

## ORIGINAL ARTICLE

### Nutritional Status in Children with Beta Thalassemia: A Systematic Review

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#### Abstract

Thalassemia is a hereditary disorder characterized by defective hemoglobin production. Chronic nature of thalassemia has impact on health status of children suffering with it. Nutritional deficiency is one of the consequences of the disease. The present systematic review was undertaken to assess the nutritional status of children suffering with thalassemia. The literature search was done using various data bases. PRISMA guidelines were followed to extract, synthesize and report the findings. Total of nine studies conducted between 2003-2017 and met the selection criteria were included in the review. The findings revealed that out of 1505 participants, majority of children with beta thalassemia were suffering with one or other form of nutritional deficiencies. Micronutrient deficiencies were prevalent in majority of the subjects. Further, the overall nutritional status of these children was found to be poor when compared to their age and gender matched counterparts.

The nutritional status of thalassemic children is considered to be poor when compared to their normal counterparts. Measures such as nutritional counseling, nutritional supplements, periodical evaluation of health status, and proper screening to improve the nutritional well-being of thalassemic children are needed.

**Keywords:** Thalassemia, Children, Adolescents, Nutrition, Body mass index, Food record

#### Introduction

Thalassemia is an autosomal recessive disorder characterized by defect in synthesis of globin chains in hemoglobin molecule.<sup>1</sup> Based on the type of globin chains affected, it is classified into alpha or beta thalassemia.<sup>2</sup> Beta thalassemic children usually become symptomatic by about 4 to 6 months of life after birth. They may develop progressive anemia and lead to decreased growth and development without proper treatment.<sup>3</sup> Due to iron overload, these children will develop many complications. Nutritional deficiencies are very common among them.

#### Aim

The aim of this review was to systematically review and critically appraise the findings reported by various studies related to nutritional status of children and adolescents with beta thalassemia. This review focused on the data related to nutritional well-being and deficiency status of different nutrients.

#### Objective

- To summarize the overall nutritional status of children and adolescents suffering with beta thalassemia

## Methodology

### Search strategy

The search strategy using text words, thesaurus headings, MeSH terms relating to thalassemia, children and adolescents, nutritional status, factors were developed for various data bases. Literature search for articles published from 2003 to 2017, in English language was performed. The data bases used for the present review were Pubmed, Research gate, Proquest, Index Medicus and Google scholar. PRISMA guidelines were used to refine the articles.

### Type of participants

The participants were children and adolescents diagnosed with beta thalassemia major in the age group of 6-8 years.

### Type of studies

Studies with cross sectional, longitudinal and exploratory research designs were used.

### Outcomes

To find out the effect of disease condition on nutritional status of thalassemic children

### Setting

Hospital based studies

### Inclusion criteria

- Studies related to nutritional deficiencies among thalassemic children and adolescents
- Comparative studies on health status of thalassemia children versus their normal counterparts

### Exclusion criteria

- Articles published in languages other than English
- Letter to editor and response to an article
- Conference proceedings and abstracts

The PRISMA flow chart shows the process of identification and selection of studies for review (Figure 1). Of the 141 articles retrieved from the data bases, 43 were removed as they were duplicates. After screening for 98 articles, with abstracts and title, a total of 13 full articles were assessed for eligibility and finally nine articles that fulfilled the criteria were selected for review.

