

REVIEW

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## The Role of Nutrition in Sickle Cell Disease

H.I. Hyacinth, B.E. Gee and J.M. Hibbert

Morehouse School of Medicine, 720 Westview Drive SW, Atlanta, GA 30310, USA.  
Corresponding author email: [jhibbert@msm.edu](mailto:jhibbert@msm.edu)

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**Abstract:** Finding a widely available cure for sickle cell anemia (HbSS) still remains a challenge one hundred years after its discovery as a genetically inherited disease. However, growing interest in the nutritional problems of the disease has created a body of literature from researchers seeking nutritional alternatives as a means of decreasing morbidity and improving quality of life among HbSS patients. This review demonstrates that over the past 30 years the role of protein/energy deficiency in HbSS has been more clearly defined via direct measurements, leading to the concept of a relative shortage of nutrients for growth and development, despite apparently adequate dietary intakes. Although there is still a paucity of data supporting the efficacy of macronutrient supplementation, it is becoming clearer that recommended dietary allowances (RDAs) for the general population are insufficient for the sickle cell patient. A similar shortage is likely to be true for micronutrient deficiencies, including recent findings of vitamin D deficiency that may be associated with incomplete ossification and bone disease, which are well known complications of HbSS disease. We conclude that there is need for more effort and resources to be dedicated to research (including supplementation studies of larger sample size) aimed at establishing specific RDAs for HbSS patients, much like the specific RDAs developed for pregnancy and growth within the general population.

**Keywords:** nutrition, sickle cell disease

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## Introduction

Sickle cell disease refers to a group of hemoglobinopathies in which at least one sickle (S) beta-globin gene is inherited together with another type of abnormal hemoglobin. The most common of these diseases are sickle cell anemia (HbSS), hemoglobin SC disease (HbSC) and hemoglobin S $\beta$  thalassemia (HbS $\beta^{\text{thal}}$ ) minor and major.<sup>1</sup> Of this group, patients with sickle cell anemia (HbSS) suffer most severely and people of African descent are primarily affected. Although the initial mutation has been traced to west Africa<sup>2,3</sup> HbSS has assumed worldwide geographic distribution via slave trade and migration. Today, the sickle hemoglobin is known to interact with diverse gene and environmental factors, producing a multisystemic disease with several phenotypes.<sup>4</sup> This review addresses HbSS, with typically high severity and costly treatment.<sup>5,6</sup>

Since HbSS was first described in 1910, effort has been made to develop clinical care to lessen the severe clinical problems, mainly frequent hospital admissions for recurrent painful episodes. However, only since the late 1980's has under-nutrition been considered as a serious complication of the disease that should be treated as part of required clinical care.<sup>7-9</sup> Given the chronic nature of HbSS symptoms,<sup>10-12</sup> the best hope for most patients is a low-cost self-administered oral therapy. Currently, the only such treatment is hydroxyurea used for its benefit of increasing fetal hemoglobin level and which is reported to improve growth in children with the disease,<sup>13</sup> but this has many side effects.<sup>14</sup> Since the late 1980s, under-nutrition has been identified as a critical feature of sickle cell disease,<sup>15-20</sup> but this focus has still not been addressed adequately at an empirical level, despite recent increased awareness engendered by the first review published about this subject two decades ago in 1987 by Reed et al<sup>21</sup> and a succinct editorial on the subject by Prasad in 1997.<sup>22</sup> This paper attempts to access the most recent progress since the publication of those reports. It is hoped that this review will also serve as a stimulus for further research into the role of nutrition in sickle cell anemia and the search for novel nutritional approaches for the clinical management.

## Direct Evidence for Nutritional Deficiencies

### Macronutrient deficiencies

At the time of the first review in 1987 addressing nutritional problems in sickle cell disease,<sup>21</sup> evidence for a role of macronutrient deficiencies was primarily indirect and scanty, and this situation has continued into the recent decade.<sup>12,23-27</sup> However, early data indicating lower than normal anthropometric measurements in adult and adolescent HbSS patients,<sup>28,29</sup> have been confirmed by more recent evidence<sup>12,23,26</sup> and this reduction in body habitus is reportedly more pronounced in males than females.

