Nutritional Status of Sickle Cell Patients: A Literature Review

Minjoon Hur

Abstract
Sickle cell disease (SCD) is a lethal, life-long condition characterized by a mutation in the gene that codes for hemoglobin. To alleviate the pain experienced by sickle cell (SC) patients, adequate nutrition levels are vital as deficiencies of vitamins or minerals may cause other symptoms. The objective of this review is to outline the nutrient status of SC patients and propose research areas where further study is needed. This review summarizes twelve primary research papers that measured the level of vitamins A, C, D, E, B-2, B-6, B-12, folate, magnesium, iron, zinc, and copper in SC patients. The majority of SC patients had suboptimal vitamin A levels and were vitamin D deficient. Their zinc and vitamins B-6, C, and E levels were adequate, while their folate, copper, and iron levels were elevated. There were notable differences in some of the measurement methods used for the same nutrient levels. There is more research needed to find the optimal amount of vitamin A supplement for SC patients, and the effect of zinc supplementation on copper levels and the cause of low zinc levels in SC patients remains unexplored.

Keywords
Sickle Cell Disease, Nutrient Deficiency, Vitamins, Minerals

Introduction
Sickle cell disease (SCD) is a group of inherited genetic disorders characterized by a mutation in the gene that codes for hemoglobin subunit β.[1-2] The gene mutation replaces the glutamic acid with valine at position 6 in the β-globin chain.[1] The change in the primary structure of the polypeptide alters the product from Hemoglobin A to Hemoglobin S (HbS), resulting in the production of erythrocytes with sickle shape.[2] Increased sickle erythrocyte concentration causes vaso-occlusion (blockage of blood vessels), which leads to insufficient oxygen transport to tissues and organs.[2] Vaso-occlusion then causes frequent pain in bones and joints, inflammatory response, and oxidative stress.[2] These symptoms are not uncommon, as about one in twenty people in the human population carry the trait gene for hemoglobin (Hb) disorders: HbS.[3] Patients with SCD have a significantly lower life expectancy of 54 years, making it a lethal condition as those without SCD have a life expectancy of 76 years.[4]

The severity of the disease is determined by the concentration of HbS, which depends on the genotype of the patient.[2] The most severe genotype is HbSS, followed by $HbS\beta^0$-thalassemia, $HbS\beta^+$-thalassemia, and HbSC.[2]

Good nutrition is vital for overall health as it provides the body with essential nutrients for proper organ function, cellular repair, and an effective immune system.[6] These crucial nutrients include vitamins, minerals, carbohydrates, proteins, and fats. When one lacks any of these nutrients, they are likely to develop malnutrition, anemia, and chronic diseases.[7,8]

With abnormal nutrient levels commonly found in them, sickle cell (SC) patients are at risk of developing these diseases.[5] The abnormal nutrient levels may also decrease their quality of life and increase their mortality. To prevent SC patients from developing the symptoms mentioned above, the paper will outline the nutrient deficiencies and elevations present in SC patients by using the primary data gathered by researchers. Most of the primary data will be from papers published after the year 2010, as a review paper discussing nutrition in SCD had been published that year.[5] With the latest primary data, this paper will provide an updated review of the nutrition status of SC patients.

Discussion

Twelve primary research papers that investigated nutrient levels in SC patients were collected and summarized. Of the 12 research papers collected, two were randomized clinical trials and the rest were cross-sectional studies. The nutrients evaluated in the papers were vitamins A, C, D, E, B-2, B-6, B-12, folate, magnesium, iron, zinc, and copper. For each nutrient, the nutrient deficiency cutoff was researched and noted. Units of the deficiency cutoff values were manually converted to match the units of the measured values in the primary research papers. The cutoff values were then compared to the values obtained from SC patients to determine whether deficiencies or elevations of the nutrient were evident in SC patients.

