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Research Article

Bone Mineral Density and Endocrinopathies in Adults with Transfusion-Dependent Beta-Thalassemia Major Patients from Oman

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Abstract:

Objective: The study aims to assess the endocrine and metabolic complications in a cohort of regularly transfused and chelated beta thalassemia major patients. **Methods**: This is a retrospective cross-sectional study in adults aged ≥13years, with beta thalassemia major who were treated at a tertiary center between January 2013 to December 2022 with regular blood transfusion and chelation therapy. Iron overload was monitored by serial serum ferritin (SF) along with cardiac and liver T2* studies by MRI. Patients also underwent a comprehensive endocrine and metabolic bone disease evaluation, including screening for delayed puberty, hypogonadism, altered glucose metabolism with diabetes mellitus, hypothyroidism, hypoparathyroidism and adrenal insufficiency. Bone mineral density was evaluated by dual energy X-ray absorptiometry (DEXA) scanning along with serial serum calcium, alkaline phosphatase and 25(OH) Vitamin D studies. **Results**: Out of 91 patients (41 males) who are transfusion-dependent, the median (IQR) age was 33 (9) years. Hypogonadism was the commonest endocrine deficiency seen in 47 (51.6%), followed by abnormal glucose metabolism in 43 (47.3%), low bone mineral density in 34 (37.4%), delayed puberty in 31 (34.1%), hypothyroidism in 17 (18.7%), and hypoparathyroidism in 9 (9.9%) patients. Diabetes mellitus was seen in 17 (18.7%) patients with IDDM in 10(10.9%). Although, 25 (27.5%) patients had no endocrinopathy, 66 (72.5%) had at least one endocrinopathy. **Conclusion**: Tissue iron overload is an inevitable eventuality due to the current standard of care of beta thalassemia major patients. Hence, early screening and robust monitoring are essential to prevent complications of iron overload leading to endocrinopathies.

Keywords: BMD, endocrinopathies, delayed puberty, hypoparathyroid, hypothyroid, diabetes mellitus

Introduction

Beta Thalassemia major is a group of hereditary blood disorders caused by defective b-globin synthesis leading to an imbalance between a-and b-globin chains [1]. This imbalance causes ineffective red blood cell production, hemolysis and increased red blood cell turnover in the bone marrow. The manifestations of this ineffective erythropoiesis will vary, depending upon the severity of an array of genotypic variations, and ranges from clinically asymptomatic to a severely anemic phenotype who are transfusion dependent [2].

The management of this anemia necessitates regular blood transfusions and chelation to offset the inevitable iron overload, which is also potentiated by an increased intestinal iron absorption [3]. Further, although regular blood transfusions and iron chelation have greatly increased the life expectancy of transfusion-dependent beta thalassemia major (TDTM) patients, osteoporosis and osteopenia remain a serious complications, even in optimally transfused and chelated patients [4]. Chronic endocrinopathies and

metabolic bone disease are thus the major health issues in these groups of patients [5]. Multiple endocrine dysfunctions including delayed puberty with growth failure, hypogonadism, diabetes, hypothyroidism, hypoparathyroidism and, less frequently, adrenal insufficiency [6]. Numerous factors contribute to the genesis of bone disease in TDTM including bone marrow expansion [7], hypogonadism [8], defective growth hormone-insulin-like growth factor-1 (GH-IGF-1) axis [9], altered pattern of cytokines [10], and iron deposition in bone [6,11].

According to the World Health Organization (WHO), diagnosis of osteoporosis is based on the T- or Z score for bone mineral density (BMD), assessed at the lumbar spine or the femoral neck. Osteoporosis is defined by a BMD that is 2.5 standard deviation (SD) below the mean value for a young adult female (T-score less than or equal to -2.5 SD) [12]. While the T score compares an individual's BMD to that of a healthy young adult of the same gender, the Z score compares the individual's BMD to that of other people of the same age, gender, and body size. Similarly, osteopenia is described and Z-score 1.5 SD below the mean value.

In this study, endocrine dysfunction namely delayed puberty with hypogonadism, impaired glucose tolerance with diabetes mellitus, hypothyroid, and hypo-parathyroid along with low BMDs in adults with TDTM are reported. Changes in BMDs due to administration of calcium/vitamin D along with bisphosphonate therapy during follow-up are also reported. Lastly, improvements in iron overload over the study period in spite of several endocrinopathies is also reported.

