

Assessment of serum calcium levels and its outcome among transfusion dependent beta thalassemia major patients on chelation therapy

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ABSTRACT

Objective: To analyze the serum calcium levels and its outcome among blood transfusion dependent β -Thalassemia major patients on Chelation therapy.

Material and Methods: cross-sectional study design was employed to conduct the study. A total of 250 children diagnosed (5-12 years old) with beta thalassemia major undergoing regular blood transfusions, presented to the pediatric ward of CMH Bahawalpur between June 2024 and June 2025 were included in the study. The approval of the ethical review board and written informed consent of the respondents and their guardians were obtained for conducting the study. The patients with their guardians were then approached for data collection. Laboratory analysis of the fresh blood samples of the patients, under aseptic measures, was conducted for serum calcium levels with the documentation of results.

Results: This study found a significant association between hypocalcemia and the occurrence of clinical symptoms in transfusion dependent thalassemia patients. Carpopedal spasm (4.5%), numbness (13.4%), bone pain (46.3%), and fractures (19.4%) were observed exclusively in patients with hypocalcemia, while none of these symptoms were present in those with normocalcemia. The associations were statistically significant, with p-values < 0.05 for all variables except seizures, which were not reported in either group.

Conclusion: Hypocalcemia was significantly associated with carpopedal spasm, numbness, bone pain, and fractures in transfusion-dependent thalassemia patients, with females showing a higher burden of complications. Regular calcium monitoring is essential to reduce morbidity in this population.

Key words: Beta thalassemia, Blood transfusion, Chelation therapy, Hypocalcemia.

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INTRODUCTION

Beta thalassemia major is an autosomal recessive condition that requires regular transfusion and chelation therapy throughout the life of a patient [1]. Beta thalassemia major has an incidence of about 5,000 new cases per annum in Pakistan [2]. The patients of Thalassemia show severe hemolytic anemia that is treated by frequent transfusions. Transfusions help to improve the life expectancy. Effective iron chelation is also another cause of the improved life expectancy, as secondary hemochromatosis

is a significant complication among such patients [3]. The iron overload precipitates certain endocrinological conditions such as hypocalcemia that manifests as neurological symptoms such as carpopedal spasm and seizures [4]. The calcium levels in the body are linked to various physiological function including those of cardiac cells, skeletal muscle cells, nerve conduction, vascular tone management [5]. Increased levels of serum ferritin are highly linked to hypoparathyroidism that subsequently results in hypocalcemia [6]. Chelation therapy is crucial in the lowering of serum ferritin levels, which are closely linked with normalization of serum calcium levels. [7].

The hypocalcemia affects the human life in many ways. One of the studies showed 22.2% of Transfusion dependent beta thalassemia major patients showed osteoporosis. Keeping in mind these patients had significant lower calcium

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levels [8]. 48% were found to have low serum calcium, and the frequency was greater in patients who took deferoxamine than other oral iron chelators, which indicates a potential disruption in calcium homeostasis related to its use [9].

Hypocalcemia is a complication associated with transfusion-dependent β -thalassemia major patients because they have iron overload and require long-term chelation therapy, which causes bone pain and fracture. Although thalassemia is very common in Pakistan, there are limited local data on calcium disturbances and their consequences. The rationale behind this study was to measure serum calcium and complications associated with it with a view to producing evidence that could help in enhancing screening and management in our context.

MATERIAL AND METHODS

This cross-sectional study was conducted at Combined Military Hospital, Bahawalpur from 1st June-2024 to 30th June-2025. To assess the serum calcium levels and its impact on the transfusion dependent beta thalassemia major patients who are receiving chelation therapy. The study was approved by institutional ethical committee. Sample size was calculated using WHO sample size calculator taking confidence level 95%, margin of error 5.6%, taking prevalence of hypocalcemia 27.72% [10].

Inclusion criteria included the patients aged from 5 to 12 years, who were the diagnosed cases of beta thalassemia major (using electrophoresis) and were receiving regular blood transfusions. The patients who were included in this study were receiving chelation therapy for at least 6 months. The patients of other hemoglobinopathies, having known history of parathyroid disorder, chronic kidney disease, any mal-absorption syndrome. Patients who were taking or had taken supplements of vitamin D or calcium from last three months. Patients who had any acute illness or any recent hospitalization in the past 2 weeks or unwilling to participate were excluded from the study.