Zinc

Zinc is essential for cellular and subcellular metabolism; it is an essential component of the catalytic sites of enzymes and may have a specific role in many other biological proteins.[9] Zinc is also responsible for the absorption, mobilization, transport, and metabolism of vitamin A.[10] The most widely used biomarker for measuring zinc content in our body is serum zinc, with the cutoff value for zinc deficiency being <60 µg/dL.[11] This method was used by a cross-sectional study that took place in India.[10] After recruiting 33 homozygous SC patients and 33 age and sex-matched healthy controls, the study compared the serum zinc level in SC patients to that of normal controls.[10] The main objective of the paper was to evaluate plasma vitamin A, C, and E levels and serum zinc and copper levels in adolescent patients with HbSS.[10] All subjects were aged 10-20 years and had no history of blood transfusion within 3 months, a factor that may significantly affect the concentration of zinc.[10] Subjects with chronic ailments, diabetes mellitus, or SCD cases with an acute crisis, together with patients on multivitamin supplementation, were excluded from both the patient and control groups[10]. The serum zinc concentration in SCD and normal control were 83 ± 9 µg/dl and 104 ± 6 µg/dl respectively[10]. This indicated that none of the SC patients were zinc deficient, as all subjects in the study had serum zinc concentrations greater than 80 µg/dL.[10, 11]

A cross-sectional study that took place in Saudi Arabia also concluded that there was no zinc deficiency in SC patients.[12] Using the same measurement method with 25 SC patients that have severe sickle cell anemia (SCA), the study was designed to evaluate levels of vitamins A, C, and E and elements zinc and copper.[12] The exclusion criteria of the study were individuals younger than 15 years of age, the presence of β- or α-thalassemia trait, glucose-6-phosphate dehydrogenase deficiency, regular blood transfusion, treatment with hydroxyurea, use of vitamin and trace element supplements other than folic acid, illness other than sickle cell manifestations, or pregnancy.[12] The mean measured serum zinc level was about 65 µg/dL, which is above the

deficiency cutoff.[12] Nevertheless, the results still show that SCA patients have lower serum levels of zinc when compared to the controls.

Both papers show that SC patients have serum zinc levels that are lower than the normal controls but are above the zinc deficiency cutoff value. Therefore, the SC patients in these studies do not have a zinc deficiency.

Vitamin A

Vitamin A is responsible for immune function, growth, development, reproduction, and, most importantly, vision.[13] Its concentration in the body is commonly measured by the plasma retinol test, with a concentration of <20 µg/dL considered deficient, and a concentration of 20-29 µg/dL considered suboptimal.[13] Vitamin A deficiency in patients may lead to night blindness, a decrease in growth rate, and a decrease in bone development rate.[14] To determine whether SC patients are also at risk of developing disorders related to vitamin A deficiency, a randomized controlled trial in the United States investigated the effect of giving supplemental vitamin A to children with SCD by measuring their plasma levels before and after the supplementation.[13]

The study aimed to determine whether 3 different doses of supplemental vitamin A (300, 400, or 600 µg of retinyl palmitate per day) on SCD would optimize vitamin A status in SC patients with the HbSS genotype. Subjects aged 2-13 years were enrolled.[13] The exclusion criteria included chronic transfusion therapy or a transfusion within the past 2 months, hydroxyurea therapy, history of stroke, liver enzymes >3 times the reference range, height >2.0 standard deviations above the age and sex mean, participation in another intervention study, pregnancy, and other chronic conditions known to affect growth, dietary intake, or nutritional status.[13] The mean initial plasma retinol concentration of children with SCD was 26 ± 8 µg/dL, which is considered suboptimal, but not deficient.[13] Low levels of vitamin A were also witnessed by Hasanato et al., as their SC patients also had lower mean plasma retinol concentration than that of normal, healthy controls.[12]

Both of these papers lean towards the conclusion that SC patients have lower vitamin A levels than healthy controls, but none of them noted that SC patients were vitamin A deficient. Therefore, there was no vitamin A-deficient SC patient in the studies reviewed.