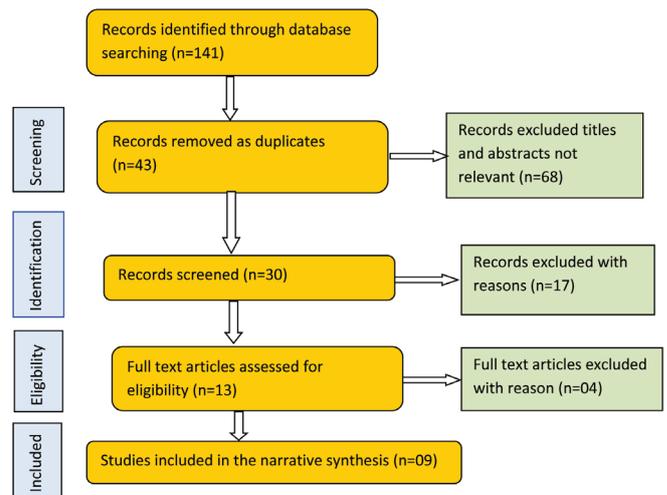


Figure 1: PRISMA flow chart

The nine eligible studies included five descriptive cross sectional studies, two case control studies, one exploratory research and one prospective longitudinal cohort study. The detailed sample characteristics of studies are shown in table 1.

Table 1: Data extraction table

S. No	Author	Year	Country / setting	Aim	Sample size	Participants	Outcome
1.	Fung EB	2010	USA, Children Hospital and Research Center, Oakland	Assessment of nutritional deficiencies in patients with thalassemia	Cases. n=38; con. n=36	Thalassemia clients and ethnically similar healthy controls	Low circulating level of fat and water soluble vitamins and other essential nutrients
2.	Thongkipreecha P, Kangsadalampai O, Pongtanakul B, Meksawan K	2010	Thailand, Siriraj Hospital	Assessment of nutritional status among thalassemia intermedia children	n=30	Thalassemia intermedia children between 5-15 years of age	Thalassemic patients were both under weight and stunting. Further their average energy intake was lower than the recommended daily allowance
3.	Kumari V, Up-hadyay SK, Gupta V, Piplani SK, Bhatia BD	2012	India, Institute of Medical Sciences, Banaras Hindu University	Nutritional status, hemoglobin and serum ferritin estimation among children with thalassemia	n=74	Thalassemia children between the age group of 3-10 years of age	Thalassemic children had low hemoglobin, high serum ferritin level; growth retardation and under nutrition

4.	Sheikh MA, Shakir MU, Shah M	2015	Pakistan, Bahawal Victoria Hospital	Assessment of nutritional status of thalassemia major children by Body Mass Index	n=305	Children with beta Thalassemia major between 2 to 16 years of age	Majority of the children were under weight and there was significant association between nutritional status and factors like age and duration of illness of these children.
5.	Asadi-Pooya AA, Karamifar H	2003	Iran, Dastegheib Hospital	Assessment of body mass index	n=565	Thalassemia children below 18 years of age	BMI was <10 percentile for age and gender of children. There was significant difference in BMI of male and female thalassemic children.
6.	Mirhosseini NZ, Shahr S, Majid Ghayour M, Kamaruddin NA, Banihashem A, Mohd Yusoff NA <i>et al</i>	2013	Iran, specialized center for thalassemia, Mashad	Determination of factors affecting nutritional status	n=140	Transfusion dependent beta thalassemia children between 8-18 years of age	44.3% of males and 19.6% had malnutrition. Also, the same percentage of boys and 37.7% of girls were short stature. Age, age at transfusion and starting chelation therapy were positive predictors whereas gender, puberty and fasting blood sugar level were negative predictors of nutritional status of nutritional status.
7.	Sherief LM, Abd El-salam SM, Kamal NM, El-safy O, Almalky MA, Azab SF <i>et al</i>	2014	Egypt, Zagazig Pediatric hospital,	Estimation of nutritional biomarkers and their relation to age and iron burden	Case. n=108; con. n=60	Beta thalassemia major children (2-17 years) and normal healthy children (4-17 years)	The nutritional biomarkers and trace elements levels were significantly less in chronically transfused children.
8.	Wood J. C, Claster S, Menteeer J. D, Hofstra T, Khanna R, Coates T.	2008	USA, Children's Hospital, Los Angeles	Evaluation of vitamin deficiencies and cardiac status of chronically transfused thalassemia patients	n=24	Thalassemia patients with the mean age of 14.7±7.6 years	Marked reduction in Vitamin D25-OH level; significant relationship between D25-OH/D1-25 ratio and abnormal cardiac function. There was moderate correlation between serum ferritin level and cardiac function status
9.	Fung E.B, Xu Y, Trachtenberg F, Odame I, Janet L.K, Neufeld E.J <i>et al</i>	2012	USA, Canada & UK; 10 hematological outpatient units	Assessment of nutritional status in large contemporary sample of patients with thalassemia	n=221	Patients with thalassemia in the age group of 19±11.3 years	More than 30% of clients had inadequate intake of vitamins and minerals. There was significant association between age and nutritional deficiency.