Materials & Methods

This study was conducted in the Department of Hematology, Sultan Qaboos University Hospital, Oman, by enrolling the current cohort of adult patients with TDTM. Ninety-one patients, who are alive today from amongst the total number of TDTM patients (n=145), aged more than thirteen years, and who were on regular follow ups with blood transfusions and chelation, were included in the study. During their day care visits for blood transfusion, these patients underwent evaluation for underlying endocrine and metabolic bone disease in addition to the routine full blood counts, serum ferritin levels (SF) and blood chemistry studies. The height, weight, and body mass index (BMI) of all participants were measured by standard techniques and were interpreted against WHO standards [13]. All patients underwent screening for underlying delayed puberty with hypogonadism, altered glucose metabolism and diabetes mellitus, hypothyroidism, hypoparathyroidism and adrenal insufficiency on a six-monthly basis. Apart from hormonal evaluations, they also underwent screening for metabolic bone disease with serum 25(OH) vitamin D and dual energy X-ray absorptiometry (DEXA) scan of lumbar spine on a yearly basis. Additionally, serial serum calcium, alkaline phosphatase and liver transaminases as well as renal function studies were performed every three months while serum ferritin levels were done every month. Further, iron overload was also assessed by in house 1.5 and 3 Tesla MRI machine (Siemens LTD, MAGNETOM Aera and MAGNETOM Vida respectively) and the cardiac and liver T2* values were calculated using the licensed CMR tools software [14].

Females with breast stage 1 after 13 years of age, or males with testicular volume <4 mL after 14 years of age were diagnosed to have delayed puberty, whereas, short stature was defined as height less than 2 standard deviations [5]. Failure to progress to the next Tanner stage in 6 months was labelled as arrested puberty. Patients without any sign of puberty beyond 16 years were diagnosed to have hypogonadism and evaluated with specific hormonal studies [5]. Diagnoses of impaired glucose tolerance, impaired fasting glucose with elevated fructosamine test for glycated albumin was used to diagnose diabetes mellitus, while the diagnosis of hypothyroidism, hypoparathyroidism, and vitamin D deficiency were made as per standard guidelines using the serum hormonal levels and other diagnostic tests [15-17]. Hormonal assays were performed on Cobas E 601 fully automated analyzer using electrochemiluminescence (ECL) technology for immunoassay analysis including Cortisol, Estradiol, FSH, LH, PTH, hCG, Prolactin, Testosterone, T3, T4, & TSH levels. Liver function tests, Renal function test, Serum electrolytes, S. calcium, phosphorous, alkaline phosphatase were tested by spectrophotometric methods using the fully automated clinical chemistry analyzer (COBAS C 501 analyzer) and plasma glucose was measured by the hexokinase method. DEXA scan of the lumbar spine was done in the these patients, using the Hologic Horizon W machine, and BMD was interpreted as per International Society for Clinical Densitometry (ISCD 2019) criteria, after adjusting for height [18].

Statistical Analysis:

Clinical and laboratory parameters were compared and quantitative data were expressed as mean ± standard deviation and range. The students T test was used but the Wilcoxon–Mann-Whitney test was used when data was not normally distributed and expressed as median with interquartile range. Spearman's rank of correlation coefficient (rS) was used to study the correlations of the various SF levels in different categories of endocrinopathies. A correlation was considered poor if rS was <0.4, moderate if rS was between 0.4-0.6, good or substantial if rS was between 0.6-0.8 and excellent if rS was > 0.8. Multiple means were compared using the ANOVA test and a p value <0.05 was considered as statistically significant. All data recording, statistical analysis and results extraction were achieved using program of Statistical Package for the Social Sciences (IBM SPSS, USA, version 23).

Results

The baseline demographic characteristics of the TDTM patients (n=91) are described in Table I. Although the median BMI was 23.8 kg/m^2, 3 (3.3%) and 8 (8.8%) patients were severely underweight and underweight respectively, whereas, 13 (14.2%) patients were obese. Data of metabolic bone disorder and endocrinopathies are shown in Table II and Table III respectively. Seventeen patients (18.7%) had at least one endocrinopathy, whereas 49 (53.8%) had two or multiple endocrine deficiencies, but twenty-five patients (27.5%) did not have any endocrinopathy.