Vitamin E

Vitamin E is the major lipid-soluble component in the cell antioxidant defense system.[15] As an antioxidant, it is shown to be effective against diseases caused by oxidation.[15,16] The most widely used method for its measurement is the serum α-tocopherol test, with a concentration of 5 µg/ml marking vitamin E deficiency.[17] This test was used by Wasnik et al. in 2017 to evaluate the vitamin E status of SC patients.[10] The design for this study has been thoroughly described in the subsection on zinc. The serum α-tocopherol count in SC patients and controls in the study were 9 ± 1 µg/mL and 12 ± 2 µg/mL respectively.[10] As the mean serum vitamin E of SC patients was greater than the cutoff, most SC patients in the study were not vitamin E deficient, and they are not expected to experience the symptoms of vitamin E deficiency.[17] Even so, lower levels of vitamin E should not be ignored as tissues in need of α-tocopherol may be damaged when needs exceed the amounts available.[17]

Low levels of vitamin E were also witnessed by Hasanato et al., as the mean serum vitamin E concentration of SC patients was about 2 µg/mL.[12] This value is far below the cutoff deficiency, and if the measurement was accurate, SC patients are at risk of experiencing increased infection, anemia, and stunting of growth.[17] The difference between the measured values may be due to their different measurement methods: the study of Wasnik et al. used the modified method of serum E estimation, while the study of Hasanato et al. used the long-term freezer storage method.[10,12,39,40] As the long-term freezer storage method may be erroneous due to the potential degradation of the sample over time, the values obtained by the study that took place in India are probably more accurate.[39] Though their measurement methods differ, both papers show suboptimal vitamin E levels in SC patients.[10,12] Therefore, it is likely for SC patients to have suboptimal vitamin E levels.

Vitamin C

As an antioxidant, vitamin C is a micronutrient with pleiotropic functions.[19] It supports the human immune system and is a cofactor for a family of biosynthetic and gene-regulatory enzymes.[19] It is commonly measured by plasma ascorbic acid (a type of vitamin C), with a cutoff value for deficiency of <11 µmol/L.[21] Hasanato et al. examined the vitamin C status of 25 patients by measuring their plasma levels of ascorbic acid.[12] The design for this study has been thoroughly described in the subsection on zinc. The study found that the mean plasma vitamin C in patients was approximately 57 µmol/L, indicating that SC patients were not vitamin C deficient.[12] Furthermore, the plasma levels of vitamin C in the SC patients were about half as large as those of the controls.[12]

Low vitamin C levels were also observed by a cross-sectional study in Nigeria.[44] 80 SC patients with HbSS aged 1-15 years and 80 age and gender-matched healthy HbAA controls were recruited.[44] The exclusion criteria included the presence of febrile illness, history of blood transfusion in the past three months, history of hydroxyurea or chronic blood transfusion, and history of taking antioxidant supplements.[44] The study aimed to explore the relationship between the frequency of vaso-occlusive crises and plasma levels of antioxidant trace elements including vitamin C.[44] The vitamin C level of SC patients and controls in the study was 38 ± 10 µmol/L and 63 ± 17 µmol/L respectively.[44] These values support the ones obtained by Hasanato et al. as the vitamin C levels in SC patients are above the deficiency cutoff but are lower than the controls.

The big difference between the plasma ascorbic levels in patients and controls made researchers conclude that SC patients have vitamin C deficiency; but as their plasma vitamin C levels are higher than the deficiency cutoff, SC patients have adequate vitamin C and are unlikely to experience the common symptoms of vitamin C deficiency.[12,20]

Copper

Copper is required in redox chemistry for the production of many proteins, including enzymes[22]. The most widely used biomarker for evaluating copper status is serum copper, with a value of 64-140 µg/dL considered adequate.[23,41] By measuring this biomarker, a cross-sectional study in Ghana measured and compared copper levels in 90 SC patients aged 14-53 years and 50 healthy controls aged 22-43 years.[22] Of the 90 SC patients, 41 had the HbSC genotype and 49 had the HbSS genotype.[22] All 50 controls held the HbAA genotype, and any subjects with diabetes, renal disease, gastrointestinal disease, or coronary artery disease were excluded from

the study.[22] As it aimed to evaluate serum iron, copper, and zinc levels in SC patients, the study also excluded patients with a history of blood transfusion 3 months before the study.[22] The mean serum copper levels of SC patients and controls were 221 ± 28 μg/dL and 114 ± 16 μg/dL, respectively.[22] As the mean copper level of SC patients in this study was elevated, SC patients in the study were at risk of developing stomach pain, extreme thirst, and changes in taste that may lead to decreased appetite.[23,24]

