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ORIGINAL ARTICLE

Parathyroid hormone in pediatric patients with β-thalassemia major and its relation to bone mineral density; a case control study

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Abstract *Background:* Thalassemia syndromes are heterogeneous groups of inherited anemias. Its treatment depends on recurrent blood transfusion with a problem of iron overload, which leads to multiple endocrinopathies including hypoparathyroid. The aim of the study is to estimate the level of serum parathyroid hormone and its relation to bone mineral density in transfusion dependent beta-thalassemia major children.

Subjects and methods: We measured serum calcium, phosphorus and parathyroid hormone in a sample of pediatric patients with thalassemia, compared them with age and sex matched healthy control. Measurement of bone mineral density by dual-energy X-ray absorptiometry was done in 2 sites: lumbar spine (L2–L4) in the anteroposterior position and left femur neck using Lunar Densitometry in osteoporosis Unit Ain Shams University Hospital for thalassemia patients.

Results: Thalassemic patients had significantly higher alkaline phosphatase and lower bone mineral density.

Conclusion: Osteopenia in β-thalassemia major patients is multifactorial and is mainly predisposed by defective function of the parathyroid gland and excessive iron deposition.

1. Introduction

Beta-thalassemia is an inherited anemia caused by unbalanced globin chain synthesis with ineffective erythropoiesis and peripheral hemolysis [1].

The aim of treatment in thalassemia is to prevent anemia and bone marrow hyperplasia by regular blood transfusion [2]. Suboptimal transfusion causes bone marrow expansion

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and decreases cortical and trabecular bone tissues and osteoporosis [3].

With advance in blood transfusion management, classical thalassemic bone changes reduced markedly. However, well transfused patients require adequate iron chelation therapy such as desferrioxamine. The latter has direct toxic effect on bone growth [4,5]. It also chelates zinc which is a co-factor for alkaline phosphatase. Iron overload may result in end organ damage, especially in endocrine glands as parathyroid glands [6]. Parathyroid hormone plays a central role in calcium–phosphate metabolism thus bone remodeling and turn over.

The etiology of bone disease in beta thalassemia is multifactorial. Factors such as bone marrow expansion, increased iron load, hormonal deficiency, desferrioxamine side effects and calcium/vitamin D deficiencies all seem to have a serious impact on the impaired bone metabolism in the disease [7].

With this background, we were stimulated to assess bone mineral density in children with beta-thalassemia major and to find its relation with serum parathyroid hormone level.

2. Methods

This case-control study was conducted on 60 cases with beta-thalassemia major diagnosed by elevated Hb F and A_2 in hemoglobin electrophoresis, attending Hematology clinic, Pediatric Hospital, Ain Shams University.

They were 38 males and 22 females with male: female ratio of 1.7:1. Their age ranged between 5 and 15 years with a mean age of 9.4 ± 3.2 years.

The controls were 30 age-and sex matched, non-anemic healthy children from Pediatric Outpatient clinic of Ain Shams University Pediatric Hospital.

All study procedures were approved by the Ethics Committee of the Ain Shams University. All subjects were informed orally about the procedures and the aim of the study and gave written consent to participate. The consent of participation in the study was signed by the parents or legal guardians of the studied subjects. The work has been carried out in accordance with the World Medical Association (declaration of Helsinki) for experiments in humans.

All patients were subjected to the following:

1. Detailed history taking laying stress on patient age, disease duration, frequency of blood transfusion, history of bone pain or fracture, type and frequency of chelation therapy.
2. Thorough clinical examination with special emphasis on weight, height, size of liver and spleen, presence of spleenectomy scar, pallor, skeletal deformity bone fracture and signs of haemosiderosis.
3. Quantitative measurement of serum calcium and phosphorous, alkaline phosphatase and parathyroid hormone (PTH) for whole study population i.e. patients and controls in order to detect variation in their levels in comparison with normal population even when levels are within normal ranges:
   (a) Serum calcium and phosphorous with synchron CX-7 auto-analyzer (Bechman Instruments Incorporation).
   (b) Alkaline phosphatase by kinetic photometric method (Diagnostic Systems International Kit).
   (c) Parathyroid hormone (PTH) with Immulite Analyzer using chemiluminescent immunometric assay.
4. Measurement of bone mineral density for thalassemia patients by dual-energy X-ray absorptiometry in 2 sites: lumbar spine (L2–L4) in the anteroposterior position and left femur neck using Lunar Densitometry.