The first and most direct evidence of insufficient macronutrient intake, demonstrated by clinical improvement following dietary intervention, was reported by Heyman et al in 1985,<sup>8</sup> via a small diet supplementation trial, in which the researchers studied 5 growth-retarded children with HbSS, each below the fifth percentile for both weight and height. Two of the growth retarded children showed clinical improvement and accelerated growth after naso-gastric supplements of protein and calories, in addition to their regular diets. The results showed that protein and energy supplements could improve clinical status and growth in HbSS children, whereas vitamin and mineral supplements alone did not change clinical status or growth. Interpretation of these data is limited because only 5 patients (aged 3 to 16 years) were studied using 4 different supplementation protocols. Still, these results demonstrated a role for malnutrition as one of the complications of HbSS and a possible benefit of routine food supplements. However, there are still currently no special dietary recommendations for protein and/or energy for HbSS patients, despite the large body of data to suggest that the very nature of the disease is to increase the food requirement, much like pregnancy or growth.<sup>30</sup>

Although the Heyman et al study was limited by the small sample size and nature of the design, more recent reports of feeding high protein and L-arginine supplements to sickle mice<sup>31-34</sup> and n-3 fatty acids to HbSS men<sup>9</sup> have shown significant reductions in inflammation, oxidative stress, red cell density and pain episodes, and improved microvascular function. In particular, the feeding of a high protein diet



(35% of energy from dietary protein) to weanling Berkeley transgenic sickle mice, improved rate of weight gain and reduced circulating levels of inflammatory proteins, C-reactive protein and interleukin-6 (IL-6), compared with sickle mice fed normal dietary protein (20% of energy from protein),<sup>31</sup> thus improving clinical outcome in this sickle mouse model. Arginine supplementation alone has also been reported to improve muscle function in S + S-Antilles sickle cell mice,<sup>35</sup> possibly via increased nitric oxide (NO) synthesis and therefore vasodilatation and blood flow to the organ. The advent of the transgenic-knockout sickle cell mouse model in the 1990s, manifesting a human phenotype of the disease, has enabled a more rapid and economical way to pretest concepts regarding sickle cell pathophysiology. In contrast, L-arginine supplementation in HbSS children was apparently not as successful for increasing circulating NO or other clinical variables as reported for the mouse models,<sup>36</sup> possibly because of inadequate dosing. However other previous supplementation trials for amino acids using other end points such as oral L-arginine therapy for reducing pulmonary hypertension in HbSS adults<sup>37</sup> and L-glutamine supplements<sup>38</sup> which lowered resting energy expenditure in HbSS children, were successful. Low circulating levels of several amino acids were reported 20 years ago for sickle cell anemia<sup>39</sup> and the idea of macronutrient shortage has been proposed.<sup>40</sup> However, more research is needed to confirm clinical benefits of and the most practical application for macronutrient therapy. Indeed a major challenge may be that the increased macronutrient requirement for HbSS patients is too high to be simply provided by diet, as HbSS patients often endure anorexia due to general chronic malaise. But first, specific dietary requirements for these patients must be established.

In 1989, Badaloo et al reported the first direct physiological measurements of elevated protein turnover and energy expenditure in HbSS adults, suggesting increased protein and energy requirements.<sup>16</sup> Several subsequent reports have confirmed higher than normal energy requirements in children,<sup>17,41,42</sup> and teenagers<sup>43</sup> in steady state by direct measurements of resting energy expenditure (REE). Increased protein turnover<sup>17,44</sup> and protein catabolism<sup>45,46</sup> have also been confirmed by direct stable isotope measurements in

HbSS children and adults respectively. Protein metabolism consumes approximately 30% of energy at rest, and recent data indicate that the high REE in HbSS is determined primarily by energy needs for cardiac compensation and increased protein metabolism.<sup>41</sup> These reports have confirmed previous indirect signs of protein and/or energy deficiencies, such as delayed growth and development,<sup>28,29,22,15</sup> concurring with the proposal of an increased demand for macronutrient metabolism to match the significantly increased erythropoietic rate toward more rapid red cell replacement in HbSS patients. Clearly, this physiological adaptation results in a shortage of substrates for growth and development, and the normal diet is inadequate to close the gap.

### Micronutrient deficiencies

Traditionally, the dietary information available about HbSS has addressed only associations with a variety of micronutrient deficiencies, including iron, zinc, copper, folic acid, pyridoxine and vitamin E.<sup>21</sup> The role of these deficiencies has long been extensively studied, including their involvement in immunity<sup>47,48</sup> and growth.<sup>49,50</sup> Several studies have investigated the role of these micromolecules in the pathogenesis of sickle cell disease, by measuring static circulating levels and/or effects observed from dietary supplementation studies. We have reviewed major studies and new findings to date.