Elevated copper levels in SC patients were also seen in research done by Emokpae and Fatimehin.[45] Seeking to evaluate the levels of serum copper and zinc in SC patients, 100 confirmed SCD patients with a mean age of 19 ± 1 years and aged-matched healthy subjects were recruited in the study.[45] The mean serum copper levels in SC patients and the controls were 184 μg/dL and 107 μg/dL respectively.[45] The mean copper level of SC patients in this study, too, was elevated.[23,45]

Both of these papers show higher levels of copper in SC patients, so there was copper elevation in SC patients in the studies reviewed.

Vitamin D

Vitamin D is crucial for calcium absorption and maintenance of normal serum calcium and phosphate levels.[25] It also plays a vital role in immune function, cell proliferation, differentiation, and apoptosis.[26] These crucial tasks may not be completed efficiently when an individual is vitamin D deficient. Vitamin D deficiency (VDD) may also lead to osteoporosis (brittle bones) and increased fragility fractures.[42] VDD is commonly diagnosed by measuring the biomarker serum 25-hydroxyvitamin D (25(OH)D).[26] A serum 25(OH)D concentration of 30-60 ng/mL is considered optimal, while values below 30 ng/mL and 20 ng/mL are considered suboptimal and deficient, respectively.[26] By measuring and comparing the serum 25(OH)D level of 640 SC patients to the cutoff values, a cross-sectional study in Saudi Arabia evaluated the vitamin D status in SC patients.[26] All patients enrolled in the study were 12 years old and older, and there were no controls.[26] About 82% of the patients had suboptimal 25(OH)D, while 67% were deficient.[26] Middle-aged (45-65 years) and elderly (>65 years) patients had higher 25(OH)D levels than young patients, with females having slightly higher 25(OH)D levels than males.[26] Furthermore, SC patients with crisis had higher average 25(OH)D levels than those patients in steady state condition.[26] As the majority of SC patients have insufficient serum 25(OH)D levels, they are also vitamin D deficient.

Folate, vitamins B-2, B-6, and B-12

Folate (vitamin B-9) is essential for the production of red blood cells and is vital in one-carbon metabolism, which is essential for the synthesis of DNA and RNA.[27] Vitamins B-2, B-6, and B-12 are required for the production of the universal methyl donor, S-adenosylmethionine.[27] To determine whether these metabolic reactions were carried out efficiently in SC patients, a cross-sectional study in Canada measured the folate concentrations and B-vitamin levels in the blood of Canadian children with SCD supplemented with 1 mg of folic acid daily as their regular treatment.[27] All 11 patients were aged 2-19 years, with 8 holding the HbSS genotype, 2 holding the HbSC genotype, and 1 holding the HbSβ^0 -Thalassemia genotype.[27] The obtained concentration of each B vitamin and the cutoff value for the deficiencies are listed below:

Table 1.
Obtained concentrations and the cutoff values for B vitamins. B-vitamin biomarker concentrations were measured in plasma (n = 8) and serum (n = 3) for folate forms, in plasma (n = 10) and serum (n = 1) for vitamin B-12, and in plasma for pyridoxal 5′-phosphate (n = 11) and vitamin B-2 (n = 11).[27]

Vitamin type	Obtained concentration (nmol/L)	Deficiency cutoff value[27] (nmol/L)
B-2	15.9	N/A
B-6	36.9	30
B-9	62.0	10
B-12	0.4	0.15

