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Growth Failure in Thalassemia Major Patients in Samples of Iraqi Patients

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Abstract

Introduction: Thalassemia, a hereditary autosomal recessive blood disorder, arises from genetic abnormalities leading to a diminished synthesis rate of one of the globin chains constituting hemoglobin. The integration of transfusion and chelation therapies has significantly elongated the lifespan of individuals diagnosed with thalassemia. This study aims to understand growth failure among individuals with beta-thalassemia major when compared to typically developing children of similar age groups. Additionally, the research explores the potential hormone treatment requirement in this situation. **Methods:** Between November 1, 2019, and June 7, 2020, case-control research was carried out at the Thalassemia Centre of the Maternity and Children Hospital in Diwaniyah. The dataset included data from 100 thalassemic patients receiving blood transfusions and normal follow-up visits at the hospital. The patients ranged in age from 5 to 15 years. In addition, data were collected from 100 individuals without thalassemia, also within the same age range. Collected data encompassed age, gender, height, and weight, evaluated using the clinical growth chart from CDC. Further details recorded included the frequency of blood transfusions, the chelating agent used, serum ferritin levels, and hormone levels. **Results:** We discovered that, with a P value less than 0.0001, there is a significant difference in normal weight between healthy children and beta thalassemic patients. Additionally, the healthy children were found to be taller than the beta thalassemic patients. **Conclusion:** The study has revealed that the growth failure rate is directly linked to recurrent blood transfusion, and iron overload & resulting endocrine dysfunction.

Keywords: Short Stature, Beta Thalassemia Major, Endocrine Complications. Growth Failure, Iron overload.

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INTRODUCTION

Thalassemia's encompass a set of inherited autosomal recessive disorders marked by a reduction or absence in the process of creating one of the two polypeptide chains (α or β) that make up an average human hemoglobin molecule. This process causes the amount of hemoglobin in red blood cells to decrease, which results in anaemia.¹

Beta-thalassemia major represents a critical manifestation of Beta-Thalassemia, distinguished by profound anemia that necessitates recurrent transfusions of red blood cells.²

A hereditary autosomal recessive blood condition caused by genetic abnormalities is beta-thalassemia major which led to a decreased synthesis rate of Beta globin chains, essential components of haemoglobin.²

Beta-thalassemia major typically induces profound anemia, accompanied by various health complications such as splenomegaly, skeletal abnormalities, diminished height, diabetes, and hepatitis infection, and necessitates ongoing, lifelong transfusion treatment, therapeutic measures, and medical oversight.²

Youngsters with Thalassemia major have a unique development pattern that lasts until they are between 9 and 10 years old. After this time, there is a noticeable slowdown in growth rate and either a reduction in or non-occurrence of the typical pubertal growth surge. The growth impairment is caused by a variety of inter-related conditions.³

The resilience of individuals with beta-thalassemia major hinges on the lifelong requirement for blood transfusions, which subsequently results in iron accumulation. This excess iron poses detrimental effects on various organs, including the endocrine glands.⁴

The buildup of iron in the endocrine glands is responsible for a variety of endocrine problems seen in thalassemia major.⁵

Patients with thalassemia major frequently experience thyroid problems. Nevertheless, its occurrence and intensity exhibit inter-cohort variability, and the entire life course is still not fully understood. When iron excess is treated with deferoxamine, there is still a significant chance of developing secondary endocrine dysfunction. Hypogonadism was shown to be one of the most common endocrine problems in that particular investigation.⁶ Other common conditions include hypocalcemia, low stature, impaired glucose tolerance, and overt and subclinical hypothyroidism.⁷ One of the

most prevalent endocrinopathies in transfusion-dependent thalassemia is growth failure.^{8,9} Thalassemia pathogenesis has a multifactorial aetiology.^{10,11,12}

Key causative elements to delayed growth in patients with thalassemia major include chronic anemia.¹⁰⁻¹² and chelation toxicity.^{11,13}