### Minerals

#### Iron

Fairly recent reports from India<sup>51,52</sup> and Nigeria,<sup>53</sup> describe low iron stores in the bone marrow of 36%–67% of the patients they studied. In contrast, Vinchinsky et al reported that only 16% of their non-transfused patients in the United States showed evidence of iron deficiency.<sup>54</sup> This difference could be attributed to the difference in environment, ie developing versus developed country and one could deduce that lower socioeconomic status in developing countries may be associated with a lower dietary iron intake. Indeed, iron deficiency is less of a problem in sickle cell disease in the United States; iron excess is more often observed as many more patients receive chronic blood transfusion here than in other



countries.<sup>55</sup> Although it is an important component of red cells, excess iron has been shown to contribute to the generation of free radicals, which lead to lipid peroxidation, severe membrane damage and worsening of hemolysis in HbSS patients.<sup>56–58</sup> The complications of chronic blood transfusion may be increasing due to the advent of the successful STOP study,<sup>59</sup> demonstrating that children with HbSS and abnormally high results for transcranial doppler ultrasonography (TCD) were at lower risk for a first stroke, when treatment included frequent transfusions, compared with those who received only standard care. However, there is concern about the finding that high transfusion volume is more significantly associated with hepatic iron overload than serum iron markers.<sup>55</sup> This raises the need for safer alternatives to the standard chelation therapy, which is not without attendant side effects. Unfortunately, discontinuation of frequent transfusion for prevention of stroke in HbSS children, resulted in reversion to abnormal TCD velocities and stroke.<sup>60</sup> This result demonstrates the importance of limiting volume when transfusions are necessary and finding less harmful remedies for complications such as high TCD values and stroke, which require chronic transfusions for effective control.

### Zinc

In the context of sickle cell disease, far more attention has been focused on zinc than any other mineral. Many health consequences of zinc deficiency have been reported, including immune dysfunction, abnormal or slowed sexual maturation, abnormal growth pattern, poor wound healing and decreased level and activity of zinc metallo-proteins.<sup>61</sup> Interestingly, virtually all of these complications have been associated with the HbSS pathophysiology,<sup>8,25–27,42</sup> and Prasad et al, in 1975, first reported that HbSS patients had decreased zinc levels in plasma, erythrocytes and hair associated with increased urinary excretion, compared with controls.<sup>62</sup> They conducted a small supplementation trial including 7 men and 2 women with HbSS over 49 weeks; the results showed that eight of the participants gained weight, two 17 year old males gained 5 and 7 cm in height and 5 of the males showed increased sexual maturation based on changed external genitalia and growth of pubic hair. The authors suggested that hyperzincuria might be associated with the zinc deficiency in these patients.

Subsequent findings indicated a combination of hyperzincuria, high protein turnover (due to increased hemolysis) and inadequate dietary intake as contributing to the significantly increased zinc requirement demonstrated in the HbSS patients.<sup>63</sup> Prasad et al also reported increased serum testosterone<sup>64</sup> and reduced infections and hospital admissions,<sup>65</sup> following zinc supplementation in adult HbSS patients and Leonard et al confirmed that low plasma zinc was associated with significantly decreased Tanner scores for pubic hair, breast and genital maturation, among HbSS patients older than 9 years.<sup>66</sup> More recently, Zemel et al demonstrated increased linear growth among HbSS patients after 12 months of oral zinc supplements.<sup>50</sup> Early findings by Prasad et al suggesting that zinc deficiency in sickle cell could lead to hyperammonemia,<sup>67</sup> have recently been confirmed by a case report of HbSS zinc deficiency associated with hyperammonemia and encephalopathy.<sup>68</sup> Defective wound healing, indicated by chronic leg ulcers among HbSS patients, has shown improvement after zinc supplementation.<sup>69,70</sup> Zinc has also been reported to decrease oxidative stress and inflammatory cytokines and increase anti-inflammatory proteins concomitantly.<sup>71</sup>