Age, at study entry (years), median (IQR)		33 (28-37)
Males, n (%)		41 (45)
Females, n (%)		50 (55)
Height in cm, median (IQR)		158(152-165)
Weight in kg, median (IQR)		60(50-70)
BMI, median (IQR)		23.8(20.8-26.9)
BMI Status, kg/m2		
Severely Underweight	<16.5, n (%)	3(3.3)
Underweight	<18.5, n (%)	8(8.8)
Normal	18.5 – 24.9, n (%)	45(49.5)
Overweight	25-29.9, n (%)	24(24.2)
Obese	>30, n (%)	13(14.2)
Pre-transfusion hemoglobin, (g/dL) median (IQR)		9.5 (9.2-9.8)
Transfusion index (mL/kg/y), median (IQR)		201 (169-226)
Deferasirox treatment, n (%)		44(48)
Deferasirox dose (mg/kg/d), median (IQR)		24.7(18.2-27.7)
Deferiprone treatment, n (%)		31(34)
Deferiprone dose (mg/kg/d), median (IQR)		95.7(72.6-101.3)
Deferiprone + Deferasirox treatment, n (%)		16(18)
S. Ferritin (ng/mL) levels	One way	ANOVA
At First Visit, median (IQR), n=91	1500 (533-3161)	
At start of chelation, median (IQR), n=91	2077 (1253-4502)	p=0.009*
Highest during chelation, median (IQR), n=91	4922 (3361-7472)	p<0.001*
At last visit median (IQR), n=91	1881 (820-3789)	p=0.06*
At abnormal OGTT, median (IQR) n=43	2511(1739-4138)	p=0.08**
At diagnosis NIDDM, median (IQR) n=7	2566 (1354-5957)	p=0.09**
At diagnosis IDDM, median (IQR) n=10	3990 (2331-6176)	p<0.001**
At diagnosis Hypogonadism, median (IQR) n=47	2687(1876-4284)	p=0.01**
At diagnosis Hypothyroidism, median (IQR) n=17	2473(1634-4206)	p=0.06**
At diagnosis Hypoparathyroidism, median (IQR) n=9	3691(1504-4121)	p=0.002**
S. Ferritin >2000 ng/ml, n (%), n=91		44 (48)
Splenectomy, n (%)		31 (34)
Outcome, Overall Treated Cohort, n=145		
Alive, n (%)		91(62.8)

Post-BMT alive, n (%)		42(28.9)
Total Dead, n (%)		54(37.2)
Post-BMT-dead, n (%)		12(8.3)
Dead without BMT, n (%)		42(28.9)
Key: * One way ANOVA compared to first visit S. Ferritin levels; ** One way ANOVA compared to Ferritin levels at start of chelation		

Table 1: Demographic characteristics, in Adults with Transfusion-dependent Thalassaemia cohort (n=91).

Metabolic bone disease, n=34		
Bone mineral density (BMD)		
Normal, n (%)	57(62.6)	
Osteopenia, (Z score <-1.5)		
Initial, n (%)	8 (23.5)	
Last, n (%)	24 (70.5)	
Osteoporosis, (Z score <-2.5)		
Initial, n (%)	26 (76.5)	
Last, n (%)	10 (29.4)	
DEXA Scan, L1-4, Z score,	Initial, n=34	Last, n=34
Median (IQR)	-2.8 (-3.5 to -2.5)	-2.2 (-2.5 to -1.9)
Wilcoxon–Mann-Whitney test, Initial V/s Last, p value	<0.001*	
Alkaline Phosphatase, U/L [RR : 40-129]	Initial, n=34	Last, n=34
Mean (Range)	186(84-1229)	62(40-86)
Students paired T test,Initial V/s Last, p value	<0.001**	
Serum Calcium, mmol/L [RR : 2.15 – 2.55]	Initial, n=34	Last, n=34
Mean (Range)	2.11(1.59-2.23)	2.18(2.09-2.4)
Students paired T Test,Initial V/s Last, p value	0.001**	
Vitamin D Levels, nmol/L,	Initial, n=34	Last, n=34
Deficient: < 50, n (%)	24 (70.5)	1 (3)
Insufficient: 50 - < 75, n (%)	8 (23.5)	8 (23.5)
Sufficient: 75 - 250, n (%)	2 (6)	25 (73.5)
Vitamin D levels, mmol/L,	Initial, n=34	Last, n=34
median (Range)	38(12-92)	88(46-134)
Students paired T test,Initial v/s last, p value	<0.0001**	
Key: *Wilcoxon–Mann-Whitney test, **Students Paired T test		

Table 2: Metabolic Bone Disease in Adults with Transfusion-Dependent Thalassemia (n=91).

