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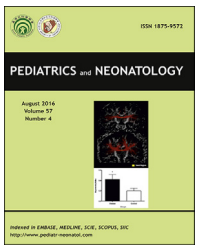

Original Article

Age-related changes in biochemical bone profile in thalassemic children

Ehab S. Abd El-Moneim [a,b,*], Mohammed A. Zolaly [a], Zakaria M. Al-Hawsawi [c], Abeer A. Abdelmoneim [a,b], Mostafa M. Abosdera [b]

[a] *Pediatric Department, College of Medicine, Taibah University, Almadinah Almonawara, Saudi Arabia*
[b] *Pediatric Department, Faculty of Medicine, Sohag University, Sohag, Egypt*
[c] *Madinah Maternity and Children Hospital, Almadinah Almonawara, Saudi Arabia*

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Key Words
osteopathy;
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Background: Osteopathy is an important cause of morbidity in β-thalassemia major (TM). Although many of the etiopathological factors implicated in thalassemic osteoporosis commence in early disease phases during childhood, limited information exists on bone turnover in children with TM. This study was conducted with the objective to compare bone turnover markers (BTMs) in thalassemic children at different ages.
Methods: In a cross sectional case control study, 47 children (age range, 1.5–18 years) with TM were recruited. BTMs were compared to eighteen age- and sex-matched healthy controls and to 16 adults (age range, 19.67–31.08 years) with TM.
Results: Thalassemic children displayed unbalanced bone turnover with an increased bone resorption (shown by high levels of tartrate-resistant acid phosphatase 5b (TRACP5), receptor activator of nuclear factor-kappa B ligand (sRANKL) and sRANKL/osteoprotegerin (OPG) ratio) and a decreased bone neoformation (shown by low levels of osteocalcin (OC)) when compared to healthy children. TRACP5b was the only BTMs studied that showed a significant correlation with age in thalassemic children. For the whole thalassemic children group, regression analyses showed an influence of sex hormones replacement therapy on TRACP5b; pretransfusion hemoglobin and splenectomy on sRANKL; pretransfusion hemoglobin on sRANKL/OPG; and pretransfusion hemoglobin and serum ferritin on OC.
Conclusion: The present study confirms that TM has profound effects on bone metabolism starting from early childhood. The early onset of bone turnover disturbances in TM indicates the need to investigate possible option to intervene early.

* Corresponding author. Department of Pediatrics, College of Medicine, Taibah University, Almadinah Almonawara, Saudi Arabia.
E-mail address: ehab_saoud@yahoo.com (E.S. Abd El-Moneim).

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1. Introduction

Osteopathy is an important cause of morbidity and disability in β-thalassemia major (TM). The improvement in survival of TM patients was accompanied by increasing incidences of osteoporosis and higher fracture risk.[1] Multiple etiopathological factors have been implicated in thalassemic osteopathy. These included accelerated hematopoiesis, iron toxicity, iron chelators toxicity, endocrinopathies, and genetic factors.[2,3] Despite optimizing transfusion and chelation regimens and adequate hormone replacement, bone demineralization was still detectable in 92.7% of thalassemic adults.[4]

Although many of the factors identified as promoters for thalassemic osteoporosis commence in early phases of the disease during childhood, most attention has been directed toward bone changes in thalassemic adolescents and adults. Several studies have shown significant changes in bone turnover markers (BTMs) and/or bone mineral density (BMD) in thalassemic peripubertal adolescents and adults.[5–10] Studies that have examined metabolic activity of bone tissue in pediatric TM patients, especially at early ages, are limited and conflicting. In a heterogeneous group of children with mixed hemolytic anemia diagnoses, the degree of hemolytic disease activity was found to influence bone metabolism, mainly promoting the imbalance in the receptor activator of nuclear factor-kappa B (RANK)/RANK ligand (RANKL)/osteoprotegerin (OPG) system resulting in higher serum RANKL/OPG (sRANKL/OPG) ratio and lowering the bone formation marker, osteocalcin (OC).[11] Lower OC levels were also associated with evidence of hypoparathyroidism in another group of thalassemic children.[12–14] However, this finding was not supported in other studies,[11,15] in which thalassemic children showed significantly higher OC levels compared to controls.