### Copper

There are reports of increased plasma copper levels in individuals with HbSS,<sup>72–74</sup> and erythrocyte copper is either normal<sup>75</sup> or increased.<sup>76</sup> The clinical significance of this elevation in plasma copper is unclear, but it has been reported to occur in the event of decreased plasma zinc levels.<sup>72–74</sup> Prasad et al observed decreased plasma copper levels in a patient who was receiving zinc as an anti-sickling agent,<sup>77</sup> albeit with some hematologic consequences (microcytosis, and relative neutropenia) which were easily corrected with copper supplementation. In addition they reported decreased ceruloplasmin levels, also reversed by the copper supplementation.<sup>77</sup> The mechanism for absorption of dietary copper was unclear, but the authors suggested that overdose of metals such as zinc might inhibit copper absorption, due to similar valence and competition for the same binding sites, and possibly accounting for the observed inverse relationship.<sup>78</sup> More recently, the interactive roles of copper and zinc have been found to be based mainly on zinc level.<sup>79</sup> Hence, a high zinc intake sustained



over weeks is reported to induce intestinal synthesis of metallothionein, a copper-binding protein that traps copper within intestinal cells, blocking its absorption. However, typical zinc intakes do not block copper absorption and high copper intakes do not affect zinc absorption. The findings of low circulating zinc and concomitant high circulating copper levels have been consistent in patients with severe HbSS.<sup>80</sup> Copper excess may be contributing to free radical production and oxidative damage in HbSS.<sup>81</sup> These data suggest the need for a delicate balance between zinc and copper supplementation in general and for patients with severe HbSS in particular.<sup>82</sup>

### Magnesium

Reports on the levels of magnesium (Mg) in sickle cell disease patients have been increasing with variable results. Some studies have measured normal circulating levels<sup>74,83</sup> while others are reported to be low.<sup>84</sup> Low levels of total Mg in sickle cell erythrocytes have been associated with increased sickling due to propensity for red cell dehydration and hence, increased HbS polymerization.<sup>7,85</sup> It has been demonstrated that the dehydration is due to abnormally high red cell permeability and loss of potassium ( $K^+$ ) via at least three loosely connected pathways, in which the relative contribution of each is not yet known. One of these pathways, the K-Cl co-transport, is abnormally activated by low cell  $Mg^{2+}$ .<sup>85</sup> This causes rapid irreversible loss of  $K^+$  and  $Cl^-$  ions, with water following osmotically. These inferences were derived from studies in which oral Mg supplements were observed to improve several hematological indices in adult HbSS patients, including significant improvement of red cell hydration indicated by reduction in number of dense sickle erythrocytes, absolute reticulocyte count and immature reticulocytes, while erythrocyte Mg and K content were significantly increased.<sup>7,85</sup> Zehtabchi et al subsequently confirmed these postulates when comparing 74 patients with sickle cell anemia and 61 controls. They reported that the participants with HbSS had significantly lower levels of serum  $Mg^{2+}$  ( $0.52 \pm 0.05$ ) compared with healthy ethnicity matched controls ( $0.57 \pm 0.04$ ) and Caucasian controls ( $0.62 \pm 0.03$ ),  $P < 0.001$ . By measuring serum  $Mg^{2+}$  and  $Ca^{2+}$ , they were able to define a subset of HbSS patients with hypomagnesemia and elevated  $Ca^{2+}/Mg^{2+}$  ratios, who might benefit from magnesium supplementation.<sup>84</sup>

In another study, Brousseau et al reported a decrease in the length of hospital stay from approximately 5 days to an average of 3 days ( $P < 0.01$ ) in children admitted to the hospital for painful crisis, who were given IV Mg.<sup>86</sup> Although two of these were un-blinded studies, they showed that indeed there exists deficiency or insufficiency of Mg among individuals with HbSS, which may be related to erythrocyte dehydration. The low Mg concentrations of HbSS patients are reportedly due to hypoxia-induced red cell sickling associated with increased membrane permeability and Mg efflux, via increased activity of a putative Na/Mg exchanger.<sup>7,87</sup> In HbSS, dehydrated sickle red cells are particularly prone to hemolysis, contributing to many of the clinical complications such as stroke, leg ulcers and general poor nutrition. Preventing cellular dehydration would help to reduce complications by blocking pathways leading to red cell  $K^+$  permeability and replacing nutrient losses. A Phase I study of combination therapy using hydroxyurea and Mg treatment in restoring red cell hydration by blockade of KCl co-transport in HbSS was recently reported.<sup>88</sup>

