatment for the diseases. Nutritional supplements that have been tried include omega-3- fatty acid, vitamins E, and D and the minerals zinc and magnesium. Additionally, the phytochemistry compounds such as Niprisan and Cikalvit have been utilized. These nutritional supplements and investigational treatments (phytochemistry) have shown promise in the reduction of the number of pain crises with people who have sickle cell disease.

The purpose of this paper is to extensively review several nutritional supplements and phytochemistry that may potentially help to reduce the number and/or severity of pain crises in order to improve the quality of life for people with sickle cell disease.

Purpose of the study

Sickle cell disease can lead to serious complications, such as stroke, acute chest syndrome, pulmonary hypertension, organ damage, blindness, skin ulcers, gallstones and priapism. Additionally, patients with sickle cell disease usually have several pain crises during the year, which means they have to be admitted to the hospital a couple days or weeks in order to treat these crises by pain relievers through IV line or veins. This necessitates quite often that the patient would be absent from their jobs or schools. Frequent absences may cause people with sickle cell disease to experience stress which in turn leads to a higher incidence of pain crises. Therefore, people with sickle cell disease should have awareness about possible supplements that can decrease the numbers of pain crises during the year, so they can live their lives like their peers with less pain and complications. The purpose of this study is to review the options for pain relief available for people with sickle cell disease. Specifically, this paper will review and summarize the literature related to the relationship between both nutrition supplements and phytomedicine and their potential to alter the number and severity of crises events that occur in a year.

Significance of the study

Patients with sickle cell disease suffer from pain crises, which often result in hospitalization for a couple days to receive the proper treatment. In addition, these crises could happen several times within a year. Some patients have few or no severe pain episodes a year while others have 15 or more a year (Kwaku Ohene-Frempong, 2006). However, severe crisis may cause the pain to last for weeks and even months (Yale, Nagib and Guthrie, 2000). Pain crises usually occur on the back, legs, knees, arms, chest and abdomen. In general, the crisis affects two or more sites. In other words, sickle cell

patients live with pain for most of their lives, and they have to take pain reliever medicine, and cope with pain. The traditional treatment focuses only on the pain and not the root cause of the disease, so the pain may come back at any time. Moreover, some of the treatment options have side effects, which can increase the chances of experiencing more complications. For example, hydroxyurea may cause infertility. Which means the patients has to choose between having a lower number of pain crises, but they may not able to have children. Another example, blood transfusion help the patients but may cause iron overload, which may lead to organ failure. Finally, a bone marrow transplant has many side effects; the most important is that patients may get an infection, which is a major cause of deaths. Therefore, patients should look for alternative therapies that can decrease the number of pain crises a year without side effects. There are two aims for this paper. First, not all doctors are knowledgeable about the use of nutritional supplements in the care of patients with sickle cell disease. Second, not all patients have the educational background to sift through and understand the scientific papers dealing with nutrition supplemental. For these reasons, this paper will review and summarize nutritional therapy and phytomedicines for sickle cell disease to help patients with this condition to have less pain crises during the year without any side effects.

Delimitation

The delimitation of the study are:

- (a) Searching for journal articles in the online databases: Google Scholar, PubMed, and Wiley Online Library.
- (b) Availability of articles in the English Language.

(c) The articles available for this study were limited to those that are available through the University of Northern Iowa and interlibrary loan.

(d) Due to the quantity of research studies, the current study is not going to review every aspect of sickle cell disease.

Limitations:

Limitations must be considered in order to acknowledge the weaknesses of the research.

The following limitations were identified in this study:

(a) This paper has shown that there is a limited research that specifically deals with nutritional supplements and decreasing the number of the sickle cell crises a year.

(b) This study does not focus on a specific group, which means it includes all ages and both sexes.

(c) The study is not limited to the United States.

(d) Use of nutritional supplements is often antidotal and not extensively researched.

(e) Although sickle cell arises from two different genetic mutations, research articles rarely identify the genetic basis of the disease.

Assumptions:

The study's assumptions include the following:

(a) The articles examined in this study had correct information along with honest results.

(b) The journal articles were all written by professionals in their fields.

(c) The participants of the studies were representative of the patients with sickle cell disease.

(d) The statistics found in the studies were all accurate.

(e) The online databases used for the literature review worked properly with no errors.

Definition of Terms

Abnormal hemoglobin: An abnormal version of beta-globin called hemoglobin S or HbS.

In this condition, hemoglobin S replaces both beta-globin subunits in hemoglobin.

Blood transfusion: A procedure in which patients receive blood through an intravenous (IV) line inserted into one of patients' blood vessels.

Blood vessels: Any of the vessels, as arteries, veins, or capillaries in which blood circulates.

Hemoglobin: The protein molecule in red blood cells that carries oxygen from the lungs to the body's tissues and returns carbon dioxide from the tissues to the lungs.

Hemoglobin A: Is a type of hemoglobin that presents in adults.

Hemoglobin F: Is a type of hemoglobin that appears in newborn babies and fetuses.

Hemoglobin S: It differs from normal adult hemoglobin only by a single amino acid substitution (a valine replacing a glutamine in the 6th position of the beta chain of globin).

Hydroxyurea: A drug that reduces the severity of sickle cell disease by stimulating production of hemoglobin F.

Pain reliever medicine: Medicines are prescribed by a doctor to relieve the severe pain either by mouth or IV line

Omega-3-fatty acids: Omega-3 fatty acids are considered essential fatty acids: They are necessary for human health but the body cannot make them -- you have to get them through food. Omega-3 fatty acids can be found in fish, such as salmon, tuna, and halibut, other seafood including algae and krill, some plants, and nut oils. Research shows that omega-3 fatty acids reduce inflammation and may help lower risk of chronic diseases such as heart disease, cancer, and arthritis.

Protein: Hemoglobin normally consists of four protein subunits: two subunits of beta-globin and two subunits of another protein called alpha-globin. Each of the four protein subunits of hemoglobin carries an iron-containing molecule called heme, which is necessary for red blood cells to pick up oxygen in the lungs and deliver it to cells throughout the body

Red blood cells: Any of the oval or disc-shaped cells that circulate in the blood, it contains hemoglobin, and give blood its red color.

Sickle cell disease: A genetic blood disorder that affects the hemoglobin within the red blood cells

Sickle cell crises: A common painful complication of sickle cell disease; acute episodes of severe pain are the primary reason that these patients seek medical care in hospital emergency room.

Transplant bone marrow: A procedure that destroys patient's bone marrow and replaces by a donor's bone marrow to help patient cure from sickle cell disease.

Vitamin D: A steroid vitamin which promotes the intestinal absorption and metabolism of calcium and phosphorus

Vitamin E: Alpha-tocopherol, an antioxidant vitamin which binds oxygen free radicals that can cause tissue damage. Deficiency of vitamin E can lead to anemia.

Alternative name

Sickle Cell Disease; Sickle Cell Anemia; Hemoglobin S Disease.

Chapter 2

History:

Walter Clement Noel was a dental student from the island of Grenada, who lived in United States in the early 1900s. He went to Dr. James B. Herrick with complaints of pain, and symptoms of anemia. Dr. Herrick, a cardiologist, was not interested in Walter Noel's case, so he assigned Dr. Ernest Irons to the case. Dr. Irons examined Noel's blood under the microscope and observed abnormally shaped red blood cells (RBC's). These abnormal RBC's were sickle shaped. After that, Dr. Herrick became interested in Walter Noel's case because he thought that this might be a new, unknown disease. Afterwards, he published a report about a patient who suffered from a strange disease including such symptoms as asthmatic conditions and blood flow problems including body ulcers (Linde, 1972). This was the first published account of sickle cell disease. It was not until 1949 that the mechanism behind the sickle shape was identified by Linus Pauling and colleagues. It was demonstrated that sickle cell disease occurs as a result of an abnormality in the hemoglobin molecule. Then Pauling and associates linked the abnormal protein to a mutation in the patients DNA (News Medical, 02-01-2014).

We now know that sickle cell disease is a result of a mutation in the hemoglobin, beta (HBB) subunit. "Hemoglobin consists of four protein subunits, two subunits called alpha-globin and two subunits called beta-globin. This protein is a responsible to carry the oxygen from lung to all the body. The HBB gene provides instructions for making beta-globin. Various versions of beta-globin result from different mutations in the HBB gene. One particular HBB gene mutation produces an abnormal version of beta-globin known as hemoglobin S (HbS)." (Genetics Home Reference, 02-01-2014). The

consequences of this alteration in that RBC's cannot fully transport oxygen from lung to all body. (Genetics Home Reference, 02-01-2014).

“In people with sickle cell disease, at least one of the beta-globin subunits in hemoglobin is replaced with hemoglobin S. In sickle cell anemia, which is a common form of sickle cell disease, hemoglobin S replaces both beta-globin subunits in hemoglobin. In other types of sickle cell disease, just one beta-globin subunit in hemoglobin is replaced with hemoglobin S.”(Genetics Home Reference, 02-01-2014).