2.1. Statistical analysis

Data were statistically analyzed using SPSS statistical package version 10 (Echosoft Corp, USA, 2006).

3. Results

Thalassemia patients enrolled in the study were all transfusion dependent, receiving approximately 15 ml of packed red blood cells per kilogram body weight every 2–3 weeks. Patients were on chelation therapy with desferrioxamine 4 times per week in the form of overnight subcutaneous infusion over 8 h, dose 40 mg/kg body weight.

Mean age of patients was 9.37 ± 3.17 y, weight 30.47 ± 9.26 kg, and height 124.5 ± 17.5 cm and mean hemoglobin level was 8 ± 1.41 gm/dl. Calcium blood level was 8.8 ± 1.35 mg/dl for patients and 10.1 ± 0.63 mg/dl for controls.

Phosphorous level was 4.24 ± 0.96 mg/dl for patients and 2.69 ± 0.67 mg/dl for controls and alkaline phosphatase value was 234 ± 62 IU/L for patients and 199 ± 76.9 IU/L for controls.

Parathyroid hormone was higher in patients than in controls, 75.9 ± 76.28 versus 46 ± 15.55 with no statistical difference (P-value > 0.05).

Among thalassemia patients 31 had normal bone mineral density with z-score 0.55 ± 0.003 and 29 patients had decreased bone mineral density with z-score −1.96 ± 0.54 (see Fig. 1 and Table 1).

Patients with osteopenia are predominantly males (38 patients-63.3%), and 29 females (36.7%). Among them 21 patients (72.4%) gave a history of bone ache and 9 (31%) had a history of fracture.

Comparing both groups, thalassemia patients and the healthy controls concerning calcium, phosphorous, alkaline phosphatase and parathyroid hormone showed that calcium,

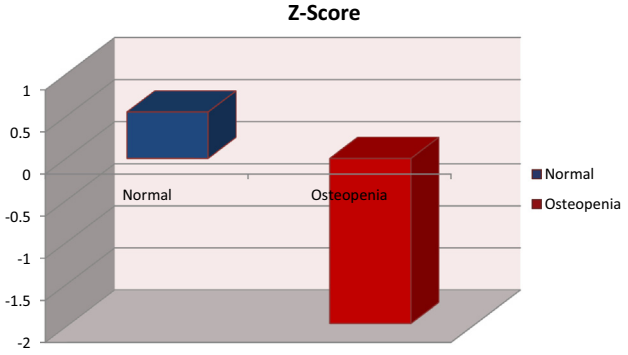

Figure 1 Comparison of Z-score of patients with normal bone mineral density versus patients with osteopenia.

Table 1 Results of bone mineral density of beta-thalassemia patients group.

Parameter	Patients with normal BMD (n = 31)	Patients with decreased BMD (n = 29)	P
Z score	0.55 ± 0.003	−1.96 ± 0.54	<0.001

Parameter	Patients with normal BMD (n=31)	Patients with decreased BMD (n=29)	P
Calcium (mg/dl)	9.42±0.98	8.18±1.4	<0.001
Phosphorous (mg/dl)	3.97±0.89	4.51±0.958	<0.05
Alkaline phosphatase (IU/L)	230±67.2	238±56.86	>0.05
Parathyroid hormone (pg/ml)	110±88.2	39.5±35.56	<0.001
Ferritin (ng/ml)	591.6±294	1603±717.9	<0.001

Figure 2 Comparison of bone markers between patients with normal bone mineral density versus patients with osteopenia.

parathyroid hormone were higher in thalassemia patients with normal bone mineral density while phosphorous, alkaline phosphatase and serum ferritin were higher in thalassemia patients with osteopenia (see Fig. 2).