As seen in Table 1, SC patients who were supplemented with 1 mg/d of folic acid were not vitamin B-6, B-9, or B-12 deficient. However, without the supplement, a decrease in the number of patients with vitamin B-6 deficiency is expected as supplemental folic acid can reduce plasma levels of pyridoxal 5'-phosphate (PLP), an activated form of vitamin B-6.[27,46] None of the patients showed folate deficiency.[27] In fact, the mean total folate level (62.0 nmol/L) exceeded the limit for normal folate (45.3 nmol/L), indicating that the patients had elevated folate after the supplement. 73% of the participants in the study had plasma riboflavin (a type of vitamin B-2) concentration below the change point of 26.5 nmol/L, which indicates vitamin B-2 deficiency.[27] However, as no validated cut-off for the nutrient exists, it is not possible to confirm whether vitamin B-2 was deficient in SC patients without the presence of normal, healthy controls.[27]

Magnesium
Magnesium is key in many cellular processes including intermediary metabolism, DNA replication and repair, and transporting potassium and calcium ions.[28] Serum magnesium is used to measure magnesium levels in the body, with a deficiency cutoff value of 0.8 mmol/L.[29] Using serum magnesium as an indicator of magnesium status in subjects, a cross-sectional study measured the magnesium content in 120 SC patients with HbSS and HbSC genotypes and 48 healthy controls with the HbAA genotype.[32] Patients with coronary artery disease, diabetes mellitus, hypertension, renal failure, pregnancy, and a history of blood transfusion within three months before the study were excluded.[32] The patients and the controls had serum magnesium levels of 0.80 ± 0.24 mmol/L and 0.90 ± 0.11 mmol/L, respectively.[32] As both values were above the cutoff value for magnesium deficiency, SC patients were not magnesium deficient.

Lower magnesium content in SC patients was also shown by a randomized trial that measured the magnesium content in 10 HbSS treated with oral magnesium supplements (0.6 meq/kg per day of magnesium pidolate).[30] The study aimed to evaluate whether magnesium supplementation to SC patients reduces the number of sickled erythrocytes. The trial enrolled

45 patients who were 19 years and older, along with 17 controls with a mean age of 32 ± 9 years.[30] The inclusion criteria included normal renal and liver function, performance status of 70% or greater, and no blood transfusions during the preceding 3 months.[30] Using plasma magnesium and erythrocyte magnesium as the biomarkers, the authors measured the magnesium content in HbSS and HbSC patients before the supplementation, 14 days after the supplementation, and 28 days after the supplementation.[30] The initial erythrocyte magnesium levels in HbSS and HbSC patients and the controls were 7 ± 1 mmol/kg Hb, 6 ± 1 mmol/kg Hb, and 9 ± 1 mmol/kg Hb respectively.[30] The paper does not show the data on plasma magnesium as there were no significant differences between the plasma magnesium levels of HbSS patients, Hb SC patients, and normal controls.[30] The magnesium content after 14 and 28 days of supplementation was only measured on 10 HbSS patients, and this data is represented in the table below.[30]

Table 2.
Mean plasma and erythrocyte magnesium concentrations in HbSS patients at baseline, 14, and 28 days after supplementation

Time (days)	Plasma Magnesium (mmol/L)	Erythrocyte Magnesium (mmol/kg Hb)
Baseline	0.86 ± 0.06	5.18 ± 0.24
14	0.95 ± 0.11	9.34 ± 2.30
28	0.94 ± 0.09	11.40 ± 1.20

As shown by Table 2, there was a significant increase in sickle erythrocyte magnesium content in HbSS patients.[30] There was no significant change in the plasma magnesium level, though.[30]

Both papers show that SC patients have a magnesium level that is above the deficiency cutoff, so SC patients in the studies had adequate magnesium levels in their bodies. However, with a mean serum magnesium value that is close to the deficiency cutoff value, SC patients are at risk of developing symptoms including chronic diseases, insulin resistance, and type-2 diabetes.[33]

Iron
Iron is an essential element as it is responsible for blood production as it is a component of hemoglobin.[34] It is also an essential component for electron transport and DNA synthesis.[43] The iron status of an individual is commonly assessed by measuring the biomarker serum ferritin, with a reference range of 12-300 ng/mL.[35]

