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Prevalence and risk factors of osteoporosis and osteoarthritis among beta thalassemia patients

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ABSTRACT

Objective: This study aims to examine the clinical and radiological features of skeletal changes in patients with thalassemia and provide a comprehensive overview of osteoporosis and osteoarthritis in these patients.

Materials and Methods: We conducted a retrospective analysis of patients with transfusion-dependent thalassemia, both adults and children, who received follow-up care at our thalassemia center between 2019 and 2020.. Thalassemia was diagnosed via hemoglobin electrophoresis. Transfusion-dependent patients were defined as those who received transfusions every 2-4 weeks, while the control group consisted of individuals with thalassemia trait/carriers.. Both groups were analyzed for clinical characteristics, and Dual-energy X-ray absorptiometry (DEXA) scans, and radiographic images of the knee and wrist were evaluated.

Results: DEXA scans of the femur and lumbar spine showed that the prevalence of osteoporosis , Synovial hypertrophy of the wrist joint , wrist effusion , knee effusion, and Power Doppler signals on wrist ultrasound scans was statistically significantly higher in transfusion-dependent thalassemia compared to patients with thalassemia carriers.

Conclusion: Beta thalassemia is an inherited multisystem disease that leads to various musculoskeletal abnormalities. Knowledge of the musculoskeletal manifestations of thalassemia allows clinicians to guide their treatment. Familiarity with the radiological features of beta thalassemia is crucial for physicians in the timely diagnosis and management of thalassemia and its complications.

Keywords: thalassemia, osteoporosis, osteoarthritis, musculoskeletal, transfusion

INTRODUCTION

Beta thalassemias are a heterogeneous group of autosomal recessive disorders characterized by hypochromic microcytic anemia resulting from defective synthesis of one or more of the hemoglobin (Hb) chains. Thalassemia carriers is the most common type and does not require any treatment. Babies born with beta transfusion-dependent thalassemia (TDT) have normal clinical features at birth because beta globin chain synthesis does not increase early on. In healthy children, hemoglobin (Hb) F is high in the early postnatal period, but Hb A becomes the predominant hemoglobin because of increased synthesis of the beta-globin after the sixth month of life. In thalassemia, defective production of the beta-globin chain causes disease-specific clinical signs and symptoms to appear between six months and two years of age. In thalassemia non-dependent transfusion, the need for transfusion occurs later, albeit less frequently (1). Severe anemia develops as a result of ineffective erythropoiesis and a shortened lifespan of erythrocytes (less than 20 days) (2).

This condition can cause growth retardation, jaundice, pallor, muscle weakness, hepatosplenomegaly, extramedullary hematopoiesis-related mass formation, as well as bone changes. Skeletal changes include deformity in the long bones and a typical craniofacial appearance (frontal prominence, malar prominence, flattening of the nasal bridge) (3). Splenomegaly causes more erythrocytes to be retained in the spleen, leading to hypersplenism over time. Ineffective erythropoiesis and premature breakdown of erythrocytes cause hyperbilirubinemia and cholelithiasis (2). Repeated transfusion due to ineffective erythropoiesis leads to transfusion-associated hemachromatosis, which can cause organ damage (4). Previous studies have reported a correlation between beta thalassemia and certain rheumatologic and non-rheumatologic autoimmune disorders. It has been argued that the β-globin locus is located in proximity to key autoimmunity genes and that minimal expression of hemorphins, endogenous opioid peptides with anti-inflammatory effects, in thalassemia patients may trigger systemic autoimmune diseases (5).

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The management of patients with thalassemia has improved markedly over the last few decades with the introduction of transfusion programs and chelation therapy, significantly improving life expectancy and quality of life for these patients. With increasing life expectancy, hemoglobinopathies have been associated with various bone disorders such as bone pain, delayed bone age, spinal deformities, pathologic fractures, osteopenia, and osteoporosis (6). Furthermore, drugs used in iron chelation therapy may contribute to osteopenia and osteoporosis (7). Osteoporosis is a major cause of morbidity in these patients and leads to an increased risk of fracture due to low bone density and decreased bone strength (8,9). Currently, dual-energy X-ray absorptiometry (DEXA) is a widely used non-invasive and safe method for measuring bone density to assess the severity of osteoporosis and osteopenia (10). The aim of this study is to evaluate the clinical and radiological skeletal changes, as well as DEXA scans, in patients with transfusion-dependent beta thalassemia to determine the prevalence of osteoarthritis and osteoporosis, and to provide an overview of these conditions in these patients.