Other contributing elements included hypothyroidism, hypogonadism, growth hormone deficiency, zinc deficiency, and malnutrition. Malnourishment is a substantial reason for growth retardation in thalassemia kids existing in deprived nations.^{14,15} Fundamentally three chelation drugs available are deferoxamine (DFO), deferiprone (DFP) and deferasirox (DFX). The initial treatment option available for iron overload was deferoxamine (DFO). This hexadentate iron chelator is not absorbed orally, hence necessitating parenteral administration, often through subcutaneous infusion lasting 8 to 12 hours during the night, spanning 5 to 7 nights per week. The typical dosage falls within the range of 20-40 mg/kg body weight for children and 30-50 mg/kg body weight for adults.¹⁶ A subsequent treatment option is deferiprone (DFP), classified as an orphan drug. This orally administered iron chelator has arisen from an exhaustive quest for novel approaches to address iron overload. Comparative investigations have demonstrated that this chelator, administered at dosages ranging from 75 to 100 mg/kg/day, could potentially exhibit efficacy comparable to that of DFO in eliminating bodily iron.¹⁷

A third pharmaceutical option, deferasirox (DFX), represents a once-daily, orally ingested iron chelator. Extensive clinical trials have established its efficacy in both adults and children.^{18,19} The objective of this study is to ascertain the occurrence of growth failure in individuals with beta-thalassemia major, in comparison to typically developing children within the same age group. To know the extent of their need to follow up for hormonal therapy.

PATIENTS AND METHODS

Quantitative design a descriptive study was conducted on thalassemia major Patients at the Thalassemia Centre of Maternity and Child Hospital in the city of Diwaniya to know the growth failure occurs in Beta thalassemia major patients in comparison with normal children with similar age groups and the extent to their need to follow up for hormonal therapy. Starting from 1 November 2019 to 7 June 2020.

ADMINISTRATIVE ARRANGEMENT

Setting study: The research was carried out at the Al-Thalassemia Center within Al-Diwaniya City's Maternity and Child Hospital.

The sample of the study:

The sample of the study was non-probability of 200 individuals out of which 100 were patients suffering from beta thalassemia major and the other 100 were normal.

Selective criteria

Inclusion criteria: The study encompasses individuals within the age range of 5 to 15 years who are without thalassemia and those diagnosed with beta-thalassemia major. The latter group must have been undergoing consistent blood transfusion accompanied by chelation therapy.

Exclusion criteria: Individuals afflicted with different forms of thalassemia or any blood-related disorders aside from thalassemia major were excluded from the study. Additionally, those above 15 years old or below 5 years old were not considered for inclusion.

Formal permissions were secured from the Al-Thalassemia Center at Maternity and Child Hospital.

Data Collection:

The data acquisition involved conducting interviews with patients visiting the thalassemia centre for blood transfusion along with chelation therapy. Additionally, information was extracted from the available medical records spanning from diagnosis to the data collection phase of our study.

Study Instrument: This research aims to discern the presence of growth failure in individuals with Beta thalassemia major in contrast to typically developing children of similar age groups. We gathered information directly from the patients, inquiring about their age, while also measuring their weights and heights. Furthermore, we ensured the absence of any other blood disorders.

Statistical Analysis: The collected samples were organized and reviewed to ensure their completeness. The responses were then aggregated in the form of tables and charts using statistical software, specifically SPSS, Chi Chi-Square was used and a P value less than 5 was statistically significant.