### Vitamins

#### B vitamins

Prophylactic folic acid ( $B_9$ ) use makes this the most popular vitamin in the management of HbSS. This treatment is based mainly on preventing deficiency from increased folate turnover, as in any chronic hemolytic anemia<sup>89</sup> combined with limited reports of megaloblastic changes in HbSS, responsive to folate supplementation.<sup>90-92</sup> This practice remains a fundamental part of sickle cell treatment, although there is continuing debate about the efficacy, particularly as this treatment is increasingly reported to mask occurrences of cobalamin ( $B_{12}$ ) deficiency, that if detected are treatable with regular injected or oral  $B_{12}$  therapy.<sup>93,94</sup> As the debates continue,<sup>95</sup> more clinical trials are needed to confirm or refute prophylactic use of folic acid in sickle cell disease management, since some researchers still argue that clinical folate deficiency rarely occurs in this disease.<sup>93</sup> Only one controlled trial by Natta and Reynolds in 1984 has reported vitamin  $B_6$  (pyridoxine) deficiency in sickle cell anemia.<sup>19</sup> They found that 16 patients with HbSS had significantly lower circulating pyridoxal phosphate (PLP) levels compared with 16 control subjects. Five of the HbSS patients received PLP supplementation, which was associated with significantly



increased plasma and erythrocyte PLP. Clinical improvement was demonstrated only in one patient by virtual elimination of hospitalizations for frequent painful crisis. A fairly recent report on the subject has confirmed low B<sub>6</sub> status in HbSS, associated with high reticulocyte counts,<sup>96</sup> although the supplementation study by Natta and Reynolds was not associated with improved RBC count, hematocrit or hemoglobin in the HbSS group.<sup>19</sup> However, Low B<sub>6</sub> and relative folate deficiency have been associated with hyperhomocysteinemia in HbSS patients,<sup>97,98</sup> which is a confirmed independent risk factor for cardiovascular disease and stroke. More recent findings in adults<sup>99</sup> show hyperhomocysteinemia unrelated to folate and B<sub>12</sub> status, and in children<sup>100</sup> inversely related to B<sub>12</sub> concentration but not folate or B<sub>6</sub> concentrations. Therefore, the clinical significance of B vitamin supplementation requires additional research in HbSS patients.

#### Antioxidant vitamins

Significantly low circulating levels of antioxidant vitamins A, C and E have been measured in HbSS patients,<sup>81</sup> however direct evidence of any clinical benefit for supplementing these micronutrients is still needed. Ohnishi et al reported that administration of vitamin C to human sickle red cells *in vitro*, inhibited formation of dense cells.<sup>101</sup> Other reports in the literature propose that vitamin C prevents *in vitro* Heinz Body (denatured Hb) formation in sickle red cells and normalizes blunted hemodynamic changes associated with posture adjustments.<sup>11,102</sup> Of the antioxidant vitamins, vitamin E has been investigated most in sickle cell disease. There are many reports of low circulating vitamin E in HbSS patients, although there are also contrasting reports of normal levels.<sup>103</sup> Fairly recently, reduced vitamin E antioxidant capacity in HbSS has been shown to worsen with chronic transfusion, possibly related to iron overload.<sup>104</sup> Therefore, there should be consideration that in HbSS, rather than antioxidant activity, vitamin E may function by inhibiting hemin-mediated hemolysis.<sup>105</sup> It appears likely that antioxidant vitamins may work better as a cocktail rather than individually for improving clinical status in HbSS patients.<sup>101</sup>

#### Vitamin D

Subnormal bone development and disease have long been documented for HbSS children<sup>106</sup> but evidence