Abnormal versions of beta-globin can alter red blood cells into a sickle shape because of the reduction in the number of oxygen molecules carried inside the red blood cells. The sickle-shaped red blood cells do not live as long as normal blood cells because they are constantly being destroyed by the spleen due to their shape and stiffness. The spleen is an organ that helps filter the blood of infections and sickled cells get stuck in this filter and die (Children's hospital of Wisconsin, 03-28-2014). Normal red blood cells live up to 120 days, and the bone marrow is responsible for making new red blood cells. In contrast to normal cells, sickle cells die between 16-20 days. This results in anemia due to a lower amount of red blood cells. Sometimes the sickle-shaped cells get stuck in small blood vessels. this can lead to serious medical complications, such as stroke, acute chest syndrome, pulmonary hypertension, organ damage, blindness, skin ulcers, gallstones and priapism.

These complications may happen anytime in addition to the symptoms of disease, which are usually anemia, episodes of pain, weakness, fatigue, pale skin, jaundice, shortness of breath, dizziness, headache and delayed growth. All of these symptoms and

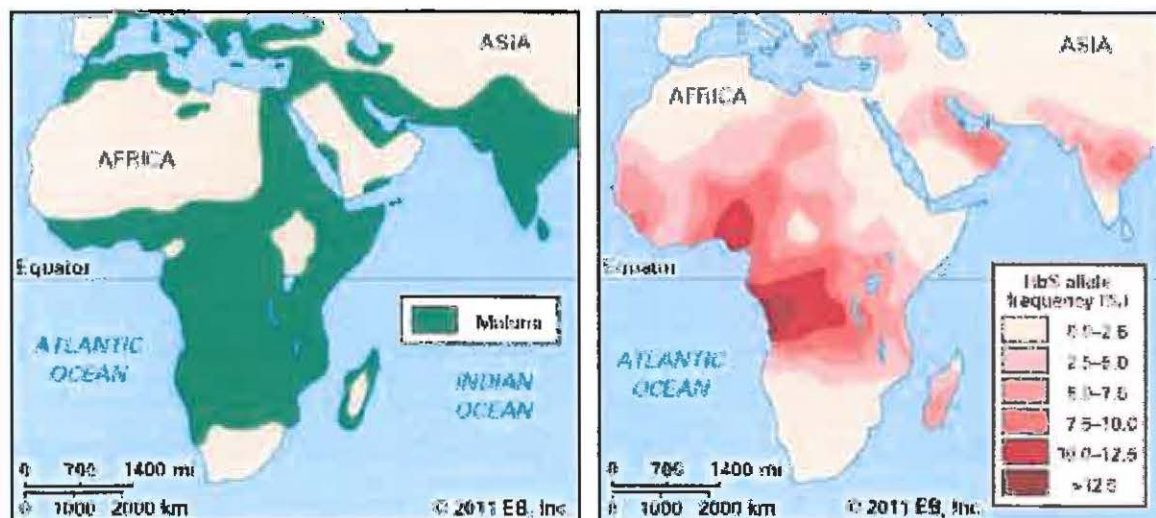
complications lead to a painful life. Additionally, these complications significantly reduce the lifespan of people with sickle cell disease (University of Utah Health Science)

Even though sickle cell disease is a life-threatening, there is no universal cure to date. Today, one hundred years later, scientists and physicians continue to move forward in new understanding of the disease and new ways to treat it. The goal of a universal cure often it was first identified has not been reached yet, but great progress has been made. Hopefully, this goal will be reached within my lifetime

Epidemiology:

It is most common among people whose ancestors come from Africa; Mediterranean countries such as Greece, Turkey, and Italy; the Arabian Peninsula; India; and Spanish-speaking regions in South America, Central America, and parts of the Caribbean. The area's with high levels of sickle cell are also the area's with high levels of malaria. The distribution of sickle cell disease and trait is similar to the distribution of malaria as shown in figures 1.

Figure 1: Distribution of malaria and sickle cell



Resource: (Encyclopædia Britannica, 2014)

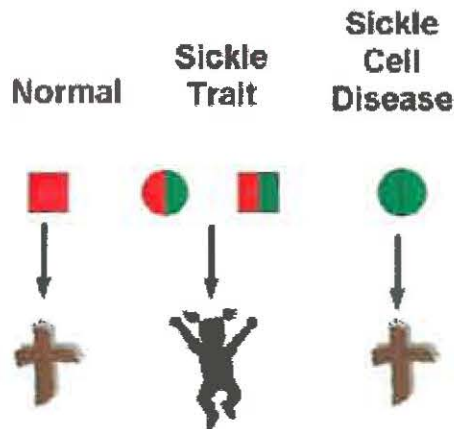
The distribution of malaria and the distribution of sickle cell anemia overlap in areas of Africa, southern Asia, and the Mediterranean.

The two diseases are believed to have coevolved. It is believed that the sickle cell mutation has occurred multiple times in history and has stayed in the population due to its protective effect from malaria.

People with normal hemoglobin are susceptible to death from malaria. People with sickle cell disease are susceptible to death from the complications of sickle cell disease. People with sickle cell trait, who have one gene for hemoglobin A and one gene for hemoglobin S, have a greater chance of surviving malaria and do not suffer the adverse consequences associated with the hemoglobin S gene (Information Center for Sickle cell and thalassemic disorder, 2002).

The malaria parasite, *plasmodium*, has a complex life cycle that requires it to spend part of it in red blood cells. In people with sickle cell trait, the presence of the malaria parasite causes the red blood cells with abnormal hemoglobin to fracture prematurely, making the plasmodium unfit to reproduce. Additionally, the polymerization of hemoglobin affects the capability of the parasite to digest hemoglobin in the first place. Therefore, in places where malaria is a problem, people's chances of survival actually increase if they have sickle cell trait, as shown in figure 2.

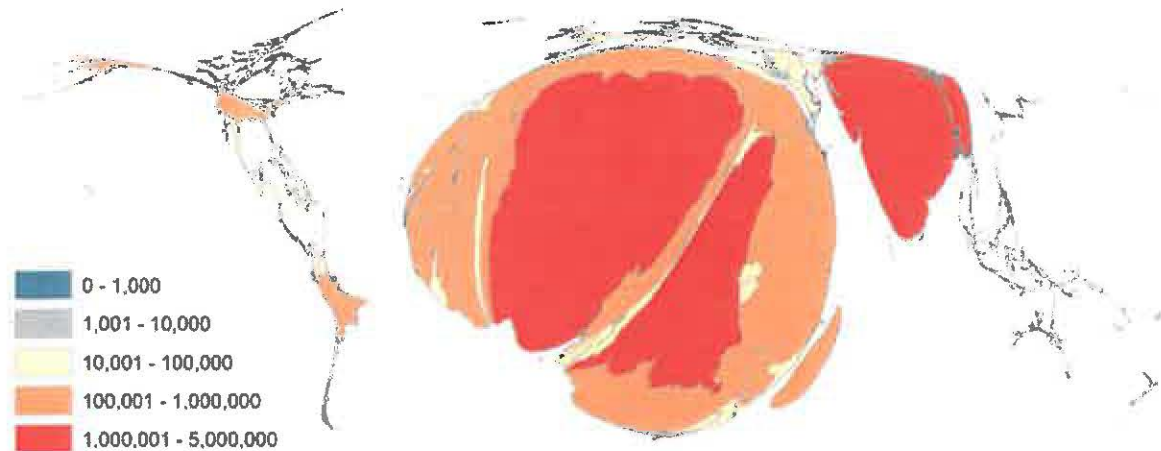
Figure 2: Schematic representation of the effect of the sickle cell hemoglobin gene on survival in endemic malarial areas



Resource: (Information Center for Sickle cell and thalassemic disorder, 2002)

Sickle cell anemia may not be as well-known as, malaria or other diseases. However, it is one of the most prevalence genetic disease in the world. Every year, hundreds of thousands of babies around the world are born with sickle cell disease. And the numbers are expected to rise about 30% globally by 2050 because there are about 300,000,000 people with sickle cell treat, and they can pass down the gene to their offsprings. As shown in figure 3.

Figure 3: A world map with each country's size based on the predicted number of babies born with sickle cell anemia between 2010 and 2050. The highest rates are expected in sub-Saharan Africa and India.



Resources (Rhitu Chatterjee, July 17, 2013)

Sickle cell disease affects two millions of people worldwide, and more three hundreds millions people have sickle cell trait worldwide. In the United States, sickle cell disease (SCD) affects 72 000 people and two million are carriers, while in Africa, more than 200 000 infants are born yearly with SCD. In the United States, mortality has decreased dramatically with newborn screening and better comprehensive care. The average age of death in patients with SCD in the United States is now 53 years for males and 58 years for females. In contrast, for sickle cell patients from Africa, where comprehensive medical care is less available, death in early childhood is the norm (Wasil Jastaniah, 2011).

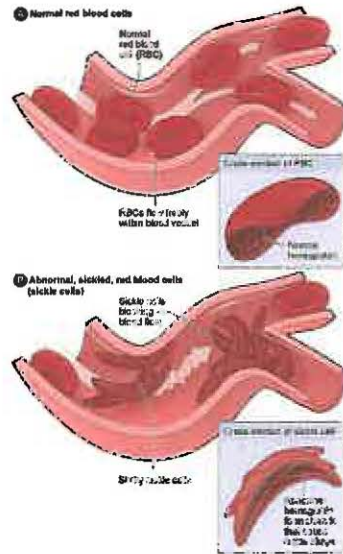
Saudi Arabia has a population of 23.98 million. Information about the prevalence of SCD in Saudi Arabia is not consistent, but studies have reported that SCD is a relatively common genetic disorder in this part of the world. The carrier status for SCD ranged from 2%-27%, and up to 1.4% had SCD, in some areas (Wasil Jasta , ..niah, 2011).