Endocrinopathies	
Hypothyroidism, n=17,	
Age, year, median (IQR)	36(34-41.5)
Male, n (%)	4(23.5)
Female, n (%)	13(76.5)

S. Ferritin (ng/ml) at diagnosis, median (IQR)	2473(1634-4206)
Associated Endocrinopathies	
Hypogonadism, n (%)	14(82)
Low Bone Mineral Density (BMD), n (%)	11(65)
Delayed Puberty, n (%)	8(47)
Diabetes Mellitus, n (%)	8(47)
Hypoparathyroidism, n (%)	4(24)
Abnormal glucose metabolism, n=43	
Impaired glucose tolerance, n (%)	43(47.3)
Diabetes mellitus, n (%)	17(18.7)
NIDDM, n (%)	7(7.7)
IDDM, n (%)	10(10.9)
S. Ferritin (ng/ml) at diagnosis NIDDM, median (IQR)	2566 (1354-5957)
S. Ferritin (ng/ml) at diagnosis IDDM, median (IQR)	3990 (2331-6176)
Hypogonadism, n (%)	47(51.6)
Associated Endocrinopathies	
Delayed Puberty, n (%)	31(66)
Low Bone Mineral Density (BMD), n (%)	23(49)
Diabetes Mellitus, n (%)	15(32)
Hypothyroidism, n (%)	14(30)
Hypoparathyroidism, n (%)	9(19)
S. Ferritin (ng/ml) at diagnosis Hypogonadism, median (IQR)	2687(1876-4284)
Hypoparathyroidism, n (%)	9(9.9)
Associated Endocrinopathies	
Hypogonadism, n (%)	9(100)
Delayed Puberty, n (%)	6(66)
Low Bone Mineral Density (BMD), n (%)	6(66)
Diabetes Mellitus, n (%)	4(44)
Hypothyroidism, n (%)	4(44)
S. Ferritin (mg/ml) at diagnosis Hypoparathyroidism, median (IQR)	3691(1504-4121)
At least one endocrinopathy, n (%)	68(74.7)
No endocrinopathy, n (%)	23(25.3)
Single Endocrinopathy, n (%)	17(18.6)
Two Endocrinopathies, n (%)	16(17.6)
Three Endocrinopathies, n (%)	11(12.1)
Four Endocrinopathies, n (%)	14(15.4)
Five Endocrinopathies, n (%)	7(5.5)
Six Endocrinopathies, n (%)	1(1.1)

Table 3: Endocrinopathies in Adults with Transfusion-Dependent Thalassemia (n=91)

Although bone mineral density was normal in the majority of patients (62.6%), osteopenia increased from 8 (23.5%) to 26 (76.5) patients, whereas osteoporosis reduced from 24 (70.5%) to 10 (29.5%) patients over the study period on bisphosphonate and regular iron chelation. This difference was statistically significant (Wilcoxon-Mann-Whitney test, $p<0.001$). Six patients (17.6%) had documented non pathological fractures. Moreover, S. Alkaline Phosphatase and S. Calcium levels also showed a statistically significant improvement in terms of the initial versus the last results in this subset with a p value of <0.001 and p=0.001(paired student's t test) respectively. However, both these parameters showed a negative correlation with Z-scores from the DEXA scans (Figure 1a & 1b) indicating that treatment with oral calcium and 25OH Vitamin D was showing the desired improvement in the BMD parameters in terms of improvement in the Z-scores. Further, z-scores were also negatively correlated with SF levels (Figure 1c).