RESULTS

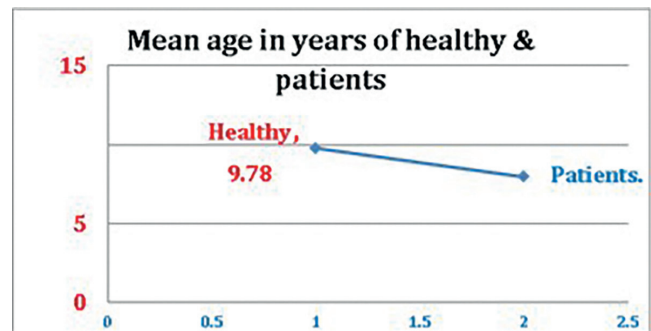


Figure 1. Mean age in years of healthy & patients

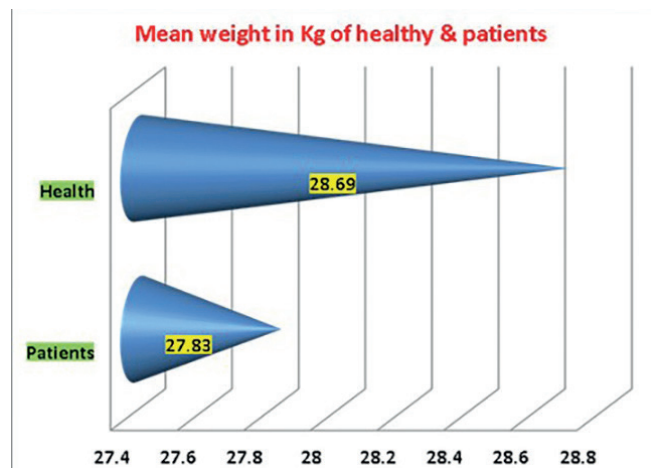


Figure 2. Mean weight in Kg of healthy & patient with thalassemia

Table1. Chi-Square Tests the weight of patients with the weight of healthy

	Value	df	Asymptotic Significance (2-sided)
Chi-Square	2545.184 ^a	2482	0.184
Likelihood Ratio	555.192	2482	1.000
Linear-by-linear association	35.673	2482	1.000
N of Valid Cases	100		

When we used Linear-by- Linear Association with Asymptotic Significance (2-sided), There is a significantly higher weight in healthy children compared with patients (thalassemia) with a P value less than 0.0001

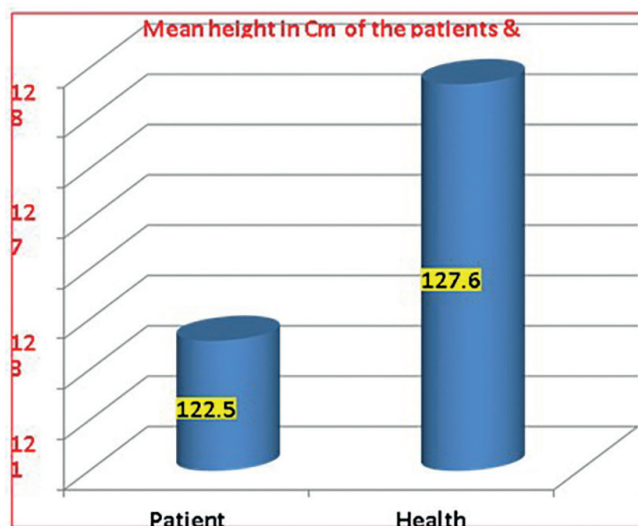


Figure 3. Mean height in Cm of patients with thalassemia & healthy.

Table 2 Chi-Square Tests the height of patients with a height of healthy

	Value	df	Asymptotic Significance (sided-2)
Chi Square	1794.60 3 ^T	1872	.898
Likelihood Ratio	518.019	1872	1.000
Linear-by-Linear Association	518.019	1872	1.000
N of Valid cases	100		

When we used Linear- by-linear Association with Asymptotic Significance (2-sided), the healthy children were taller than patients (thalassemia) with a P value less than 0.0001

DISCUSSION

The outcomes of our study indicated a notable variance in growth retardation concerning weight between thalassemia patients and the control group. Furthermore, the height percentage in the healthy group was recorded at (28.69%), while among patients, it stood at (27.83%), as depicted in Figure 2. Therefore, the findings of our study revealed a substantial contrast in height, with thalassemia patients exhibiting a height deficit of 122.58 compared to the 127.68% observed in

the control group. This translates to a stature reduction of 5.1% and a 0.86% failure in weight, as illustrated in Figure 3. Our results are similar to other studies done in other areas of the world like in Germany in 1997²⁰, in Egypt in 1995²¹ and in Malaysia in 2008²².