MATERIALS AND METHODS

Adult and pediatric patients with transfusion-dependent thalassemia (TDT), who received follow-up care at our thalassemia center between 2019 and 2020, were included in this retrospective study. Thalassemia was diagnosed via hemoglobin electrophoresis. Transfusion-dependent patients were defined as those who received transfusion every 2–4 weeks, with a control group consisting of the non-transfusion-dependent patient with thalassemia carriers. Both groups were analyzed for clinical characteristics, laboratory parameters for the last three months, renal functions, liver transaminases, ferritin levels, and for the type and duration of chelation therapy received. DEXA scans, and radiographic images of the knee and wrist were evaluated. Bone density results were categorized into normal, osteopenia, and osteoporosis based on the 2022 Osteoporosis Guidelines of the Turkish Association of Endocrinology (11) using Z-scores for lumbar spine and femoral neck for male and female adult and pediatric patients. Premenopausal women and men younger than 50 years were evaluated using Z-scores instead of T-scores. Direct radiographs were blindly evaluated by a rheumatologist, and a score was assigned to wrist and knee radiographs using the OARSI scoring system as follows: 0 for normal, 1 for mild change, 2 for moderate change, and 3 for severe change. In addition, the knees and ankles were evaluated and graded using ultrasound by the same physician (12). This study received approval from the Ethics Committee (Ethics committee 2011-KAEK-25 2020/11-10).

Statistics: Descriptive statistics were expressed as frequency, percentage, mean, and standard deviation. Categorical variables were analyzed using Pearson chi-square and Fischer's exact tests using 2 x 2 tables. Numerical variables were tested for normality using the Shapiro–Wilk test. Mean differences between the two groups were compared using Student's t-test for normally distributed variables and the Mann–Whitney U test for non-normally distributed variables. All statistical analyses were performed using SPSS (Statistical Package for the Social Sciences, SPSS Inc., Chicago, IL, USA) 21.0 software suite. Statistical significance was set at $p < 0.05$.

RESULTS

General characteristics of the patients are presented in Table 1. The groups were compared for socio-demographic characteristics and the prevalence of osteoporosis (Table 2). Comparisons found significant differences between the groups in age, age at diagnosis, mean DEXA scores for the femur and lumbar spine (L1–L4) ($p < 0.05$). The mean femur and lumbar spine (L1-L4) scores of thalassemia carriers on DEXA were significantly higher than those of transfusion-dependent thalassemia patients (0.08 ± 1.20 and -0.65 ± 1.46, respectively).There was no significant difference between the groups in the distribution of myalgia, arthralgia, arthritis, and chelation-related arthritis ($p > 0.05$). Laboratory parameters were compared between the groups (Table 4). Patients with transfusion-dependent thalassemia had significantly higher mean levels of BUN (12.81 ± 4.07) and creatinine (0.65 ± 0.17) compared to those of thalassemia carriers ($p < 0.05$). Additionally, patients with transfusion-dependent thalassemia had significantly higher mean levels of AST (26.23 ± 10.05), ALT (26.27 ± 19.87), ferritin (1664.04 ± 1025.79), phosphorus (4.17 ± 0.63), and ALP (135.08 ± 77.99) compared to those of thalassemia carriers ($p < 0.05$). The distribution of wrist and knee scores was compared between the groups (Table 5). Synovial hypertrophy (SH) of the wrist was seen in 26 (54.2%) of patients with transfusion-dependent thalassemia, which was statistically significantly more common compared with patients with thalassemia carriers ($p < 0.001$). Moderate and severe wrist SH scores were significantly more common in patients with transfusion-dependent thalassemia compared to patients with thalassemia carriers ($p < 0.001$). Wrist ultrasound scans revealed power Doppler (PD) signals in 17 (35.4%) of patients with transfusion-dependent thalassemia at a rate statistically significantly higher compared to patients with thalassemia carriers ($p = 0.029$). Moderate and severe wrist PD scores were significantly more common in patients with transfusion-dependent thalassemia compared to patients with thalassemia carriers ($p < 0.001$). Wrist effusion was seen in 8 (16.7%) patients with transfusion-dependent thalassemia, a rate statistically significantly higher than patients with thalassemia carriers ($p = 0.022$). Knee effusion was seen in 10 (20.8%) patients with transfusion-dependent thalassemia, which was statistically significantly higher than patients with thalassemia carriers ($p = 0.002$).