for a nutritional etiology has been slow to develop. However, there is increasing data demonstrating low serum levels of vitamin D among HbSS children, possibly linked to decreased dietary intake<sup>107,108</sup> and in some cases to seasonal variability in food intake.<sup>107</sup> Buison et al<sup>107</sup> and Rovner et al<sup>108</sup> reported low levels of serum 25-hydroxyvitamin D (25-OHD) in children with sickle cell anemia HbSS compared with their age and racially matched peers. A commonality of both studies was the agreement that the children with low vitamin D levels tended to report less than optimal dietary intake of vitamin D. Buison et al were also able to characterize whole body bone mineral content (WBBMC) and WB bone area (WBBA) in HbSS children using the dual x-ray absorptiometry method, much more accurately than by the conventional X-ray. They found significantly lower WBBMC and WBBA among the HbSS than the controls with normal hemoglobin. Although the HbSS participants also had lower than normal vitamin D status and low calcium and vitamin D intakes, no associations between these nutrients and WBBMC were found. The investigators suggested that duration of vitamin D and/or calcium intakes might have greater impact on WBBMC, which is a measure of long-term bone mineral accretion.<sup>109</sup> These findings were confirmed in a similar study by Chapelon et al suggesting instead, abnormal bone formation as the underlying mechanism for the osteopenia.<sup>110</sup> However, Adewoye et al demonstrated a response of sickle cell bone disease to vitamin D and calcium supplements in adults. They administered vitamin D and calcium to 14 adult HbSS patients who had vitamin D deficiency as well as osteopenic values for bone mineral density (BMD) in critical bony areas such as femoral neck, lumbar spine, ulnar and radius. BMD and vitamin D were measured before and after 12 months of treatment. 25 hydroxy vitamin D was restored to normal levels and BMD improved, despite no changes in markers of bone resorption.<sup>111</sup> Goodman et al has confirmed high prevalence of low vitamin D status in HbSS adults. 98% of their patients had suboptimal values (<30 ng/ml) and 60% were severely deficient (<10 ng/ml). They reported that low vitamin D status was not associated with age, gender, hydroxyurea use, sickle cell type or date of the lab draw.<sup>112</sup> Together, these few findings indicate a possible dietary etiology for vitamin D deficiency among HbSS patients and support a need



for routinely screening these patients for circulating vitamin D levels. HbSS patients may also benefit from routine vitamin D and calcium supplements, to reduce risk of suboptimal peak BMD and consequent fragility fractures among other bony complications.<sup>106</sup> There is still a need for setting new dietary requirements for vitamin D, based on recent evidence of increased need among healthy individuals,<sup>107,108,113</sup> and particularly for HbSS patients who are likely to have even higher than normal requirements for this vitamin.

### Proposed mechanism for developing nutrient deficiency in sickle cell anemia

Mechanisms by which nutritional deficiencies may occur in HbSS patients have generally included decreased intake, intestinal malabsorption and increased catabolism. To date, the larger body of

data indicate normal food intakes as measured by both diet history/food diaries<sup>8,23,114,115</sup> and weighed food intakes.<sup>16,40</sup> However, adequacy of dietary intake has been shown to decline with increased age.<sup>115</sup> Repeated ill health and frequent hospitalizations are thought to be associated with varying degrees of anorexia and reduced feeding time in these patients.<sup>23</sup> Fairly recent reports in the literature show that circulating levels of IL-6 pro-inflammatory cytokine can predict appetite and wasting by demonstration of an association between raised IL-6 levels with decreased appetite<sup>116,117</sup> and wasting.<sup>117</sup> IL-6 is now known to be elevated in individuals with sickle cell disease.<sup>42,118,119</sup> It has been hypothesized that this protein acts on the brain to cause appetite suppression leading to decreased food intake. Available data from reports in the literature

**Table I.** Showing summary of the identified roles of nutritional supplementation in managing the complications of sickle cell anemia.

Nutrient type	Study	Specific nutrient studied	Observed effect
Macronutrients	Archer et al <sup>31</sup>	Proteins	Improved weight gain ( $P = 0.06$ ), decrease in level of inflammation ( $P < 0.05$ )
	Dasgupta et al <sup>32</sup> Fasipe et al <sup>35</sup>	Arginine Arginine	Decreased oxidative stress Improved muscle strength and endurance
	Williams et al <sup>38</sup> Tomer et al <sup>9</sup>	Glutamate Omega-3 fatty acids	Decreased resting energy expenditure Decrease in number of pain episodes ( $P < 0.01$ ) and thrombotic activities
Micronutrients	Prasad et al <sup>47,64,65</sup>	Zinc	Improved thymulin activity and decrease in frequency of bacterial infection ( $P = 0.0026$ ) and hospitalization from painful crises ( $P = 0.0001$ ), improved sexual maturation and reproductive capacity
	Zemel et al <sup>50</sup>	Zinc	Improvement in linear growth
	Leonard et al <sup>66</sup>	Zinc	Improved sexual maturation
	de Franceschi et al <sup>7</sup>	Magnesium	Decrease in number of painful days ( $P < 0.0005$ )
	Brousseus et al <sup>86</sup>	Magnesium	Decreased length of hospital stay ( $P = 0.0006$ )
Combined <sup>1</sup>	Wang et al <sup>105</sup>	Vitamin E	Decreased lipid peroxidation and improved erythrocyte membrane stability
	Heyman et al <sup>8</sup>		Improved weight gain and decreased frequency of hospital admission
	Ohnishi et al <sup>101</sup>		Increased hematocrit ( $P < 0.001$ ) and decrease in number of painful crisis ( $P = 0.063$ )