Parents of pediatric patients and adult patients themselves gave informed consent. Patients

were interviewed using a structured questionnaire after they gave consent. Demographics, duration of disease, duration of chelation therapy, type of chelation therapy, frequency and volume of transfusions and the impacts of hypocalcemia were asked from the patients. In particular, the patients were questioned regarding the previous experience of muscle cramps, seizures, palpitations, bone pain, and fractures. Fresh blood samples were collected under aseptic measures and sent to the lab and serum calcium levels were noted and documented on the next visit of the patient the questionnaire was filled by the on-duty doctor and then the recorded form was entered in the Excel sheets.

Data was analyzed by using Statistical Package for Social Sciences (SPSS) 22.00. Normality of data was checked by using Kolmogorov-Smirnov test. Age was normally distributed and represented by mean and standard deviation (SD). Qualitative data (gender, Calcium levels and Symptoms) was represented by using percentage and frequency. Chi square test was applied to find out the association of calcium levels and symptoms. The p-value of ≤ 0.05 was considered as statistically significant.

RESULTS

Out of a total of 250 patients, 116 (46.4%) were male and 134 (53.6%) were female, with an overall mean age of 9.71(2.07) years (10.24 (2.01) years in males and 9.10 (1.99) years in females). Regarding calcium status, the majority of patients 183 (73.2%) had normocalcemia, observed in 84 (33.6%) males and 99 females (39.6%). Hypocalcemia was present in 67 (26.8%) of patients, including 32 males (12.8%) and 35 females (14%) shown in Table-I. However, Carpopedal spasm was observed in 2 males (1.7%) and 1 female (0.7%). Numbness was almost equally distributed, reported in 5 males (4.3%) and 4 females (3.0%). Bone pain was more frequent among females (14.9%) compared to males (9.5%). Similarly, fractures were also more common in females (8.2%) than males (1.7%). No patient, either male or female,

experienced seizures shown in Table-II. This study found a significant association between hypocalcemia and the occurrence of clinical symptoms in transfusion dependent thalassemia patients. Carpopedal spasm (4.5%), numbness (13.4%), bone pain (46.3%), and fractures (19.4%) were observed exclusively in patients

with hypocalcemia, while none of these symptoms were present in those with normocalcemia. The associations were statistically significant, with p-values < 0.05 for all variables except seizures, which were not reported in either group shown in Table-III.

Table-I: Demographic Characteristics of Study Participants (n=250).

Demographics	Male	Female	Total
Frequency (%)	116 (46.4%)	134 (53.6%)	250 (100.0%)
Age in years, mean (SD)	9.10 (1.99)	10.24 (2.01)	9.71 (2.07)
Calcium levels	Normo-calcemia	94 (70.1%)	183(73.2%)
	Hypocalcemia	40 (29.9%)	67(26.8%)

Table-II: Gender wise distribution of hypocalcemia related complications in transfusion-dependent thalassemia patients (n = 250).

Symptoms	Male (n=116)	Female (n=134)	Total (250)
Carpopedal spasm	2 (1.7%)	1 (0.7%)	3(1.2%)
Seizures	0(0%)	0(0%)	0(0%)
Numbness	5 (4.3%)	4 (3.0%)	9(3.6%)
Bone pain	11 (9.5%)	20 (14.9%)	31(12.4%)
Fractures	2 (1.7%)	11 (8.2%)	13 (5.2%)

Table-III: Association of calcium levels and symptoms. (n=250).

Symptoms	Hypocalcemia (n=67)	Normocalcemia (n=183)	P value
Carpopedal spasm	3(4.5%)	0 (0.0%)	0.019
Seizures	0(0%)	-	-
Numbness	9(13.4%)	0 (0.0%)	< 0.001
Bone pain	31(46.3%)	0 (0.0%)	< 0.001
Fractures	13(19.4%)	0 (0.0%)	0.029

DISCUSSION

Hypocalcemia was found to be prevalent 26.8 % among transfusion dependent major patients of beta thalassemia on chelation therapy at the present study conducted at CMH Bahawalpur. Hypocalcemia had serious musculoskeletal signs, such as bone pain, fractures, and numbness. These results are consistent with a number of research works published before.