Table 1: Patients' socio-demographic characteristics and transfusion duration

	Mean ± Sd / n(%)	Min–Max
transfusion-dependent thalassemia	48 (52,7)	
Thalassemia carriers	43 (47,3)	
Age	25,14±13,46	8-59
Female	51 (56)	
Male	40 (44)	
Diagnosis age	13,8±14,30	0-58
Transfusion duration year	14,65±8,24	0-44
Number of transfusions in last year	23,81±11,44	0-48

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Table 2. Comparison of socio-demographic characteristics

	transfusion-dependent thalassemia (n = 48) Mean ± sd /n(%)	Thalassemia carriers (n = 43) Mean ± sd /n(%)	P
Female	24 (50)	27 (62,8)	0,220
Male	24 (50)	16 (37,2)	
Age	20,06±9,76	30,81±14,81	**<0,001**†
Age at diagnosis	4,90±9,10	23,70±12,40	**<0,001**†
DEXA femur			
Normal	15 (45,5)	23 (62,2)	0,265*
Osteopenia	17 (51,5)	12 (32,4)	
Osteporosis	1 (3)	2 (5,4)	
DEXAfemur	-1,03±0,85	0,08±1,20	**<0,001**†
Lumbar (L1-L4)			
Normal	6 (18,2)	20 (54,1)	**<0,001***
Osteopenia	15 (45,5)	15 (40,5)	
Osteporosis	12 (36,4)	2 (5,4)	
Lumbar (L1-L4)	-1,99±1,12	-0,65±1,46	**<0,001**†

*P value was obtained from Pearson or Fisher's exact test, †P value was obtained from Student's t test

Table 3. Comparison of the groups in terms of chelation, myalgia, arthralgia, arthritis, chelation-related arthritis, and splenectomy.

	transfusion-dependent thalassemia (n = 48) N (%)	Thalassemia carriers (n = 43) N (%)	P
Chelation	38 (79,2)	0 (0)	….
Myalgia	16 (33,3)	14 (32,6)	0,937
Arthralgia	19 (39,6)	19 (44,2)	0,657
Arthritis	5 (10,4)	5 (11,6)	0,854
Chelation-related arthritis	0 (0)	0 (0)	….
Splenectomy	17 (35,4)	0 (0)	**<0,001**

P value was obtained from Pearson or Fisher's exact test

Table 4: Comparison of the groups for blood parameters

Variables	transfusion-dependent thalassemia (n = 48) Mean ± sd /n(%)	Thalassemia carriers (n = 43) Mean ± sd /n(%)	P
BUN	12,81 ± 4,07	10,52 ± 2,91	**0,003**†
CREATININE	0,51 ± 0,18	0,65 ± 0,17	**0,001**
AST	26,23 ± 10,05	16,57 ± 4,88	**0,001**
ALT	26,27 ± 19,87	17,42 ± 11,27	**0,012**
FERRITIN	1664,04 ± 1025,79	61,02 ± 56,32	**0,001**
SEDIM	10 ± 12,26	10,7 ± 11,89	0,784†
High sedim	9 (18,8)	7 (16,3)	0,757*
CRP	3,67 ± 1,36	3,77 ± 2,52	0,824
High CRP	6 (12,5)	4 (9,3)	0,744
URIC ACID	4,13 ± 1,77	4,16 ± 1,31	0,926
Calcium	9,48 ± 0,6	9,24 ± 0,36	**0,019**†
PHOSPHORUS	4,17 ± 0,63	3,46 ± 0,84	**0,001**
ALP	135,08 ± 77,99	84,33 ± 44,92	**0,001**
D VIT	19,26 ± 10,17	15,62 ± 11,19	0,108†
PTH	31,66 ± 21,86	36,42 ± 16,65	0,250†

*P value was obtained from Pearson or Fisher's exact test, †P value was obtained from Student's t test