Furthermore, none of the published studies followed the changes that occurred in bone turnover with age or investigated the factors affecting it during childhood and how that compared to adults in TM patients. Therefore, this study was conducted with the objectives to compare BTMs in thalassemic children at different ages and to explore for potential relationships between bone turnover and possible etiopathological factors of thalassemic osteopathy in children.

2. Materials and methods

2.1. Study setting and design

The present study is a cross-sectional case–control study that was conducted at the Thalassemia Centre at Madinah Maternity and Children Hospital (MMCH) in Almadinah Almonawara, Saudi Arabia, from September 2013 to June 2104. The study was performed in accordance with the ethical principles of the Declaration of Helsinki and approved by the 'MMCH Research Ethics Committee'. All patients and control subjects were included after written informed consent was obtained from subjects and/or guardians.

2.2. Study population

A total of 47 (23 females, 24 males) children (mean age, 9.69 ± 4.32; range, 1.5–18 years) with TM were recruited. Eighteen age- and sex-matched children were included as healthy controls. Additionally, 16 (8 females, 8 males) adult (mean age, 22.99 ± 3.11; range, 19.67–31.08 years) with TM were recruited as positive controls. Thalassemic subjects were recruited during regular (monthly) follow up visits, during which all patients were managed according to a standardized protocol that included regular packed red cells transfusions aiming at maintaining pretransfusion hemoglobin levels at 9.5 g/dL; chelation therapy using either one or a combination of the following: deferoxamine (40–60 mg/kg/day, subcutaneous infusion), deferiprone (75–99 mg/kg/day, oral) or deferasirox (10–40 mg/kg/day, oral); and clinical and laboratory regular monitoring (at 6–12 monthly intervals) for evidence of endocrinopathies. Patients with delayed puberty, defined as the inability to achieve Tanners Stage II for breast development by age 13 in girls and a testicular volume <4 ml by age 14 years in boys, underwent testing of the hypothalamic–pituitary–gonadal axis as well as puberty induction and sex hormones replacement therapy as indicated. Other evidence of endocrinopathies was managed as appropriate. As part of the regular care of thalassemic patients, annual evaluation by dietician was conducted. Patients received general recommendations for diets high in calories and low in iron. Of the studied thalassemic children 43 (91.5%) received regular vitamin D supplementation.

Exclusion criteria included any preexisting medical condition other than TM known to affect bone metabolism, evidence of chronic liver affection, chronic systemic administration of steroids, pregnancy, and active untreated evidence of endocrinopathies.

2.3. Protocol, data acquisition and processing

The thalassemic patients included in the study underwent comprehensive physical examination and detailed history-taking. The diagnosis of TM was based on identifying variant hemoglobin in hemoglobin electrophoresis. Anthropometric data of patients and controls were recorded. Standing height was measured to the nearest mm. Weight was recorded to the nearest 0.1 kg. BMI was calculated using the formula: weight (kg)/height^2 (m^2). The measurements for height and BMI were transformed into standard deviation score (SDS) based on a reference data set for Saudi children.[16] Mean pretransfusion hemoglobin and mean serum ferritin in the year prior to the study visit were obtained via chart review.

Laboratory assays. Fasting pre-transfusion venous blood samples were taken from all included subjects and serum was stored at −20 °C after separation. BTMs were determined using a quantitative enzyme-linked immunosorbent assay (ELISA) technique. As markers of bone formation, bone-specific alkaline phosphatase (bALP; Human bALP ELISA Kit, MBS704011, MyBioSource, Inc., USA; intra- and inter-assay coefficients of variation (CVs), <8% and <10%, respectively), OC (DIAsource hOST-EASIA kit, KAP1381,

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