The Saudi Premarital Screening Program estimated the prevalence of the sickle cell gene in the adult population at 4.2% for sickle cell carrier and 0.26% for SCD. With the highest prevalence noted in the Eastern province (approximately 17% for sickle cell carrier and 1.2% for SCD). In a regional experience with newborn screening for SCD in the Eastern province over a nine year period, the prevalence for sickle trait was approximately 21% and 2.6 % for SCD (compared with 17% and 1.2 %, respectively, from premarital screening) (Wasil Jastaniah, 2011).

Physiology of Sickle Cell Disease (pain):

Sickle cell disease is an inherited blood disorder that affects red blood cells. People with sickle cell disease have red blood cells that contain mostly hemoglobin S, an abnormal type of hemoglobin. There are two common types of normal hemoglobin; hemoglobin A, which is common in adult; and hemoglobin F, which is common in fetuses and newborn babies. Whereas hemoglobin S, is considered abnormal type of hemoglobin. The presence of abnormal hemoglobin (hemoglobin S) causes observed the sickle shaped of red blood cells. These sickle red blood cells have difficulty passing through small blood vessels, as shown in figure 4.

Figure 4: Movement of normal red blood cells versus sickled red blood cells through a blood vessels.

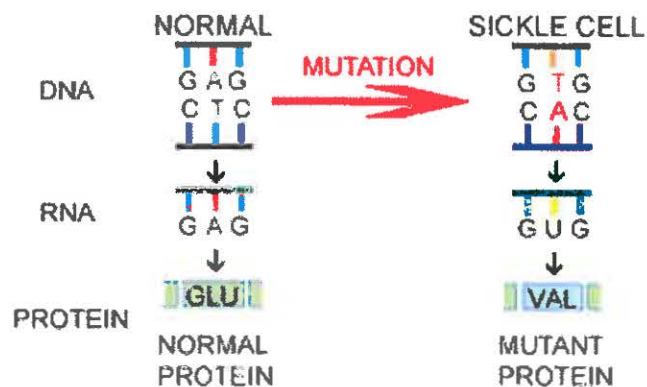


Resource: (National Institutes of Health, September 28, 2102)

Sickle cell disease is caused by a mutated version of the gene that helps make hemoglobin. Hemoglobin is a protein that carries oxygen in red blood cells. This gene mutation affect the body as following:

1- At DNA level, as shown in figure 5

Figure 5: DNA form change



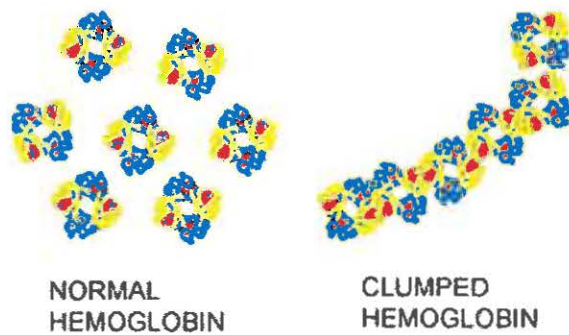
Resource: (Understanding Evolution website, 03-10-2014)

Hemoglobin S is different from hemoglobin A in just one amino acid. In normal hemoglobin, this amino acid is glutamic acid. In sickle cell hemoglobin, it is a valine.

Single base pair mutation in which the base has been replaced with the resulting protein has the amino acid valine instead of glutamine. This amino acid substitution alters the shape of the hemoglobin molecules. In normal cells thousands of separate hemoglobin bind up to 4 molecules of oxygen each. The abnormal hemoglobin clumps, preventing oxygen binding resulting in reduced oxygen carrying capacity.

2- At the protein level, as shown in figure 6

Figure 6: Change the shape of the hemoglobin molecule



Resource: (Understanding Evolution website, 03-10-2014)

DNA mutation affect the shape of the hemoglobin molecule. This cause the hemoglobin molecule to clump together.

3- At the cellular level, as shown in figure 7:

Figure 7: Change in red blood cell's shape



Resource: (Understanding Evolution website, 03-10-2014)

Red blood cells become "sickle-shaped" instead of the disc shape when red blood cells carrying mutant hemoglobin are deprived of oxygen, this shape can sometimes interrupt blood flow.

Hemoglobin is the main molecule found in mature red blood cell (erythrocytes), and made of four subunits: two alpha subunits and two beta subunits. Every subunit surrounds a central heme group that contains iron and binds one oxygen molecule, letting each hemoglobin molecule to bind four oxygen molecules. Hemoglobin helps red blood cells carry oxygen from the air in our lungs to all parts of the body. In sickle cell anemia, the shape of the red blood cell is crescent-shaped and stiffened, reducing its ability to deliver oxygen to tissues and its oxygen-carrying capacity. Sickled red blood cells cannot pass through the capillaries. This is painful when it occurs (boundless, 02-10-2014). When sickle-shaped cells block small blood vessels, less blood can reach that part of the body. Tissue that does not receive a normal blood flow eventually becomes damaged.

Normal red blood cells contain hemoglobin A. They are soft and round and can squeeze through tiny blood vessels. Normally, red blood cells live for about 120 days before new ones replace them.

People with sickle cell conditions make a different form of hemoglobin A called hemoglobin S. Hemoglobin S is abnormal types of hemoglobin. Red blood cells

containing mostly hemoglobin S lives normally about 16 days (they do not live as long as normal blood cells). They also become stiff, distorted in shape and have difficulty passing through the body's small blood vessels. Less blood can reach that part of the body, when sickle-shaped cells block small blood vessels. Tissue that does not receive a normal blood flow eventually becomes damaged. This is what causes the complications of sickle cell disease and episodes of pain (Sickle Cell Disease Association of America (SCDAA), 11-11-2013).

Episodes of pain

Episodes of pain, called crises, are a major symptom and complication of sickle cell anemia. Inadequate blood supply to body tissues cause crises. The impaired circulation is caused by the blockage of various blood vessels from the sickling of red blood cells. Pain occurs when sickled-shaped red blood cells block blood flow through tiny blood vessels to the chest, abdomen, bones and joints. The pain can be vary in intensity and duration can last for a few hours to a few weeks. Some patients experience only a few episodes of pain a year. Others experience a dozen or more crises a year. Patients may need to be hospitalized if a crisis is sever enough. (MayoClinic, 11-02-2013).

Psychosocial Support

Sickle cell disease presents great emotional challenges for patients and their families. For the family, nothing is more heartbreaking than watching their child suffer extreme pain and life-threatening medical conditions. The patient suffers not only the pain itself but also the stress of not knowing when a sickle cell crisis will occur. Also,

they have to struggle with lost time and social isolation from school and work, as well as fear of death (University of Maryland Medical Center (UMMC), 11-15-2013).

Social supports have been shown to help people with sickle cell disease to have less complications and pain. Examples of social support include:

- **Primary care medical providers.**

Children with sickle cell disease who are under the age 2 should see their primary care physician every two or three months. After age 2, they should visit the doctor every six months. Up to age 5, children with sickle cell disease should take penicillin twice daily; once in the morning and once in the evening. Studies have shown that daily doses of penicillin for babies and young children greatly reduced the number of infections they get. Doctors also recommend a vitamin called folic acid to help boost red blood cell production. Young children should regularly visit a hematologist (a blood specialist) to ensure that they do not develop any complications.

- **Nutritionist**

People with sickle cell disease should visit a Nutritionist to help them with diet selection. Usually people with sickle cell disease exhibit below average weight because the body's cells don't get the oxygen they need to function. A nutritionist can recommend some types of food that would help them to gain or maintain weight. Appendix A shows some nutritional therapies that can help patients to gain weight.

This appendix shows high calories and high fat diet. This diet in contrasts with a recommended diet for normal people and that because people with sickle patients need to gain some weight. Examples of some types of food that are recommended for people with

sickle cell disease are whole milk, fried or smothered meats and eggs, bread with butter or margarine. Food not recommended such as, fat free or low fat milk, meat cooked in water and plain bread.

- **Genetic counselinggenetic disease.**

Sickle cell disease is an example of a recessive, genetic disease. What this means is people with one copy of the abnormal gene will have sickle cell trait. Only those who inherited two defective copies will have sickle cell disease. If both parents carry one copy of the gene, they have a 25% chance of having a child with the disease.