Table 5: Comparison of wrist and knee scores between the groups

	transfusion-dependent thalassemia n(%)	Thalassemia carriers n(%)	P
Wrist synovial hypertrophy	26 (54,2)	7 (16,3)	0,001
Wrist synovial hypertrophy OARSI SCORE			
0-1	8 (30,8)	7 (100)	0,001
2	15 (57,7)	0 (0)	
3	3 (11,5)	0 (0)	
Wrist Power Doppler	17 (35,4)	6 (14)	0,029
Wrist Power Doppler SCORE			
0–1	7 (41,2)	6 (100)	0,008
2	8 (47)	0 (0)	
3	2 (11,8)	0 (0)	
Wrist effusion	8 (16,7)	1 (2,3)	0,022
Knee joint space narrowing	6 (12,5)	4 (9,3)	0,626
Knee synovial hypertrophy	4 (8,3)	1 (2,3)	0,209
Knee synovial hypertrophy OARSI SCORE			
0–1	2 (50)	1 (100)	0,600
2-3	2 (50)	0 (0)	
Knee chondrocalcinosis	8 (16,7)	2 (4,7)	0,067
Knee Power Doppler	2 (4,2)	0 (0)	0,176
Knee tendinosis	7 (14,6)	6 (14)	0,932
Knee effusion	10 (20,8)	0 (0)	0,002

P value was obtained from Pearson or Fisher's exact test

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DISCUSSION

Changes in the joint and skeletal system in patients with thalassemia are due to complex causes. Dysfunction in hemoglobin synthesis resulting in hemolysis and related hypoxia may be one of the major causes. Ineffective erythropoiesis leads to bone marrow hyperplasia, which in turn causes thinning of the bone cortex (13, 14). Recently, the introduction of chelation therapy and safe transfusions have resulted in significantly prolonged life expectancy for patients with transfusion-dependent thalassemia, but there remain several associated complications; skeletal complications, including osteoporosis, osteopenia, skeletal deformities, scoliosis, nerve compression, bone pain, and spontaneous pathological fractures are common in transfusion-dependent thalassemia (15). This study found no significant difference in the distribution of myalgia, arthralgia, and arthritis between the groups.

The most common spine problems in thalassemia include kyphosis, scoliosis, and osteoporosis, and the rate of fractures is approximately 30% despite supportive therapies (16). Osteoporosis and osteopenia are the major causes of morbidity in pediatric and adult patients with transfusion-dependent thalassemia (TDT). Femoral densitometry data appear to be a variable of great importance in the assessment of bone status, confirming the widely accepted importance of bone mineral density (BMD) as a determinant of bone strength and fracture risk (17). Thus, DEXA is the gold standard technique for assessing osteoporosis in the general population and in thalassemics, and is widely used in clinical practice, largely to define the extent of bone loss in beta thalassemia and osteoporosis (18). This study found that osteoporosis was more common in patients with TDT, with significant differences between the two groups regarding mean femur and lumbar spine (L1–L4) scores on DEXA.

Chelation is one of the major risk factors for osteoporosis; high-dose desferrioxamine therapy decreases the differentiation and proliferation of bone-forming cells, decreases collagen formation and increases osteoblast apoptosis. Chelation also worsens bone health by causing mineral and vitamin deficiencies, including zinc and vitamin D deficiency (19). The present study found no significant difference between the groups in the distribution of chelation-related arthritis.

Endocrinopathies, such as hypogonadotropic and primary hypogonadism, along with factors such as iron overload, deferoxamine toxicity, calcium and zinc deficiency, vitamin D deficiency, and inadequate physical activity can disrupt the balance of bone remodeling. These factors inhibit osteoblastic activation and increase osteoclast function, leading to bone loss, osteoporosis, and an increased risk of fractures (20, 21). Endocrine disorders such as hypoparathyroidism and hypogonadism, impaired vitamin D metabolism due to liver damage, and negative effects of chelating agents on calcium and phosphorus absorption are known to cause osteoporosis in patients with thalassemia (22). The present study found statistically significantly higher mean levels of AST, ALT, ferritin, phosphorus, and ALP in patients with TDT than in those patients with thalassemia carriers; both groups had low vitamin D levels.

Merchant et al. (23) and Shamshirsaz et al. (24) have shown that, in thalassemia, the lumbar spine is more severely affected than other BMD assessment sites. Ineffective erythropoiesis in patients with TDT leads to an expansion of the bone marrow cavity, resulting in reduced cortical and trabecular bone tissue; the lumbar spine is thought to be more severely affected because it is primarily composed of trabecular bone and has increased bone marrow activity (25). In line with this result and based on the prevalence of low BMD in the lumbar spine and femoral neck found in this study, we may conclude that the lumbar spine is more frequently and severely affected than the femoral neck.