Two studies with differing opinions regarding the deficiency of iron in SC patients were studied. The first study was a cross-sectional study that took place in Nigeria.[36] The authors determined whether iron was deficient in patients with SCD by measuring the concentration of serum ferritin in 43 HbSS patients aged more than 14 years and 43 age and sex-matched HbAA controls.[36] Exclusion criteria included a history of blood transfusion in the previous 3 months or any form of SC crisis within 2 weeks of the study. The results showed that only 7% of the SC patients were

iron-deficient and that the mean serum ferritin (559 ± 428 ng/mL) in SC patients was significantly higher than the mean serum ferritin of the controls (185 ± 120 ng/mL).[36] In fact, the value was even higher than the upper limit of the reference range (300 ng/mL). This indicates iron elevation, which may be caused by vitamin B 12 deficiency, folate deficiency, myelodysplastic syndrome, or malignancy in SC patients.[37]

The other study was also a cross-sectional study with 40 SCD patients and 30 age-matched controls enrolled.[38] All subjects were 3-18 years old, and they all had hemoglobin levels <11 g/dL.[38] The study measured the level of transferrin soluble receptors (sTfR) to determine whether iron was deficient. As the body increases the production of sTfR in response to low iron levels, iron deficiency is marked by an sTfR value greater than 1.8 mg/L.[47,48] The authors of the cross-sectional study found that 97.5% of the patients had higher sTfR values, but it is difficult to say that SCD is solely responsible for this increase as sTfR values could also be affected by hemolysis (destruction of red blood cells).[38,48]

Though the two papers have different conclusions, they both suggest that SC patients are not iron deficient, but they have elevated iron levels.

Overview, Limitations

Table 3. Overview of Nutrient Status of SC patients.

Nutrient	Measurement method/Biomarker used	Measured value	Cutoffs	Deficient/Suboptimal/Elevated
Vitamin A	Plasma Retinol	26 ± 8 µg/dL	- Suboptimal if 20-29 µg/dL - Deficient if <20 µg/dL	Suboptimal
Vitamin B-2	Plasma Riboflavin	15.9 nmol/L	No validated cut-off value exists	Unable to Determine
Vitamin B-6	Plasma PLP	36.9 nmol/L	- Deficient if <30 nmol/L	Adequate
Vitamin B-12	Plasma and Serum Vitamin B-12	405 pmol/L	- Deficient if <150 pmol/L	Adequate
Vitamin C	Plasma Vitamin C	Approximtely 10 mg/L	- Deficient if <1.937 mg/L	Adequate
Vitamin D	Serum 25-hydroxyvitamin D	14.3 ng/mL	- Optimal if 30-60 ng/mL - Suboptimal if <30 ng/mL - Deficient if <20 ng/mL	Deficient
Vitamin E	Serum α-tocopherol count	8.662 ± 1.137 µg/ml	- Deficient if <5.168 µg/ml	Adequate
Folate (Vitamin B-9)	Plasma and Serum Folate	62.0 nmol/L	- Deficient if <10.0 nmol/L - Elevated if >45.3 nmol/L	Elevated
Magnesium	Serum Magnesium	0.80 ± 0.24 mmol/L	- Deficient if <0.8 mmol/L	Adequate
Copper	Serum Copperl	220.9 ± 27.8 µg/dL	- Optimal if 63.7-140.12 µg/dL	Elevated
Zinc	Serum Zinc	83.09 ± 9.26 µg/dl	- Deficient if <60 µg/dl - Optimal if ≥80 µg/dl	Adequate
Iron	Serum Ferritin	559.33 ± 427.61 ng/mL	- Elevated if >300 ng/mL	Elevated

As shown by Table 3, it was clear that the majority of SC patients had suboptimal vitamin A levels and were vitamin D deficient. Their zinc and vitamins B-6, C, and E levels were adequate, while their folate, copper, and iron levels were elevated.