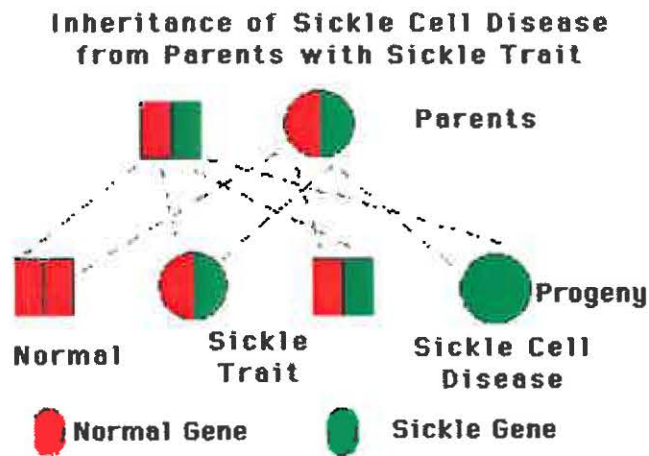
Even for educated patients, these statistics can be confusing. It is the job of genetic counselor to help them make sense of the statistics associated with this disease.

Patients with sickle cell disease or trait should visit genetic counselor. The counselor will discuss life issues including; 1) knowing the genetics for future parents. 2) Possibility of having a child with the disease.

The chances are;

- 1- Both couples have sickle cell trait; they will have chance one child in four normal, one child in four will have sickle cell disease and two children in four will have sickle cell trait.
- 2- One person has sickle disease and the other has sickle cell trait; they will two children in four with sickle cell disease and two children with sickle cell trait.
- 3- One have sickle cell disease and the other is normal; they will have four in four children with sickle cell trait.

Figure 8: inheritance of sickle cell disease from parents with sickle trait.



Resource: (Information Center for sickle Cell and Thalassemic disorders, 2002)

Therapeutics Treatments:

Even though people with sickle cell disease suffer from several pain crises every year, there is no cure for the majority of them. However, some researchers tend to treat people with sickle cell disease with therapeutics treatments, which means different options that available under health care professionals, such as blood transfusion, hydroxyurea or bone marrow transplant. While some researchers tend to treat sickle cell crises by nontherapeutics treatment, such as nutritional or phytomedicine. All these kind of treatments aimed to reduce the number of pain crises in a year expect bone marrow transplant, which aimed to cure from sickle cell disease.

Therapeutics treatment goals for sickle cell disease aims to relieve pain, prevent infections, and control complications

1/ Blood Transfusion:

Blood transfusion is so widely used that about 50% of all patients receive a blood transfusion at some stage in their lives and 5% are on chronic transfusion programs (Pinto PC, Braga JA, Santos AM, 2011). Red cell transfusion is widely used in the management of sickle cell disease. Red cell transfusion can help to deliver oxygen to the body and unblock blood vessels, which means prevention from sickle cell crises and its complications.

For example, It is documented that 7-13% of children with sickle cell disease experience a stroke, which is considered as a major cause for morbidity (Maitreyi Mazumdar, Matthew M. Heeney, Colin M. Sox, Tracy A. Lieu, 2007). Blood transfusion decreases stroke risk from 46–90% to less than 10% (Robert J Adams, Virgil C. McKie, Lewis Hsu, Beatrice Files, Elliott Vichinsky, Charles Pegelow, . . . Myron Waclawiw, 1998).

There are two kinds of blood transfusions used to treat sickle cell including:

- Simple Transfusion: it is infusion of one or two units of donor blood to improve blood and oxygen levels. It is used for moderately severe anemia, severe fatigue, acute chest syndrome and nonemergency situations to increase oxygen level
- Exchange Transfusion: it is drawing out the patient's blood and exchanging it for donor red blood cells. It is used for severe acute chest syndrome and to prevent stroke. Also, it may be used when patient's condition is deteriorating. It reduces the risk of iron overload in patients who require chronic transfusion therapy.

Despite the fact that regular transfusions have been shown to prevent stroke and vaso-occlusive pain crisis, there are some issues that make it unsuitable for long-term use. These issues are: first, studies show that when transfusions are discontinued, the risk reverts back. Which means that patients may suffer from both sickle cell risks and transfusion risks, as well. Second, patients who use this option of treatment may develop alloantibodies and iron overload. Alloantibodies means an antibody formed in response to transfusion targeted against an antigen that is not present on the person's own red blood cells. If a person receives blood cells with antigens that do not match their own, the body may reject the blood cells and make antibodies to them. These antibodies will destroy any blood that the person receives in the future that contains the same antigen (Centers for Disease Control and Prevention(CDC), 2011). Iron overload increases risk for damage to the liver, heart, and other organs. Finally blood transfusion therapy has a high cost (\$ 40 000/ year in 2000) (Sheth, S., Licursi, M., & Bhatia, M, 2013). However, insurance covers the cost for blood transfusion. For example, Medicare covers all the cost for blood transfusion, and there is no limited number for blood transfusions per patient (Caring.com-02-12-2014).

Although blood transfusion could treat the symptoms and pain crises of sickle cell disease and reduce the chances to develop stroke, there are some complications associated with transfusion therapy. These are:

- Immune reactions: patients develop antibodies that target and destroy the transfused cells. It can occur sometimes between 5 - 20 days after transfusion, which may cause severe anemia and life threatening in some

cases. Careful screening and matching of donor blood groups before the transfusion could prevent immune reaction.

- Hyperviscosity: a mixture of normal hemoglobin and hemoglobin S causes the blood to become too "thick". When the blood become thick, patients at risk for altered mental status, seizures and high blood pressure. Careful monitoring can avoid this condition.
- Transmission of viral illness: transfusions were highly associated with a risk for hepatitis and HIV, before widespread blood screening. This complication has decreased noticeably (Sickle cell disease | University of Maryland Medical Center, 10-07-2013).

2/ Hydroxyurea (HC):

Fetal hemoglobin (HbF) is normal form of hemoglobin commonly found in fetuses and newborn babies even in people who will eventually develop sickle cell disease. For most people, the form of hemoglobin gradually disappears as the child ages. Hemoglobin F helps the red blood cells keep their normal shape; soft, large and round, which helps them to flow through blood vessels. It also decreases the chance of the red cells changing to the sickle shape even in patients with sicke cell disease. Therefore, (HbF) is able to block the sickling action of red blood cells. Disease symptoms begin to appear when (HbF) level drops. Therefore, infants do not experience any symptoms, and adults who have high levels of (HbF) have a mild form the disease.

Hydroxyurea (HC) is a drug that has been found to cause the body to produce fetal hemoglobin (HbF) (University of Maryland Medical Center, 02-13-2014). However, the mechanisms of increasing (HbF) remains unclear (Segal JB, Strouse JJ, Beach MC, et

al., 2008). Hydroxyurea decreases the severity of sickle cell disease a couple of different ways including: 1) people with sickle cell disease have abnormal hemoglobin that cause red blood cells to become stiff and sticky. These red blood cells can block the blood flow through blood vessels which can cause pain and other complications. Hydroxyurea can help the body to produce hemoglobin F, and therefore decreases the level of sickling. Then red blood cells easily flow through blood vessels and 2) hydroxyurea decreases the number of a form of neutrophil (white blood cells) formed in normal blood. Neutrophils make the blood thicker that increases the chance that a sickle cell gets stuck in the veins which cause blockage and cause pain and complications. A study showed that patients receiving hydroxyurea had an almost 50% reduction in the number of painful crises and episodes of chest syndrome. In addition, patients receiving hydroxyurea required about 50% fewer transfusions and hospitalizations (National Institutions of Health, 2003).

Multiple studies showed that the beneficial effects of treating sickle cell anemia with hydroxyurea including: 1) shortening the duration of hospitalization due to acute painful episodes and 2) reducing the frequency of hospital admissions due to crises, hospitalizations decreases by 56-87% (Joseph E Maakaron, 2013) . In addition, reducing the frequency of acute chest syndrome. Further, improving the quality of life and decreasing morbidity and mortality (Samir K. Ballas, Robert L. Bauserman, William F. McCarthy, Oswaldo L. Castro, Wally R. Smith, & Myron A. Wacławiw, 2011).

Although hydroxyurea is not a cure, it is currently the only drug used to prevent acute sickle cell crises and the only drug that the Food and Drug Administration (FDA) has approved for the management of SCD. Hydroxyurea has been recommended since 1990s as a first therapy to treat adults and adolescents with moderate-to-severe recurrent

pain (occurring three or more times a year) (Ndefo, Maxwell, Nguyen and Chiobi, 2008).

Hydroxyurea is now accepted therapy for children with sickle cell disease.

For all the good that this drug does, there are some serious side effects that must be considered before use. Mild to moderate side effects include constipation, nausea, drowsiness, hair loss, and inflammation of the mouth. Severe side effects include reduction of white blood cells (neutropenia) and the cells responsible for normal blood clotting (thrombocytopenia), which can lead to increased risk for infections and bleeding (University of Maryland Medical Center, 02-13-2014). However, there is no clear information about the percentage of patients who suffer from the side effects.

Additionally, hydroxyurea has other both short-term and long-term effects. The short-term effect of hydroxyurea among men is that decreased sperm production, which may be temporary and reversible. The long-term effects are birth defects in the offspring of people using the drug, growth delays in children using the drug, and cancer in both children and adults who have used the drug. These long-term effects may be permanent and irreversible, but they are not yet proven (Otis W. Brawley, Llewellyn J. Cornelius, Linda R. Edwards, Vanessa Northington, Bettye L. Green, Charles Inturrisi, . . . Melissa Schori, 2008).