**Table 2:** Risk bias of the included studies

S. No	Author	Year	Type of study	Sample size estimation	Quality		Special features
					Sampling technique	Selection criteria	
1.	Fung EB	2010	Case control study	Not mentioned	Not mentioned	Mentioned	160 question Block food frequency questionnaire was used to collect data, the analyzed data was compared with U.S. dietary reference intake value
2.	Thongkipreecha P, Kangsadalampai O, Pongtanakul B, Meksawan K	2010	Cross sectional descriptive study	Not mentioned	Not mentioned	Mentioned	Correlation between different nutritional parameters were analyzed; the nutritional parameters of thalassemia children were compared with Thailand dietary reference intake
3.	Kumari V, Uphadyay SK, Gupta V, Piplani SK, Bhatia BD	2012	Cross sectional descriptive study	Not mentioned	Not mentioned	Not mentioned	Used Gomez classification for grading degree of malnutrition
4.	Sheikh MA, Shakir MU, Shah M	2015	Cross sectional descriptive study	Not mentioned	Not mentioned	Clearly stated	The BMI was plotted on age and gender specific CDC BMI chart to compare with standard values
5.	Asadi-Pooya AA, Karamifar H	2003	Cross sectional descriptive study	Not mentioned	Mentioned	Clearly stated	Clients BMI was compared with Age specific standard BMI curve
6.	Mirhosseini NZ, Shahar S, Majid Ghayour M, Kamaruddin NA, Banihashem A, Mohd Yusoff NA <i>et al</i>	2013	Cross sectional exploratory research design	Not mentioned	Mentioned	Clearly stated	Comprehensive nutritional assessment including 24 hrs nutritional recall, food record and anthropometry was carried out to assess nutritional status.
7.	Sherief LM, Abd El-salam SM, Kamal NM, El-safy O, Almalky MA, Azab SF <i>et al</i>	2014	Case control study	Not mentioned	Mentioned	Clearly stated	Assessment included history taking, physical examination and lab investigations
8.	Wood J. C, Claster S, Menteer J. D, Hofstra T, Khanna R, Coates T	2008	Descriptive correlational study	Not mentioned	Not mentioned	Stated	Patients records, screening and investigations were used for collecting data
9.	Fung E.B, Xu Y, Trachtenberg F, Odame I, Janet L.K, Neufeld E.J <i>et al</i>	2012	Prospective longitudinal cohort study	Not mentioned	Mentioned	Clearly mentioned	Inter-continental multi-center study; used validated food questionnaire, chart review and investigations for collecting data

### Sample characteristics

Two studies have reported determination of nutritional status by only BMI (Sheikh MA, Shakir MU, Shah M, 2015; Asadi-Pooya AA, Karamifar H, 2003). One study used Gomez classification for degree of malnutrition (Kumari V *et al.*, 2012) whereas all the other studies had collected data by the combination of anthropometry, nutritional history and laboratory investigations to evaluate the nutritional status. One study did not mention sampling criteria (Kumari V *et al.*, 2012) and none of the studies have revealed about sample size estimation.

### Type of studies

The review included descriptive, correlational, cross sectional, longitudinal, observational studies. The studies conducted by nurses and doctors in the field of thalassemia have been considered. The reviewers retrieved all the data from data bases and other sources and duplicates were removed by finding in MS Excel sheet. The full articles published in English language, and published from 2003 to 2017 were considered for the review.