Figure 1: Correlation between S. Calcium, S. Alkaline Phosphatase and S. Ferritin with Z-score for Lumber L1-L4 in Patients with Osteoporosis

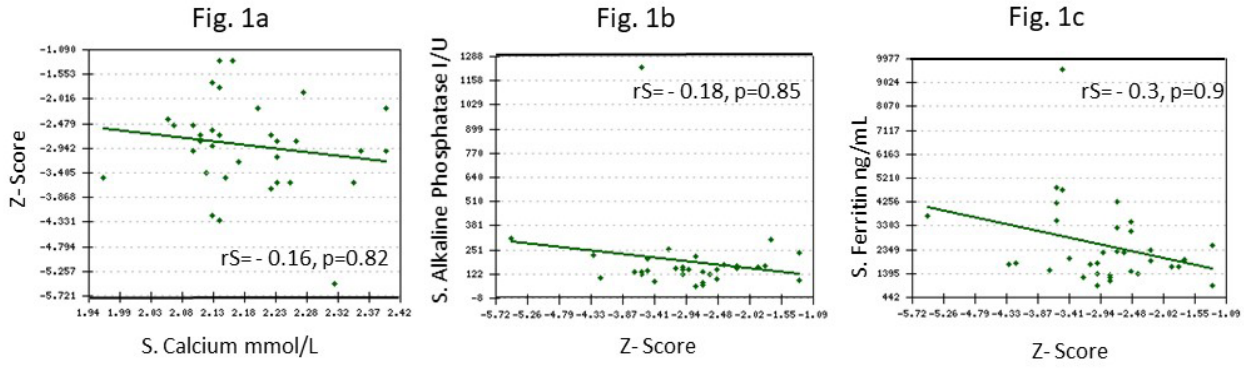

Figure 1a: Correlation between S. Calcium and Z-score for Lumbar L1-L4 BMD. **Figure1b**: Correlation between S. Alkaline Phosphatase and Z-Score for Lumbar L1-L4 BMD. **Figure 1c**: Correlation between S. Ferritin and Z-score for Lumber L1-L4 BMD

Similarly, 25OH Vitamin D levels was deficient, insufficient and sufficient, respectively in 24 (70.5%), 8 (23.5%) and 2 (6%) initially, which improved to 1 (3%), 8 (23.5%) and 23 (73.5%) respectively on regular 25OH vitamin D supplementation. Further, this change with improved 25OH Vitamin D levels over the study period was also statistically significant (paired students T test, $p<0.001$).

Hypogonadism was the commonest endocrinopathy in 47 (51.6%), followed by impaired glucose metabolism in 43 (47.3%), with IDDM in 10 (10.9%) and NIDDM in 7 (7.7%), delayed puberty in 31 (34.1%), impaired thyroid function in 17 (18.7%), and hypoparathyroidism in 9 (9.9%) patient. We did not find any case of overt adrenal insufficiency, although one patient showed subnormal cortisol levels, but the results of the ACTH stimulation test (Synacthen) were normal with no necessity of hormone replacement therapy. Although multiple endocrinopathies were seen in more than half of these patients, respectively, two, three, four, five and six endocrinopathies were seen in 16(17.6%), 11(12.1%), 14(15.4%), 7(5.5%), and 1(1.1%) patients with Table III giving the details of the associated endocrinopathies within the intra-individual categories of endocrinopathies.

Discussion

Major findings of our study was the significant prevalence of low BMD, with the early onset and high prevalence of multiple endocrine deficiencies. All this occurred in spite of regular blood transfusions along with iron chelation, including the state of art monitoring with MRI techniques, along with regular endocrine function evaluation by hormonal studies as well as BMD screening with DEXA scans.

In an overburdened system like our country, meeting the ideal transfusion and serum ferritin targets may be difficult, thus anemia and poor compliance to chelation, with resulting morbidity, including low BMD and several/multiple endocrinopathies in our patient cohort is likely to be common, especially considering the life-long treatment in absence to a recourse like bone marrow transplantation in these unfortunate patients. The median pretransfusion hemoglobin in our cohort was 9.5 with an IQR between 9.2 to 9.8g/dL and is well within the recommended range by the Thalassaemia international federation guidelines with the median transfusion index of 201

mL/kg/year [19]. The role of splenectomy is also important in the management of TDTM patients and 31(34%) patients underwent the procedure in this cohort and this was helpful in maintaining a narrow range of transfusion Index between the IQR range of 169 to 226 mL/kg/year.