Even though hydroxyurea is a worth drug for sickle cell crises, not all patients use it. Use requires that patients have to do blood work done between 1-2 times every months to check the level of white blood cells. Blood drawn so often made the patients to heat to visit a doctor and use the drug. Additionally, patients and parents have inadequate knowledge about HC and the need for close monitoring. This is considered a barrier for using this drug (Sheth, S. et al, 2013). In proper use of this drug can induce another

complications. For example, patients should wash their hands before and after touch the bottle as well as parents or caregiver wear disposable gloves when they touch the bottle (University of Maryland Medical Center, 02-13-2014).

3/ Bone Marrow Transplantation (BMT)

A bone marrow transplant is a procedure to replace damaged or destroyed bone marrow with healthy bone marrow stem cells. From a donor. BMT is considered the only curative therapy available to date. St. Jude Children's Research Hospital was the first organization to cure sickle cell disease through bone marrow transplant (St. Jude Children's Research Hospital Department of Hematology, 2009). In 1982, a St. Jude patient had both leukemia and sickle cell disease. A St. Jude doctor performed a BMT in an attempt to cure the leukemia. Surprisingly, the patient was cured of both the leukemia and sickle cell disease.

Although bone marrow transplant can cure the patients, it is not commonly performed for multiple reasons. First, suitable bone marrow donors are not easy to come by. Secondly, the risk of death from the transplant procedure is about 5% to 10%, for sickle cell patients who have a matched sibling donor. Additionally, bone marrow transplant is itself a risky procedure. Patients are at risk for infections, rejections and graft-versus-host disease (Platt, Eckman and Hsu, 2011).

In general, sibling donors have a greater chance of reducing the risk of the complications; however, siblings of people with sickle cell often are either ill themselves or carriers of the disease.

However, there are two major barriers to BMT, the lack of a suitable donor, and the risk of mortality and morbidity associated with the procedure itself. (Amrolia P, Almeida A, Halsey C, Roberts I, Davies S. Almeida A, Halsey C, Roberts I, Davies S, 2003). Possible long-term risks of transplant include organ damage, secondary (new) cancers, abnormal growth of lymph tissues, infertility, hormone changes and cataracts (clouding of the lens of the eye, which causes vision loss) (American Cancer Society, 02-13-2014).

The following paragraphs will explain in more detail the risks of associated with bone marrow transplant:

1/ Infections: chemotherapy lowers the numbers of white blood cells, which normally fight and prevent infections. This puts the patient at high risk for infection caused by bacteria, fungi, or viruses. However, medicines are given to fight these microorganisms and prevent these infections. Infections that do not respond to the treatment can lead to death in 5 to 10 percent of patients

2/ Graft-versus-host disease (GVHD): In some cases, the transplanted cells (graft cells) recognize the recipient's cells as 'foreign' and try to attack them. This condition can be acute (occurring less than 100 days after the transplant) or chronic (occurring more than 100 days after transplant). This condition may cause damage to the skin, liver, and intestinal tract of the transplanted patient. However, GVHD can be treated using immunosuppressants, which stops the transplanted tissue releasing antibodies that would otherwise attack the rest of the body. However, GVHD can lead to organ damage or even death if it does not respond to the treatment. (GVHD) is a potentially deadly complication and occurs in 25%–60% of patients (Kathryn L. Hale, 2013).

3/ Graft failure – there is approximately a 10 percent risk that the new bone marrow from a matched family member will fail to take, and 50% from half matched donor (Johns Hopkins Medicine, 03-27-2014). Graft failure has an even higher chance to occur with other types of donors. Graft failure means that the patient will not be able to make any white blood cells, red blood cells, or platelets. So, the transplant would need to be repeated. In addition, if there are no more donor cells, stem cells collected from the patient before the transplant will be given back to the patient. This saves their life, but restores the patient's original bone marrow, which means the sickle cell disease comes back.

4/ Veno-occlusive disease (VOD): after a bone marrow transplant, blood vessels that lead into and pass through the liver may suffer damage because of the chemotherapy. The chance is about 1 out of every 20 cases severe from (VOD).

5/ Nutrition problems: Nausea, vomiting, mouth sores, diarrhea, and loss of appetite may occur because the stomach and intestines are sensitive to chemotherapy. As a rule, nutrition must be given through the veins until patients are able to eat.

6/ Infertility: most patients will not be able to have their own children in the future. That is because of the drugs used while preparing for the transplant. However, there have been patients who were able to conceive children after having a transplant (St. Jude Children's Research Hospital Departments of Hematology, Patient Education, and Biomedical Communications, 2009).

Current prevention:

The chronic nature of SCD requiring life-long medical attention, expensive supportive symptomatic therapy, its specialized care, poor school attendance, so it is time to think about some methods to prevent new hemoglobinopathy births by increasing the knowledge of sickle cell disease and its prevention through using the mass media, school health services and increasing the subject in the physical and health curriculum of primary and secondary school. Additionally, prevention of the disease through carrier identification and genetic counselling remains the only realistic approach to reduce the impact of disease. These approaches will enhance the capacity of the intending couples to make informed decision, to improve their communication about their sickle cell status and to be aware of the risks of having children with SCD and of the consequence of such decisions. However, not all couples will be able to take the advantage of genetic counselling because they may not informed about it, or may not having access to health care. For those people who have sickle cell disease, and not interested in therapeutic treatment of sickle cell disease because of the potentially side effects that may occur, should look for non-therapeutics treatment that have no or less side effects and the same time can reduced the number and severity of sickle cell crises.

Non therapeutics Treatment of sickle cell in general:**1- Nutritional Alternatives:**

Finding a widely expectable cure for sickle cell anemia still remains a challenge even one hundred years after its discovery as a genetically inherited disease. With no cure in sight and current traditional therapies possessing significant side effects, researchers are

beginning to look into alternative, more natural, therapies. While these alternative treatments will not cure the disease, they may have the potential to reduce its symptoms without significant side effects. One area researchers have looked at nutritional alternatives is decrease morbidity and to improve quality of life among sickle cell patients. Fluids and diet are more important in order to stay healthy for sickle cell patients than normal people. Not having the recommended daily fluid and diet may increase the chances to develop diseases that are associated with nutrition. People with sickle cell disease should know the recommended fluid and diet to improve their health and decline the chances of having pain crises.

1- **Fluids:**

An adult patient should drink about 3-4 liters of fluid daily to prevent dehydration. Dehydration means an insufficient amount of water in the body, and this causes the blood to become thicker, which cause the sickled red blood stick it to each other, which cause a blockage in the blood circulation and then pain crises (The North West London Hospitals NHS Trust, 02-17-2014). Fluid could be water, juice and tea, ice ships, popsicles, jelly, milk or soup but could not be alcohol because it causes dehydration, which can lead to other complications. Table 1 shows the amount of fluid that a child should drink per day.

Table # 1: The amount of clear fluids a child needs per day

Child's Weight	Number of 8oz. Cups per day
10 lb	2 cups
15 lb	3 cups
20 lb	4 cups
25 lb	5 cups

30 lb	5-6 cups
35 lb	6-7 cups
40 lb	7 cups
50 lb	8 cups
60 lb	9 cups
More than 60 lb	10 or more cups

Resource: (Lessing, Vichinsky, Mann, Taylor, DuVaul et al, 2008)

2- **Diet:**

People with sickle cell disease need to have a well-balanced diet because their red blood cells break down faster. They should have adequate calories, protein, fat (macronutrients), vitamins and minerals (micronutrient). It is highly recommended that people with sickle cell disease consume food that is rich in protein, vitamins and minerals because that may be helpful with having less pain crises a year. Macronutrients and micronutrients are very important in order to keep the body away from some disease that associated with them, such as osteoporosis that associated with vitamin D deficiency.

A- **Macronutrients:**

a- **Protein:**

Children with sickle cell disease are usually thinner and shorter than unaffected children (St. Jude children's research hospital, 02-17-2014). A study with sickled mice showed that a diet with high protein (35% of energy from dietary protein) can improve weight gain and decrease of level of inflammation with sickled mice (H.I. hyacinth, B.E.

Gee and J.M., 2010). Meats, seafood, beans, eggs are considered the best quality protein resources.

b- **Omega-three fatty acids:**

Some studies suggest that omega-three fatty acids might make red blood cell membranes less fragile and possibly less likely to sickle, although no studies have proven this definitively (University of Maryland Medical Center, 11-11-2014). For example, A Daak et al, conducted a randomized, double-blind, placebo-controlled trail study to investigate the therapeutic potential of omega-3 fatty acids for SCD patients. The study consisted of 140 patients, all with sickle cell disease. Patients were selected randomly from a single center in the Sudan to receive omega-3 capsules daily containing 277.8 mg of docosahexaenoic acid (DHA) and 39.0 mg of eicosapentaenoic acid (EPA) for one year from April 2009 to May 2010. The results of the study were that clinical vaso-occlusive crisis, the number of hospitalization days due to sickle cell crisis and associated complications and annualized vaso-occlusive crisis were lower in the omega-3 group than in the placebo group. In short, supplementation of SCD patients with the omega-3 fatty acids EPA and DHA was effective in reducing the frequency and severity of vaso-occlusive episodes, severe anemia and blood transfusion rate. In addition, the reduction in the number of inpatient hospital days and improvement in school absence due to sickle cell-related illness reflect that some omega-3 fatty acids supplements can improve the quality of life for SCD patients (Daak, A. A., Ghebremeskel, K., Hassan, Z., Attallah, B., Azan, H. H., Elbashir, M. I., & Crawford, M. (2013).