Several studies have found no association between serum ferritin and osteoporosis in patients with thalassemia (26, 27). Ferritin is reported to be one of the earliest markers for changes in iron stores, but it is also an acute phase reactant. It may therefore be suggested that the true measures of iron stores and adequate chelation may be transferrin receptors rather than ferritin.

25-OH vitamin D deficiency is quite common in patients with thalassemia. Singh et al. (28) reported a vitamin D deficiency of 80% in patients with thalassemia and found a positive correlation between vitamin D levels and BMD Z-scores for the lumbar spine. Vitamin D was also found to be low in the patients included in the present study. Patients with thalassemia should be checked for vitamin D and considered for vitamin D replacement.

Bone and joint pain is common in patients with thalassemia. Onur et al. found that 60% of pediatric patients with thalassemia had musculoskeletal diseases and the most common complaints were arthralgia and back pain (29). Although the exact mechanism of arthralgia is not yet known, it is thought to be caused by microfractures and cortical osteopenia due to bone marrow expansion and iron overload resulting in synovial iron deposition (30). This study, however, found no significant difference between the groups in the distribution of myalgia, arthralgia, and arthritis.

Another problem is iron chelation-induced arthropathy, attributed by patients to the drug. Complaints were reported to be mild to moderate in severity and the incidence of arthropathy was reported to be associated with the level of iron storage (30). Low hematocrit, calcium, BMD, high ferritin, and alkaline phosphatase levels have been associated with scoliosis (31). The present study detected no arthritis in patients receiving iron chelation therapy.

Another common musculoskeletal condition affecting tubular bones is premature epiphyseal fusion, particularly in patients who start blood transfusions at an advanced age. This finding was first reported in 1964 by Currarino and Elrandson on radiographs of thalassemia patients (32). Other common sites of premature fusion include the distal femur, tibia, fibula, and proximal femur (33). Unilateral or bilateral epiphyseal fusion leads to growth retardation and subsequent short stature, short limbs, and limb-length discrepancy. It also results in skeletal deformity secondary to irregular fusion of the growth plates and subsequent epiphyseal angulation and deviation. The most common deformity is the varus deformity of the humerus (34).

Thalassemia mainly affects the knees, but can also involve other joints such as the ankles, wrists, elbows, and shoulders (35). The present study found that knee effusion was statistically significantly more common in patients with TDT compared to patients with thalassemia carriers. Drakonak et al. found abnormalities in 21/40 (52.5%) knees of patients with thalassemia and supra- or parapatellar synovial folds (8/40, 20%) and small amounts of suprapatellar effusions (21/40, 52.5%)(36).

Early-onset osteoarthritis can occur in patients with TDT and is attributed to several factors including bone marrow expansion, iron deposition, iron chelation therapy, hypermetabolic state and endocrine disorders (i.e., hypoparathyroidism). Nowadays, early-onset osteoarthrosis is no longer common in patients with thalassemia, thanks to early treatment with novel effective iron-chelating agents (37). This study found that SH of the wrist in patients with TDT (54.2%) was statistically significantly more common compared to patients with thalassemia carriers. Moderate and severe SH of the wrist was significantly more common in patients with TDT compared to patients with thalassemia carriers ($p < 0.001$). PD signals on wrist ultrasound scans were seen in 17 (35.4%) of patients with TDT, a rate statistically significantly higher than that of patients with thalassemia carriers ($p = 0.029$). In this study, effusion in the wrist joint was seen in 8 (16.7%) patients with TDT, a rate statistically significantly higher compared to patients with thalassemia carriers ($p = 0.022$).

CONCLUSION

In conclusion, although the radiological features of thalassemia help establish a correct diagnosis, additional clinical and laboratory data are required for a definitive diagnosis. Knowledge of the musculoskeletal manifestations of thalassemia is crucial for clinicians to guide treatment and initiate supportive strategies to address these specific manifestations. The underlying cause of these abnormalities is bone marrow hyperplasia. Physicians' familiarity with the radiological features of beta thalassemia is crucial in the diagnosis and timely management of thalassemia and its complications.

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Ethical approval: All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and/or with the Helsinki Declaration of 1964 and later versions. Informed consent or substitute for it was obtained from all patients for being included in the study. Written consent was obtained from each patient to use their hospital data.

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