**Note:** <sup>1</sup>Refers to studies that used a combination micronutrients or macro and micronutrients.



indicate normal intestinal function in patients with HbSS.<sup>8,120</sup>

Perhaps the most novel objective and recently widely reported mechanism for explaining nutritional deficiency in sickle cell patients, is the idea of increased metabolic requirement and relative nutrient shortage, previously mentioned in the discussion of macronutrient deficiencies. Sickle cell anemia is associated with hypermetabolism,<sup>17,40–42</sup> and it has been discovered by our research, that most of the hypermetabolism of childhood HbSS can be accounted for by the characteristic hemolytic anemia.<sup>41</sup> Multivariate analyses of the results suggested that the high REE among HbSS children was determined primarily by energy needs for increased protein metabolism linked with reticulocytosis and increased cardiac activity to compensate for severe anemia. Indeed, this directed hypermetabolism is expected to permit only limited residual energy for other metabolic work among HbSS patients. This concept is consistent with direct evidence of a relative energy shortage<sup>40</sup> that may disproportionately retard growth and development<sup>121</sup> and compromise immune status.<sup>42</sup> The direct proof of this theory must come from appropriately controlled nutritional supplementation studies. Our studies in Berkeley transgenic sickle cell mice have demonstrated that introducing a high protein diet at weaning improved rate of weight gain and attenuated the steady-state inflammation in this mouse model.<sup>31</sup> Human studies reporting the effect of dietary intervention in HbSS patients are few, with the study by Heyman et al being the most comprehensive.<sup>8</sup> Despite a small sample size, this study showed that the optimal effect of diet on HbSS complications could only be fully achieved with a combination of both macro and micro nutrient supplements.

## Summary/Conclusion

The evidence in support of nutritional deficiencies in individuals with HbSS has been increasing. Accumulation of this data has been aided in part by increasing availability of more direct stable isotope methods to measure human metabolism in vivo and other technological advances. Hence, the role of protein/energy deficiency is now more clearly defined as a complication of HbSS. Normally, lean body mass is the primary determinant of REE via a significant

positive correlation, however, HbSS patients consistently have higher than normal REE levels associated with lower than normal lean body mass. Furthermore, direct measurement of high protein and energy metabolism even with adequate dietary intakes, has led to the theory of a relative shortage of macro- and micronutrients for normal growth and development.

The role of micronutrient deficiencies has been more easily addressed and research in that area continues to reveal a range of individual deficiencies in HbSS patients, some of which can be corrected by supplements. The most recent focus is toward a possible association of vitamin D deficiency with subnormal bone development and disease in individuals with HbSS. One small study has shown improved bone mineral density and normalized vitamin D status with oral vitamin D and calcium supplements. Due to the high prevalence of severe vitamin D deficiency found in some HbSS groups, routine screening for this nutrient has been recommended. However, many more corroborating studies with larger sample size are required to define the extent of this nutrient deficiency in HbSS patients and the best mode of treatment.

As we continue to gather more cogent evidence for nutritional deficiency as a complication of HbSS and possible approaches for nutritional intervention, a prudent approach at this time would be to ultimately consider a combination of nutrients that could achieve optimal nutritional and immune status for disease prevention and to reduce morbidity and mortality in HbSS patients. Consequently, a commitment of more resources is needed toward seeking the best nutritional therapies for HbSS patients. This approach is likely to provide an effective and ultimately affordable intervention, albeit challenging. There will also be a need to determine specific recommended dietary allowances (RDAs) for this group of individuals, just as special RDAs are set to cover the increased demands for extra nutrients during pregnancy. More appropriately controlled randomized blinded studies of individual nutrients and their combinations are therefore needed, as a basis for developing special RDAs for HbSS patients.

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## Disclosure

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