Moreover, a second study by Okpala et al to evaluated the effects of supplementing the dietary intake of (DHA) and (EPA) with supplements in SCD patients, to test the

hypothesis that these effects are mediated partly by reducing inflammation. The study was designed to compare pre- and post- supplementation value of the indices of SCD and levels of inflammatory markers in sickle cell patients who receive oral supplements of EPA (15 mg/kg/day) and DHA (10 mg/kg/day) for six months.

The result of the study was the median concentration of plasma unconjugated bilirubin in steady state reduced from 14.95 μm to 8.6 μm . This reduction was associated with a drop in the median number of crisis over 6 months from 3 to 0. Also, there was a significant reduction of unconjugated bilirubin level, which means that omega-3 fatty acids protected red blood cells from hemolysis. Consequently, it was confirmed that EPA/DHA given daily by mouth to supplement the dietary intake reduces steady state haemolysis and the number of crisis in SCD (Okpala, I., Ibegbulam, O., Ocheni, S., Emodi, I., Ikefuna, A., Umar, G., . . . Herrada, S. 2011). The researchers suggest that supplementing the dietary intake of the omega-3 fatty acids DHA and EPA might reduce hemolysis during steady state in SCD. The decrease of plasma concentration of unconjugated bilirubin observed in this study was associated with a reduction in the number of sickle cell crisis (Okpala, I et al, 2011).

B- Micronutrients:

a- Zinc:

Zinc is an essential mineral that is naturally present in some foods, added to others, and available as a dietary supplement. A daily intake of zinc is required to maintain a steady state because the body has no specialized zinc storage system. Zinc can found in various foods, including lean red meats, seafood (especially herring and

oysters), peas, and beans. Zinc is also found in whole grains. The body needs zinc for normal growth and health.

Zinc is used to treat the following: burns, type 2 diabetes mellitus, Down's syndrome, eating disorders, intestine disease, infections (continuing or chronic), kidney disease, liver disease, pancreas disease, skin disorders, stomach removal, stress (continuing), trauma (prolonged), thalassemia and sickle cell disease (Mayo Clinic, 2013).

Zinc deficiency in patients with sickle cell disease was first reported in 1975. Many clinical manifestations of sickle cell disease were afterward related to zinc deficiency (Prasad, 2002). These manifestations are growth delay, hypogonadism in males, hyperammonemia, abnormal dark adaptation, and cell-mediated immune disorder. Since people with sickle cell disease experience growth delay and zinc deficiency is associated with poor growth, a study was done to determine the relationship between zinc supplementation and growth improvement for people with sickle cell disease. The study was limited to patients aged 4-7 years. Patients took 10 mg of zinc supplement every day for a year. During that time, the researchers observed their height, sitting height and knee height and saw a significant increase in all 3 parameters for the more in the zinc group versus, in the control group (Prasad, 2002).

In addition to its effects on growth, zinc supplementation has shown to decrease in frequency of bacterial infections and hospitalization from painful crises. A study showed that taking 50-75 mg zinc every day for up to 3 years resulted in significantly fewer documented bacteriologically positive infections, numbers of hospitalizations, and numbers of vaso-occlusive pain crises (Prasad, 2002).

Since priapism is one of the sickle cell disease symptoms, researchers looked at zinc ability to improve this characteristic. Research has shown that supplementation with zinc can improve sexual maturation and reproductive capacity (H.I. Hyacinth et al., 2010). Zinc supplementation in patients with SCD caused a significant improvement in secondary sexual characteristics ((H.I. Hyacinth et al., 2010).

b- Magnesium (Mg):

All organ in the body; specifically, the heart, muscles, and kidneys -- needs the mineral magnesium. Also, magnesium helps to build up teeth and bones. Additionally, it activates enzymes, contributes to energy production, and helps regulate calcium levels, as well as regulate copper, zinc, potassium, vitamin D, and other important nutrients in the body.

Symptoms of magnesium deficiency are agitation and anxiety, restless leg syndrome (RLS), sleep disorders, irritability, nausea and vomiting, abnormal heart rhythms, low blood pressure, confusion, muscle spasm and weakness, hyperventilation, insomnia, poor nail growth, and even seizures (University of Maryland, 2013).

It has been documented that low levels of total magnesium in sickle cell erythrocytes is associated with increased sickling because of propensity for red cell dehydration and hence, increased HbS polymerization. The dehydration is because of abnormally high red cell permeability and loss of potassium (K⁺). Mg supplement improves many hematological indices in people with sickle cell disease. These are improvement of red cell hydration indicated by a decrease in number of dense sickle erythrocytes and reticulocyte count and immature reticulocytes. A study by Hyacinth et al showed that

magnesium decreases both number of painful days and length of hospital stay (H.I. Hyacinth et al., 2010).

Requirements for magnesium increase as we grow and age. People with sickle cell disease should take the recommended intake of magnesium daily. The official US and Canadian recommendations for daily intake are as follows:

Infants 0-6 months: 30 mg/7-12 months: 75 mg

Children 1-3 years: 80 mg/ 4-8 years: 130 mg

Males 9-13 years: 240 mg/14-18 years: 410 mg/19-30 years: 400 mg/31 years and older: 420 mg

Females 9-13 years: 240 mg/14-18 years: 360 mg/19-30 years: 310 mg/31 years and older: 320 mg

Table 2 shows the resources of food that rich in magnesium, and the milligrams that have in one serving.

Table # 2: magnesium resources

Food	Serving	magnesium mg	% daily value
Wheat bran	¼ cup	89	22
Almonds, dry roasted	1 ounce	80	20
Spinach, frozen, cooked	½ cup	78	20
Raisin bran cereal	1 cup	77	19
Cashews, dry roasted	1 ounce	74	19
Soybeans, cooked	½ cup	74	19

Wheat germ	¼ cup	69	17
Mixed nuts, dry roasted	1 ounce	64	16
Bran flakes cereal	¾ cup	64	16
Shredded wheat cereal	2 biscuits	61	15
Fortified instant oatmeal	1 1 cup	61	15
Peanuts, dry roasted	1 ounce	50	13
Peanut butter	2 tablespoons	49	12
Baked potato (with skin)	1 medium	48	12
Blackeyed peas, cooked	½ cup	46	12
Pinto beans, cooked	½ cup	43	11
Brown rice, cooked	½ cup	42	11
Lentils, cooked	½ cup	36	9
Vegetarian baked beans	½ cup	35	9
Kidney beans, canned	½ cup	35	9

Resource: CVS Pharmacy, 08-22-2013)

c- Vitamin E:

Vitamin E is an antioxidant that protects body tissue from damage caused by substances called free radicals. Free radicals can harm cells, tissues, and organs. They are believed to play a role in certain conditions related to aging. The body also needs vitamin E to help keep the immune system strong against viruses and bacteria. Vitamin E is also important in the formation of red blood cells. It also helps widen blood vessels and keep

blood from clotting inside them. Cells use vitamin E to interact with each other and carry out many important functions (Medline Plus, 2014).

In a study by Hyacinth et al, vitamin E supplementation decreased frequency of hospital admission and number of painful crisis. In addition, it improved erythrocyte membrane stability and weight gain (H.I. Hyacinth et al., 2010). Vitamin E protects the membranes of red blood cells against free radicals. Red blood cells from people deficient in vitamin E, as well as those from people with sickle cell disease, are more vulnerable to free radical damage. Consequently, low levels of vitamin E may increase the risk of sickle cell symptoms. Additionally, frequent blood transfusions may boost iron levels, which might lead to further free radical damage to red blood cells (Challem, 2002).

The best way to get the daily requirement of vitamin E is by eating food sources. Vitamin E is available in the following foods: vegetable oils (such as wheat germ, sunflower, safflower, corn, and soybean oils), nuts (such as almonds, peanuts, and hazelnuts/filberts), seeds (such as sunflower seeds), green leafy vegetables (such as spinach and broccoli) and fortified breakfast cereals, fruit juices, margarine, and spreads. Fortified means that vitamins have been added to the food.

Getting vitamin E from food is not harmful, but in high doses supplemental may cause serious bleeding (Mayo Clinic, 11-01-2013)

d- Vitamin D:

Vitamin D helps the body absorb calcium. Calcium and phosphate are two minerals that are essential for normal bone formation. Laboratory studies show that vitamin D can reduce cancer cell growth and plays a critical role in controlling infections.

Many of the body's organs and tissues have receptors for vitamin D, and scientists are still teasing out its other possible functions (Harvard School of Public Health, 2011).

A study by Osunkwo et al showed that vitamin D can decrease pain days and increase physical activity (quality of life) (Osunkwo, I., Ziegler, T. R., Alvarez, J., McCracken, C., Cherry, K., Osunkwo, C. E., . . . Tangpricha, V. (2012). Supplementation of vitamin D may serve a dual role in SCD patients by helping to improve both bone health and the chronic pain experience. Many studies showed that the treatment of Vitamin D Deficiency (VDD) help to improvement in pain symptoms and decreased the use of pain medications in non-sickle cell subjects with chronic pain.