Hence, the outcomes depicted in Figure 1 underscore the impact of age on growth. Notably, a significant correlation emerged between increasing age and growth retardation in both height and weight, indicated by a highly significant P-value of < 0.0001. In the case of children with Thalassemia major, a distinct growth trajectory was evident. Initially, growth followed a relatively normal pattern up until approximately the age of 9–10 years. Beyond this point, a deceleration in growth velocity surfaced, accompanied by a reduction or absence of the anticipated pubertal growth spurt. The causative factors behind this growth impairment are manifold³. This suggests that thalassemia patients are prone to risk factors associated with growth failure, stemming from a direct association with iron toxicity, particularly within the endocrine glands²³. Furthermore, the influence of intensive chelation therapy, especially before the age of 10, adds to the complexity of the issue.²³ or might result from additional reasons like anaemia^{24,25}, folate insufficiency and hypersplenism²⁴, and zinc and calcium insufficiency²⁵. Growth failure together (weight & height) is increased with the growing age of patients due to increased factors affecting growth with ageing like iron overload, desferrioxamine toxicity, chronic uncorrected anemia²⁶, undernutrition, zinc deficiency and endocrine complications which increase with the ageing of thalassemia patients like hypothyroidisms²⁶. These results are compatible with former studies in other areas of the world as in Iraq (The result of the study showed that among thalassemic patients, there was an occurrence of 45.5% short stature and 40% weight failure, in contrast to the control group²⁷, and another one showed that thalassemic patient weight percentile is 26.5% and height percentile is 21%²⁸). Growth failure is associated with the increased size of the spleen which is statistically significant for height but not for weight (however, the percentage of weight failure is increased with the increased size of the spleen). Normally, the spleen filters the blood, and it removes old normal and abnormal red blood cells. In thalassemia, most red cells are abnormal, they are often stuck in the spleen and this is why the spleen enlarges and becomes bigger and bigger destroying more and more red cells until almost

all the blood you transfused just goes directly to the spleen and is destroyed²⁹, resulting in anemia leading to growth failure. Thalassemia poses a health challenge and it drastically reduces the quality of life. Nonetheless, the landscape for individuals with beta-thalassemia has undergone significant transformation over the last ten years. The treatment approach for patients, involving transfusions and the implementation of iron management strategies, has evolved substantially, driven by advancements in red cell chelation therapy. This forward momentum has significantly augmented the likelihood of thalassemic children attaining adulthood while maintaining a satisfactory quality of life.³⁰ Other factors in Thalassemia that disturb growth disorders are sub-optimal serum ferritin levels with iron deposition and chelation therapy leading to high damage to the hypothalamic-pituitary axis and growth failure.³¹

Achieving normal growth in thalassemic children hinges on sustaining a hemoglobin level within the range of 10–11 g/dL during the initial decade of life. The significance extends beyond the mere transfusion of packed red blood cells to maintain hemoglobin levels; it holds paramount importance for caregivers to vigilantly assess the iron status of these affected children, a task facilitated by serum ferritin level measurements. It is imperative to strike a balance, as both excessive serum iron and elevated serum ferritin levels pose equal risk and can result in compromised growth. The journey of thalassemia is characterized by a lifelong series of blood transfusions and chelation therapy, culminating in iron overload.³² Vigilant surveillance of growth holds the potential to facilitate the timely detection and intervention of these complications, thereby ensuring that patients attain an adult height that closely approximates the norm.³³ Advancements in therapeutic strategies, encompassing regular blood transfusions and chelation therapies, have notably enhanced the lifespan of these individuals. As a result, researchers are dedicating their efforts to examining the repercussions of endocrinological changes on the overall quality of life.³⁴ Short stature has been linked to a diminished quality of life, while an elevation in height standard deviation score (SDS) has been correlated with an improvement in overall quality of life.³⁵ Therapies involving growth hormone (GH), such as GH treatment, are emerging with a heightened potential to enhance not only height but also various parameters contributing to holistic well-being and an elevated quality of life in individuals with thalassemia.^{36,39}

CONCLUSION

The findings of this study elucidate the prevalence of short stature, weight failure, and delayed puberty among individuals with thalassemia, aligning with analogous studies conducted in different global regions. Moreover, the occurrence of growth failure demonstrated a direct correlation with factors such as the patient's age, frequency of blood transfusions, serum ferritin levels, hemoglobin levels, and the dimensions of the spleen.

"The author declare that all the procedures and experiments of this study respect the ethical standards in the Helsinki Declaration of 1975, as revised in 2008(5), as well as the national law. Informed consent was obtained from all the patients included in the study.

There are no conflicts of interest regarding this article."

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