All the studies were cross sectional except one (Fung EB *et al.*, 2012). In the nine studies, 1505 children and adolescents with beta thalassemia and 96 healthy children have contributed for the needed data for the analysis of the objective.

### Setting of the studies

All the nine studies have been conducted in thalassemia/hematology clinics of hospitals. The studies were conducted in nine different countries such as USA (1 study), Thailand (1 study), India (1 study), Pakistan (1 study), Iran (2 studies), Egypt (1 study), USA, Canada & UK (1 study). Among these, one was a multi-centered, inter-continental study (Fung EB *et al.*, 2012).

### Types of participants

The studies have included children and adolescents with beta thalassemia and on chronic blood transfusion. Two studies had included age and gender matched healthy children for comparison of nutritional status.

### Ethical considerations

All the studies obtained permission from the concerned authorities and ethical clearance certificates before initiating data collection. Informed consents were taken.

### Risk bias assessment

The extraction of data consisted of the following areas: study design, aim of the study, sampling and sampling

criteria, type of participants, special features in data collection and important findings of the study. The sample size in majority of the studies was very less and none of the studies have mentioned the sample size estimation. Even though selection criteria were clearly stated, sampling technique poses high risk of selection bias. Some studies have taken BMI or degree of malnutrition alone as nutritional parameters.

### Discussion

Adolescents with beta thalassemia major suffer with nutritional deficiency due to inadequate nutrient intake. Vitamin D, folic acid, calcium and magnesium were significantly lower than the normal peers of the same age. Even though there was no significant difference observed in the level of calories, proteins, fat and cholesterol among two groups, there was difference between intake and circulating level of nutrients in the thalassemia patients. It was felt that they may have increased need for certain nutrients due to poor nutrient absorption, elevated losses or increased nutrient turnover (Fung EB, 2010).<sup>4</sup>

Thalassemic children were found to be both stunting and wasting. Determination of nutritional status revealed that 63.3% of the participants were underweight, 60% of them were thin or wasted and 36.7% had delayed linear growth. Low body fat and muscle wasting were seen in 70% and 60% of the subjects respectively. Also, there was significant association found between various parameters of nutritional status such as weight for age, weight for height and height for age; and their anthropometric measurements were significantly correlated with body mass index. These findings indicated that there was growth impairment in thalassemia patients. (Thongkijpreecha P, Kangsadalampai O, Pongtanakul B, Meksawan K, 2012).<sup>5</sup>

Further, grading of nutritional status and estimation of hemoglobin and serum ferritin levels among thalassemia major patients found that around 70% of children had grade II and III malnutrition, 23% had grade I malnutrition and only 8% of them were with normal nutritional status. Only 2 and 3 out of 74 children had weight and height more than 50 percentile respectively. Majority of thalassemic children's weight and height were below 3<sup>rd</sup> percentile. These children had low hemoglobin and high serum ferritin levels. They were short, underweight and had significant growth retardation when compared to the other Indian children. It was suggested that in order to maintain near normal growth, the hemoglobin level should be maintained around 11 gm% and nutritional

counseling should be done (Kumari V, Upadhyay SK, Gupta V, Piplani KS, Bhatia BD, 2012).<sup>6</sup>

Comparably, assessment of nutritional status using body mass index among thalassemic children between 2 to 16 years of age disclosed that 58.69% were underweight, 36.74% were healthy, 3.28% were obese and 2.3% of thalassemia clients were obese. There was significant association between nutritional status of the thalassemic children with their age and duration of illness with mean height (118.71±19.25 cm), mean weight (20.35±7.72 kg) and BMI (14.03±2.71) (Sheikh Muhammad A, Shakir MU, Shah M, 2015).<sup>7</sup>