Sun is the best source for vitamin D. Most foods are naturally low in vitamin D, however, vitamin D is added to breakfast cereals and to some brands of soy beverages, orange juice, yogurt, and margarine.

Excess vitamin D can make the intestines absorb too much calcium. This may cause high levels of calcium in the blood. High blood calcium can lead to: calcium deposits in soft tissues such as the heart and lungs, confusion and disorientation, damage to the kidneys, kidney stones, nausea, vomiting, constipation, poor appetite, weakness, and weight loss

Multiple Vitamins:

Few studies had looked at the benefit of multiple vitamins with sickle cell disease. A study by Challem was done to exam the effects of multiple vitamins on people with sickle cell disease. One group of patients took one mg daily folic acid alone, while the other group took 6 grams of vitamin C, 1,200 IU of vitamin E, 1,000 mcg of folic acid

and 6 grams of aged garlic extract daily over six months. As a result, people taking the multiple supplements had only one-third the number of painful sickle cell episodes, compared with the other group (Challem, 2002).

Herbal antioxidants:

A study was done to test the effects of green tea extract and aged garlic extract on dehydration of sickle cells. Such dehydration of the sickle cells further exacerbates damage to the cells and may increase blockage. The authors reported that the green tea extract, almost completely inhibited sickle cell dehydration, while the garlic extract reduced dehydration by 30 percent (Challem, 2002).

2- Phytomedicines/phytotherapy

This alternative therapy using phytomedicines also called herbal medicine has proven to reduce crisis and reverse sickling. Phytomedicine refers to using a plant's seeds, berries, roots, leaves, bark, or flowers for medicinal purposes. Examples of these phytomedicines are Niprisan and Ciklaviv (ScientificWorldJournal, 2013). Medicine plants are either parts of a plant or the whole plant that possess healing properties and unlike orthodox (synthetic) medicines, which might have adverse side effects. Medicinal plants are considerably cheaper than medical treatment.

1- Niprisan:

Niprisan is a mixture of four medicine plants; Piper guineense, Pterocapus osun, Eugenia caryophyllum and Sorghum bicolor. Niprisan, is a former name for Nicosan, reported to inhibit the polymerization of the hemoglobin S. It is sold as an antisickling phytomedicine. The Nigerian National Institute for Pharmaceutical Research and

Development developed Niprisan (Ndefo, U. A., Maxwell, A. E., Nguyen, H., & Chiobi, T. L., 2008). This phytomedicine is currently available in Nigeria in encapsulated form. Recommended daily dose is between 250mg/350mg (Imaga, N., 2013). Niprisan has been shown to be affective in decreases the degree of sickling of the red blood cells in SCD patients. According to secondary sources, most patients taking Niprisan did not experience sickle cell crises while on the medication. Research performed at the Children's Hospital of Philadelphia (CHOP) and the University of Pennsylvania demonstrated the antisickling effects of Nicosan in an animal model (1). "The United States Food and Drug Administration (FDA) has determined there is sufficient safe and efficacy data for NIPRISAN to start a Phase III clinical trial." (IGIHE, 06-20-2013).

2- **Ciklavit:**

It is a plant extract preparation available for the management of sickle cell anemia condition. Ciklavit contains of the plant *Cajanus Cajan*, amino acids, vitamins (C and E) and minerals (Magnesium and Zinc). These vitamins and minerals can reduce the percentage of irreversibly sickled cells. Studies showed that zinc helps prevent sickle cell crises and reduce pain and risk complications. Magnesium can protects against potassium and water loss in sickle cells. Therefore, Ciklavit may cause reduction in pain crises and may involve the induction of fetal hemoglobin. In addition, it has reported to improve well-being of sicklers and to have antisickling properties (Imaga, N., 2013). Accordingly, Ciklavit may be a promising option for the treatment and management of sickle cell disease because of multiple reasons. First, it is demonstrated that Ciklavit may reduce the bone pains (painful crises) and promote the negative effect of sickle cell anemia on to the

liver. Second, it is commend that one of the mechanisms of action of Ciklavit may involve the introduction of fetal hemoglobin.

It is important to consult with a doctor or pharmacist before taking herbal medicines.

Some herbal medicine may contain high levels of heavy metals, including lead, mercury, and cadmium. Some herbs are toxic if used improperly or at high doses, and some may cause allergic reaction (University of Maryland Medical Center, 02-18-2014).

Chapter 3

Summary and Recommendations

Brief Summary and Evaluation of Existing Literature

The first reported cases of sickle cell anemia in the literature was in 1916s. Since that time, researchers has clearly shown that sickle cell disease is a heritable disease due to a recessive mutation in the gene that codes for the protein hemoglobin. Additionally, the consequences of that altered protein, including a sickle shape, reduced life span, and increased clotting of red blood cells, has been well documented.

While I was reviewing most available literature about sickle cell disease, I understand that sickle cell disease is a hard disease to describe. It is hard to describe how sickle cell disease is painful lifetime for not only the patients but also for patients' families and patients' friends. A child who receive two copies of sickle cell gene from both parents will born with sickle cell disease. After the fetal hemoglobin levels lower, symptoms will start. The person will suffer from pain crises for the rest of his life. The patient may develop any of the complications that are associated with sickle cell disease, such as kidney and liver failure. So, the person will live under pressure thinking that he never going to be better since there is no widely acceptable cure. The available treatments are just to treat the pain and prevent patients from complications that associated with the disease.

To date, there is no widely available and universally expected cure for sickle cell disease. Although bone marrow transplantation is an option, it's high cost and possess

significant potential for complications including death. These complications force all but the sickest individuals to forgo BMT as an option.

With no cure, many researchers have looked at possible treatments for the signs and symptoms of this disease. Most of these researchers have focused on traditional medical treatments including blood transfusions and hydroxyurea. Both of these treatments have been shown to treat some but not all of the symptoms associated with sickle cell. For example, they both can treat anemia and reduce of the pain severity, but they cannot relieve all the pain that patient's has. Both blood transfusion and hydroxyurea are associated with serious side effects. For example, patients who receive blood transfusion therapy may develop new antibodies, which is make dangerous to transfuse patients again. These new antibodies may result in rejection any of blood transfusions in the future. Additionally, with hydroxyurea, the biggest concern is that patients who used this option he may not be able to have children in future because infertility is one of hydroxyurea's side effects. I found, both in the literature and through personal experience, that doctors are not willing to explain or do not realize the side effects associated with these treatments. The majority of patients are not aware about the side effect of the treatment options, they just follow doctor recommendations. Unfortunately, not all doctors tells their patients about potential side effects of the treatment. For example, one of my son's doctor recommended hydroxyurea for my son as the best option for his sickle cell disease. When I have asked him about the side effects, his answered was that the side effects are nothing compared to his pain and complications of the pain. Although he mentioned that my son would have less pain crises a year, but he never mentioned that my son may not have children in the future as a side effect of

hydroxyurea. Another doctor recommended bone marrow transplant for my son when he was just one year old. When I have asked him about possible side effects, he mentioned that my son may get an infection. That was his entire answer. He did not tell me the infections may lead to death or that my son may develop leukemia as a side effect. My view is that not all patients have enough knowledge about health and disease issues. They may do what doctors see the best. Then they get disappointed with the side effects.

As a patient, patient's mother, reader and researcher I would rather have pain crises forever than developing some of these other complications from medical treatment. The major concern with sickle cell disease is that patients with sickle cell disease suffer of pain crises lifelong. Since the major cause of pain crises is the blockage of blood flow and anemia, I think it is time to think about alternative therapies that could help with the blood flow get have less side effects.

The purpose of this study was to investigate alternative therapies, such as nutritional supplement and phytomedicine to alter sickle cell pain crises among people with sickle disease and to look at the possible side effects associated with them. Alternative treatments, particularly nutritional supplementation have shown promise for treating sickle cell disease. As reported, people with sickle cell disease may not be able to practice their lives as normal people; they may need to take rest or hospitalizations for days or weeks to recover from pain crises.

While reviewing the available literature I found no shortage of information about the signs and symptoms of the disease but little information about alternative therapies. The available data about the relationship between sickle cell pain crises and alternative

therapy are limited and recent. In addition, there is inadequate literature about negative side effects associated with these alternative therapies.

There is some literature that talks antidotal about how nutrition therapy may be able to improve sickle cell patients' health and have less pain crises, and help to gain weight. The majority of these studies have been done using sickled mice, not human with sickle cell conditions. Furthermore, a literature about phytochemicals and sickle cell disease is also limited, and these literatures explained how that phytochemicals work inside patients' body to help them improve their health status. However, there is a lack information about phytochemicals (Niprisan and Ciklavit) and its effect on sickle cell disease. I could find no information about possible side effects associated with phytochemical in people with SCD. However, it is reasonable to assume that the side effects will be similar to those found in normal people.