However, there were some limitations in some of these research papers: sample sizes were often small,[12,27] the most accurate method may not have been used,[30,36] and exact numerical values were not recorded.[12] For instance, for iron, two studies used different biomarkers to assess iron status in SC patients,[36,38] one used the serum ferritin method, while the other used sTfR. Ironically, both authors favored the other method over the method they used. The author who used serum ferritin stated that measuring sTfR is a more reliable index of iron status in SC patients than serum ferritin due to the low sensitivity of serum ferritin in SCA.[36] The author who used sTfR, on the other hand, stated that serum ferritin is a better biomarker for iron deficiency as sTfR could be affected by hemolysis and therefore has limits in terms of accuracy.[22,38] Despite the conflicting views of the two, both papers concluded that SC patients had elevated iron.[36,38]

The differences in methods used were also seen in papers that measured magnesium content in SC patients.[30,32] One paper measured serum magnesium,[32] while the other measured erythrocyte magnesium.[30] It has been suggested that measuring the erythrocyte magnesium content is not the most accurate way to represent magnesium content in one's body,[31] so data from the paper that measured serum magnesium could be considered more reliable. Despite the difference in their measurement methods, both papers claimed that SC patients had reduced magnesium content but are not magnesium deficient.[30,32]

There were limitations in other reviewed studies as well. The study that measured vitamin D did not analyze other factors that may have affected the vitamin D levels in the subjects.[26] These factors include nutritional status, physical activity, lack of sun exposure, medications that alleviate SCD crises, and other illnesses.[26]

For the measurement of the vitamin C level in SC patients, none of the studies used the most accurate method, which is measuring vitamin C in neutrophils. This may be due to the fact that the equipment required to ensure vitamin C in neutrophils is not widely available. Therefore, researchers who conducted the studies used the plasma vitamin C level instead to determine whether SC patients were vitamin C deficient.[12,44]

For vitamin B-2, its status is usually determined using the erythrocyte glutathione reductase activation coefficient, which was not available in the study conducted by Williams et al.[27]

Conclusion

Though many nutrient deficiencies in SC patients were initially suspected, SC patients were only deficient in vitamin D. Instead, they had elevated levels of vitamin B-9, copper, and iron. Low plasma riboflavin levels in the patients were shown,[27] but it is not possible to confirm vitamin B-2 deficiency as there is no established deficiency cutoff for the nutrient. The patients also had adequate levels of vitamins B-6, B-12, C, and E, magnesium, and zinc as none of the measured values of these nutrients were below the deficiency cutoffs. However, though they had adequate levels of these nutrients, SC patients generally had lower levels of these nutrients than the

healthy population. As both lower and elevated nutrient levels impede normal body function, SC patients are at risk of experiencing various toxic effects. There is more research required to understand the sodium/magnesium transporter in order to find the cause of reduced magnesium content found in SC patients.[30] There is also a need for another study that involves age and sex-matched healthy control to determine whether SCD is solely responsible for VDD, and not the other factors. Furthermore, further research is needed to confirm whether VDD worsens chronic pain in SC patients.[26] With no improvement of vitamin A status in those taking 600 µg of vitamin A every day, a study that tests the effect of a daily supplemental dose of retinyl palmitate of over 600 µg on those aged 14-18 years with SCD must be conducted. Such an age group is selected as according to the National Institutes of Health, the upper limits for supplemental vitamin A for individuals aged 14 years and above are 900 µg per day.[18] The effect of zinc supplements on the vitamin A levels of SC patients must also be explored. The confirmation of whether low zinc levels in SC patients are due to excessive destruction of red blood cells or excessive excretion is required.[10] The effect of zinc supplementation on copper levels in SC patients must also be studied.[22] This literature review analyzed the existing studies that measured the nutrient status in SC patients.

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Author

The author, Minjoon Hur, is a high schooler at Raffles Christian School in Indonesia passionate about nutrition science and biomedical sciences. He hopes to become a pharmaceutical researcher or a nutritionist and plans to conduct quantitative primary research in the near future.