Our findings are consistent with the available literature in establishing hypocalcemia as a common complication of transfusion in patients with thalassemia which is dependent on transfusion. The prevalence in our cohort is however lower than in other studies in Pakistan. Hypocalcemia was also reported in 66.6% of routinely transfused beta thalassemia major patients in a prospective cross-sectional study of

Southern Pakistan, with hypophosphatemia 19.4%, vitamin D deficiency 72.2%, hyperparathyroidism 8.3% and hypocalcemia 66.6% [11]. Our findings are contradictory to these higher rates where Hypocalcemia was reported in 49% of transfusion-dependent patients in another Pakistani study (n = 100), and hyper-phosphatemia was observed in over half of the hypocalcemic cases. Suspected hypoparathyroidism existed in approximately 26% of cases [12].

In a cross-sectional study of Iranian transfusion-dependent thalassemia patients (8-18 years old) (n=140), the authors reported hypocalcemia in 22% of participants, hypophosphatemia in 18.2% participants, and vitamin D deficiency in more than 85% of the participants. Also, 82% (lumbar

spine) and 52% (femoral region) of participants had low bone mineral density (BMD) [13]. Additional evidence confirms the relation between growth and skeletal abnormalities and hypocalcemia. According to Bou-Fakhredin *et al.* short stature was reported in patients with thalassemia in relation to hypocalcemia [14]. Another study done by the Cao A. *et al* also stated that the osteopenia and osteoporosis were related to the hypocalcemia caused in the transfusion dependent beta thalassemia patients [15]. Theppornpitak *et al.* emphasized the importance of compliance with iron chelation therapy and noted that non-compliance leads to uncontrolled iron overload, exacerbating endocrine disturbances including hypocalcemia [6]. Hence our study and the other studies show that results are consistent. The incidence of numbness was 3.6% and carpopedal spasm was 1.2%. the bone pains were 12.4% and fractures were 5.2% in our study. Similar study by the iron chelation had an effect on growth retardation [16]. Although the impacts discussed by this study have been rarely discussed by any other study but the incidence of impacts of hypocalcemia is very high among the thalassemia patients. This needs to be studied in detail and their impact in the low socioeconomic countries are exaggerated as they have low availability of nutritional supplements.

LIMITATIONS

This research has some limitations. As it was cross-sectional in nature it was not able to determine any temporal or causal links between chelation therapy, hypocalcemia and clinical outcomes. Neither serum parathyroid hormone nor 25-hydroxy vitamin D levels were regularly measured thus, restricting the possibility to explore the underlying mechanisms of calcium imbalance in full. Advanced modalities, including MRI T2, were not used to measure iron overload, which limited the correlations between iron load and calcium metabolism. In addition, since the research was carried out in one tertiary care center, the results were not necessarily applicable across all the thalassemia populations

in Pakistan. There was also no long-term follow-up, and no possibility of assessing progression and long-term complications.

CONCLUSION

This study presents the significance of serum calcium monitoring in transfusion-dependent major patients with β -thalassemia who are undergoing chelation. To decrease the complications and enhance patient outcomes, it is necessary to identify and treat calcium imbalances to minimize related complications. Further studies are justified by the need to explore more deeply the underlying mechanisms and provide evidence-based interventions to manage the situation over the long term.

CONFLICT OF INTEREST

Authors declare no conflict of interest.

GRANT SUPPORT & FINANCIAL DISCLOSURE

Declared none

AUTHORS CONTRIBUTION

Kaynat Ali: Study Concept, research design, literature review, data analysis, final approval, accountable for all aspects of publication.

Sohail Shahzad: Research Design, final approval, accountable for all aspects of publication.

Farooq Ahmed: Manuscript drafting, critical review, final approval, accountable for all aspects of publication.

Naila Hamid: Data interpretation, critical review, final approval, accountable for all aspects of publication.

Hina Basharat: Acquisition of data, critical review, proofreading, final approval, accountable for all aspects of publication.

Huzaifa Usman: Manuscript drafting, proofreading, final approval, accountable for all aspects of publication.

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