In a similar fashion, among 565 thalassemic children who were assessed for body mass index as an indicator for growth, BMI was less than 10<sup>th</sup> percentile in 19% of girls and 7% of boys below 10 years of age, 32% girls and 58% boys above 10 years of age (Asadi-Pooya AA, Karamifar H, 2003).<sup>8</sup>

A comprehensive evaluation of nutritional status using anthropometric measurement, food record and biochemical profile among 140 children with beta thalassemia major between 8 to 18 years of age revealed that 44.3% of boys and 37.7% of girls were found to be of short stature and malnourished. 7.4% were lean and 60.7% had wasting. The average intake of daily nutrients of thalassemic children and adolescents was around 74% of daily recommended allowance. The positive predictors of nutritional status included age at first transfusion, age of starting chelation therapy. There was positive correlation between energy intake and micronutrients with anthropometric measurements. Puberty, gender and fasting blood sugar levels were identified as negative predictors of nutritional status. It was recommended to monitor the nutritional status and to focus on nutrition education and supplementation, treatment protocol and blood sugar control among thalassemic children and adolescents. These factors might play an important role in enhancing Quality of Life of these children (Mirhosseini NZ, Shahar S, Mobarhan MG, Kamaruddin NA, Banihashem A, Mohd Yusoff NA, Esmail HA, Tavallaei S, 2013).<sup>9</sup>

In addition, nutritional biomarkers estimation among chronically transfused thalassemia children found that vitamins A, C, E and B12 as well as trace elements such as zinc, copper, selenium were significantly low when compared to healthy controls. Hence it was recommended to evaluate these children for nutritional status at regular intervals and provide supplementation. (Sherief LM, Abd El-Salam SM, Kamal NM, El safy O,

Almalky Mohamed AA, Azab SF, Morsy HM, Ghariieb AF, 2014).<sup>10</sup>

Assessment of vitamin D deficiency, cardiac iron and cardiac function among 24 clients with beta thalassemia major with the mean age of 14.7±7.6 years revealed that the level of vitamin D25-OH was markedly depressed. Thirteen clients had D25-OH values below the lower limit of normal range i.e. 50 nmol/L. However, the level of D1-25OH was elevated and calcium was within normal level among them. All the clients were taking vitamin E and folate supplements and only one person was on vitamin D supplementation. Cardiac iron overload was found in six cases. The findings suggested that the decreased level of vitamin D25-OH might be due to the combined effect of decreased intake of dairy products and less exposure to sunlight because of indulging in more indoor activities (Wood JC, Claster S, Menteeer JD, Hofstra T, Khanna R, Coates T, 2008).<sup>11</sup>

A prospective longitudinal cohort study on dietary intake of 221 thalassemic patients with age group ranging between 3 years to more than 19 years showed that more than 30% of the participants had inadequate amount of vitamin A, D, E, K, folate, calcium and magnesium in their daily diet. However, the level of riboflavin, vitamin B12 and selenium were adequate in more than 90% of patients. Dietary inadequacy increased with increase in age. Majority of the patients had taken calcium and vitamin D supplements. But level of 25-OH was less than normal in around 61% of the cases. Majority of key nutrients were insufficient in the diet of thalassemia patients. Hence nutritional monitoring should be done to determine the greatest risk for nutritional deficiency. It was recommended to conduct studies on effect of dietary quality and health status on health outcomes in thalassemic children. (Fung EB, Xu Y, Trachtenberg F, Odame I, Boudreaux J, Quinn CT, Vichinsky EP, 2012).<sup>12</sup>

### Quality of evidence

Overall the quality of findings regarding nutritional status of thalassemia children was average due to the risk of bias.

### Conclusion

The nutritional status of thalassemic children is considered to be poor when compared to their normal counterparts. Measures such as nutritional counseling, nutritional supplements, periodical evaluation of health status, and proper screening to improve the nutritional well-being of thalassemic children are needed. Nutritional counseling must be given regarding the

type of food to be included, restricted and avoided in thalassemic clients.

### Conflict of Interest

None.

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