4. Discussion

Historically, beta-thalassemia major has been associated with marked osseous changes, originally described by Coley et al. The life expectancy of patients with β-thalassemia has greatly improved with increase in serious complications including osteopenia and osteoporosis [8]. With advances in blood transfusion, classical thalassemia bone changes showed a mild reduction, however suboptimal blood transfusion together with inadequate iron chelation therapy lead to chronic anemia, hypoxia and iron overload [4]. As a consequence, impaired growth and delayed puberty are common findings; therefore, skeletal changes in these patients are prominent despite a lesser severity of disease [7].

The current study revealed a marked reduction in calcium level and increase in phosphorus and alkaline phosphatase levels in thalassemia patients compared to the control group. Saboor et al. reported same findings [5]. Lasco et al., also reported the same and mentioned that this calcium phosphorus unbalanced ratio resulted from parathyroid affection as a part of multiple endocrinopathies resulting from iron overload. In contrast [4], Mahackolertwattana et al., reported that calcium and phosphorous were nearly the same in both groups' thalassemia patients and controls [7].

In our research, we studied the level of parathyroid hormone in both groups and found a non significant difference with a higher level in patients group. Also, Napoli et al. reported hypoparathyroidism in 15% of β-thalassemia major patients despite the presence of hypocalcemia and hyperphosphatemia in most of them. This could be attributed to the wideness in parathyroid hormone level range or the young age of patients [8].

Abdel-Hafez and colleagues conducted a prospective research evaluating endocrinal status in β-thalassemia children and they found a significant decrease in parathyroid hormone levels in the thalassemia group compared to the control group. They owed their findings mainly to iron deposition in the parathyroid gland due to frequent blood transfusion and inadequate chelation therapy [9].

Regarding the blood picture evaluation, hemoglobin level was significantly lower in thalassemia patients compared to controls, total leucocyte count is found to be higher in thalassemia patients compared to controls, and this is mostly due to increased susceptibility to infection present in the former group [6].

Platelets count is markedly increased in the thalassemia group, mostly as a part of increased abnormal activity of bone marrow precursors in response to tissue hypoxia [10].

The present study reported unbalanced calcium, phosphorous ratio in thalassemia patients having osteoporosis which could be a predisposing factor for bone affection. This in agreement with Vaskaridou et al. who stated also that longer duration of disease, is associated with more affection to bone density [11].

Serum ferritin was higher in osteopenic patients among the thalassemia group. Jensen et al. stated that bone mineral density is affected in thalassemia patients with normal ferritin levels, but Oudit et al. found high serum ferritin in osteopenic patients [12]. This is could be explained by inhibition of osteoblastic activity by iron, affection of anabolic factor as IGF as a part of endocrinopathies or inhibition of DNA synthesis by desferrioxamine which is an infrequently used iron chelator.

Regarding the parathyroid hormone level, our study found that the level of the hormone is markedly decreased in the osteopenic group than in the normal bone mineral density group. Skordis et al. found that the difference in the hormone level between the two groups was insignificant [13].

Aim of thalassemia treatment in pre-pubertal children has been changed from not only treatment of anemia and skeletal changes to treatment of bone morbidities but also osteoporosis which became an important problem [14]. The decrease in bone density starts early in childhood and becomes progressive with age. Even in some well chelated population a problem of low bone mineral density still exists, especially those treated with desferioxamine [15]. However, no significant relationship between its use and bone mineral density was found in our study.

In conclusion, our study showed that osteopenia which is a common complication in β-thalassemia major patients is multifactorial and is mainly predisposed by defective function of parathyroid gland and excessive iron deposition in various body organs.

Conflict of interest

The authors declare no conflict of interest.

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