In conclusion, I believe that I have reviewed most of the information that is available on nutrition supplementation, such as protein, vitamin D, vitamin C and zinc with sickle cell disease for further research, and come to the conclusion that further research is needed. Further research should decide the daily requirement for these supplements for people with sickle cell disease. In addition, further study should investigate another nutrition supplement that could help with the sickle cell pain. Finally, I would recommend that for future studies to investigate multi-nutritional supplements for sickle cell disease; studying all these supplements together instead of studying them as individually will be easier for sickle cell patients to deal with it.

Overall, this study showed another options besides medical treatment for sickle cell disease that could help to decrease the severe and length of pain crises. However, it

would be more helpful if patients use combinations of medical therapy and nutritional therapy recommendations and treatments.

Recommendation

Individual level Recommendations:

1. Patients with sickle cell disease should avoid temperature extremes, excessive heat or cold can cause pain crises. Wear warm clothes outside in the cold weather, and inside home id air-condition turn on in the hot weather.
2. Sickle cell patients should avoid stress; stress can be trigger for pain crises. They should get enough rest and sleep.
3. Sickle cell patients should exercise regularly, but do not exercise hardly. Also, they should avoid swimming in cold water.
4. Patients should not exposure for smoking or second hand exposure. There a study estimated that patients with sickle cell disease who are exposure to smoking have chance to increase their crisis risk by 90% (University of Michigan Health System, 2009).
5. A heating pad is useful for patients who are complain from join pain.
6. Patients with sickle cell disease should drink plenty of water, so can avoid dehydration, which cause pain crises. They should drink eight glasses; 12 ounces at least.
7. Patients with sickle cell disease should take one-milligram folic acid daily because it documented that folic acid helps to raise hemoglobin level (Ndefo et al, 2008).

8. Sickle cell patients should eat and drink as recommended serving of all the nutrition serving to avoid any complications that could worsen the disease.

As personally recommendation, I believe that people with sickle cell disease should start dealing with alternative therapies for sickle cell disease; nutritional supplementation and phytomedicines for multiple reasons. First, they have no or less that we know of side effects compared with medical options. Second, they can help people with sickle cell disease to practice their normal lives as their peers with having less pain crises, which is a major symptom of the disease.

Organizational Level Recommendations:

1- Schools should have a class to raise the awareness of disease, its treatment, so patients can learn to keep their health away from risk complications. Schools are considered as a greatest source for students to gain knowledge.

2- Schools and daycares in United States have a rule that take children outside to play in the playground from half an hour to hour even if the weather is really cold. They should note that children with sickle cell disease can have pain crises from the cold weather. Therefore, they should make exception for children with sickle cell disease because of their conditions.

3- Work places should give workers with sickle cell disease additional time to take rest, so workers with sickle cell disease can have less stress, which can help to keep those workers away from pain crises; therefore, they will not be absent from their work for several days or weeks in order to treat their conditions.

- 4- Hospitals should have screening program for sickle cell disease for newborn babies, so they can get well treatment it before any complications.
- 5- Doctors and health care provider should encourage patients to get a flu vaccine. A flu vaccine may prevent from getting cold.
- 6- Government should establish screening program for sickle cell disease for people who wants to married. If the screening showed both have sickle cell trait or disease, they should not get married because this the only way to get decrease the incidence of the disease.
- 7- Government should encourage researchers and spend more money on research that are dealing with sickle cell disease treatments, so hopefully with extensive study and research can reach the cure treatment for the disease.
- 8- Government should have centers, clinics and hospitals special for sickle cell disease, so patients can regularly followed up by physicians, which help to prevent these patients from developing any complications.
- 9- Hospitals should increase the people's awareness about sickle cell disease. And how to reduce the incidence of the disease by making videos, handouts and programs that show the problem and treatment options and solutions for the next generations.

Suggestion for Future Research:

Sickle cell disease is a chronic disease, which means people with sickle cell disease will live their whole lives with pain. Because there is no widely and universally cure treatment for the disease, I highly suggested for further research to focus on how can

decrease the number and severity of the pain crises that occur in a year by nutrition. I suggest for further research to focus more on nutritional supplementation because it has shown potential to decrease the number and severity on pain crises with few side effects compared with the available medical treatments. Specifically, future research into nutrition should focus on: 1- Food and sickle cell crises, which food can help to increase red blood cell, which can prevent from severe complication. 2- Food and fetal hemoglobin, which food can increase fetal hemoglobin in the blood. When the fetal hemoglobin increased, the pain crises decreased

Appendix 1

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Sickle Cell Disease Nutrition Therapy—Page 1

Client Name _____ Date _____

RD/DTR _____

Email _____ Phone _____

Sickle Cell Disease Nutrition Therapy

This nutrition therapy will help you gain or maintain weight.

Recommended Foods

Source: Adapted from High-Calorie/High-Protein Diet. In: Nevin-Folino NL, ed. Pediatric manual of clinical dietetics, 2nd ed Update. Chicago, IL: American Dietetic Association; 2008: 642-643.

Beverages

- Whole milk with instant breakfast
- Liquid supplements
- Fruit nectars

Soups

- Creamed meat, bean, or pea soups

Meat and meat substitutes

- Fried or smothered meats (chicken, fish, beef, pork)
- Fried or smothered eggs
- Baked or refried beans
- Peanut butter

- Nuts
- Add dry milk powder to milk, soups, sauces, and casseroles.

Vegetables

- All vegetables made with added fat (margarine, butter, or cheese) Vegetables fried in oil
- Dark green or yellow vegetables like acorn squash, greens, sweet potatoes (sweet potato pie), carrots, pumpkin, broccoli, or spinach

Fruits

- Canned fruit in heavy syrup
- Fresh fruits such as blackberries, oranges, strawberries, or kiwi
- Yellow fruits such as apricots, cantaloupe, or peaches

Bread/cereals/starches

- Hot cereals made with milk, butter or margarine, and sugar
- Breads, pasta, rice, or potatoes made with butter, oils, margarine, or cheese
- Granola and other cereals with dried fruit

Milk

- Whole milk and milk products (yogurt, ice cream, cheese, shipped cream, half & half, heavy cream)
- Low-lactose milk if milk not tolerated
- Add dry milk powder to cream soups, cream sauces, and casseroles

Fats

- All oils, butter, margarine, mayonnaise, olives, salad dressings, gravy

Beverages

- Drinks with caffeine such as tea, coffee, and some soft drinks

Soups

- Low-calorie broths

Meat and meat substitutes

- Meats cooked in water or broth
- Baked meats should include gravy

Vegetables

- Plain vegetables cooked in water and served without added fat

Fruits

- More than two servings of fresh fruit per day

Bread/cereals/starches

- Nonfat and/or low-calorie breads and cereals
- Plain bread, cereals, rice, or pasta

Milk

- Fat-free and reduced-fat dairy products
- Fats Fat-free and reduced-fat foods

Source: Adapted from High-Calorie/High-Protein Diet. In: Nevin-Folino NL, ed. Pediatric manual of clinical dietetics, 2nd ed Update. Chicago, IL:

American Dietetic Association; 2008: 642-643.

Sickle Cell Disease Nutrition Therapy—Page 3

Meal Planning Tips

Ways to get more calories and protein

- Use light cream instead of milk
- Have cinnamon toast, pancakes, waffles, or French toast instead of plain toast at breakfast
- Use cream mixed with evaporated milk to make drinks like eggnog, milkshakes, or malted milk.
- Add skim milk powder to regular milk, soup, pudding, or hot cereal.
- Have gravies and sauces when you can.
- Snack on dried fruits or nuts between meals.
- Add mayonnaise, oils, salad dressings, margarine, or butter to sandwiches, salads, or vegetables.
- Have ice cream or whipped cream with desserts.
- Add jams, jellies, or preserves with butter or margarine to plain bread.
- Drink high-calorie, high-protein liquid supplements between meals and with meals. Keep chilled cans at the bedside of patients so they can drink anytime (St. Jude Children's Research Hospital, 2003).

Sickle Cell Disease Nutrition Therapy—Page 4

Sample 1-Day Menu

Breakfast

- ½ cup orange juice
- 1 cup cornflakes with 1 tablespoon sliced almonds and 1 tablespoon raisins
- 1 cup whole milk
- 1 slice toast with 1 teaspoon margarine and 1 tablespoon jelly

Lunch

- Turkey sandwich: French roll, 2 ounces turkey, 1 ounce Swiss cheese, 2 tablespoons mayonnaise, 1 slice tomato
- 1 banana
- 4 chocolate-covered graham crackers

- 1 cup whole milk

Evening meal

- 3 ounces meatloaf
- Baked potato with 1 tablespoon margarine and 4 tablespoons sour cream
- ½ cup green beans with 1 teaspoon margarine
- Dinner roll with 1 tablespoon margarine and 1 tablespoon jelly
- 1 cup tossed green salad with 2 tablespoons ranch dressing
- ½ cup canned fruit cocktail with ½ cup ice cream
- 1 cup whole milk

Source: Farmer G. Pass the Calories, Please! Chicago, Ill: American Dietetic Association; 1994:12-13.

Approximate Nutrition Analysis:

Calories: 2,730; Protein: 76g (11% of calories); Carbohydrate: 318g (46% of calories); Fat: 135g

(43% of calories); Cholesterol: 3237mg; Sodium: 2,924mg; Fiber: 20g

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