Regular blood transfusion regimen is the cornerstone of TDTM patients' world over, but this results in a significant iron overload. Excessive iron is deposited in almost all tissues but primarily in the liver, the heart and the endocrine glands. The iron overload scenario amongst our patient population was catastrophic as can be seen from the significantly high SF levels in spite of the use of optimal therapeutic measures as well as monitoring as per standard international guidelines [19]. Almost half of this cohort (48%) are receiving Deferasirox (DFX) in the recommended range with median of 24.7 mg/kg/day. 34% of this patient cohort is on Deferiprone (DFP) treatment with a median treatment dose of 95.7mg/kg/day and almost one fifth (18%) of the patient are on double agent treatment with DFX and DFP. Yet, if we analyze the SF levels at the start of treatment and onset of endocrinopathies, there are statistically significant differences (Table 1).

The average median SF, ng/mL at the start of chelation therapy increased from 1500 at base line (first visit) to 2077 at the start of chelation therapy ($p = 0.009$, ANOVA); to the highest SF on chelation therapy of 4922 ($p<0.001$, ANOVA). The genesis of several endocrinopathies due to the underlying iron overload can thus be understood on this basis. Further, with diligent efforts and robust counseling, we have been able to get the average median SF levels to lower levels at 1881 ($p=0.06$, ANOVA) on the last visit data. However, although the average SF levels increased from the basal levels of 2077 to 2473, 2511, 2566 in the subset of patients with manifested with hypothyroidism, abnormal OGTT, and NIDDM it was not statistically significant with the respective p values being 0.06, 0.08,and 0.09 (ANOVA). But the rise of average SF levels was statistically significant in the subset of patients with hypogonadism, IDDM and hypoparathyroidism, with the relative SF levels being 2687, 3990 and 3691 with the corresponding p values being 0.01, <0.001 and <0.001(ANOVA) respectively. This analysis demonstrates the thin line of demarcation between the two groups above where it becomes difficult to assess the cut off levels of SF that is associated organ damage leading to Endocrinopathies [20, 21]. Nevertheless, the takeaway message here is that the treating physician needs to control SF levels at all costs. This is also further highlighted by the fact that in this cohort, SF levels above 2000 were seen in almost half of the patients. So it is again the important to emphasize the point that one needs to keep a watchful eye to not only maintain the SF levels under 2000ng/mL to avoid these unfortunate sequelae and preventable complications, but also to initiate hormone replacement as soon as possible to mitigate and control the likelihood of damage to the endocrine glands.

Metabolic bone disease in TDTM mostly affects vertebral bodies leading to vertebra fractures [22]. The diagnosis of osteoporosis in adults should not be made on the basis of densitometric criteria alone, as in the absence of vertebral compression fractures, the diagnosis of osteoporosis is indicated by the presence of both a clinically significant fracture history and BMD Z-score less than or equal to -2.0 SD [12]. However, vertebral fractures are mostly asymptomatic, making active screening the only way for early recognition and treatment [23]. The prevalence of fractures in this cohort was 17.6% although literature review has reported prevalence rates ranging between 16 to 49% in studies mostly from adults [23-24]. Further, as per ISCD guidelines, vertebral fractures alone are sufficient to diagnose osteoporosis, in the absence of trauma or local pathology [18]. Incidentally, where BMD is feasible, it will add to the overall assessment of bone health, but should be interpreted after correcting for height as per international recommendations [18].

In spite of following a regular transfusional regimen coupled with optimally recommended chelation, and receiving adequate sex hormone replacement, TDTM patients show imbalanced bone turnover. This is believed to be due to an increased resorptive phase that is not followed by an appropriate neoformation rate, resulting in a decreased BMD, particularly at the vertebral level, where trabecular bone is mostly represented [24-26]. It is also believed that numerous acquired factors are responsible for the inhibition of osteoblastic activity, such as a defective GH-IGF-1 axis, iron deposits in bone, or DFP toxicity [24, 27, 28]. The mechanism responsible for this osteoclast activation in well-treated thalassemic patients could be related to the altered cytokines network, namely the receptor activator of nuclear factor kappa-ß (RANK)/RANK ligand (RANKL)/osteoprotegerin (OPG) system that regulates the activation and proliferation of osteoclast precursors [28]. Osteoblasts and osteoclasts are responsible for bone remodeling at the cellular level and in adult thalassemic patients, RANK/RANKL-OPG system disorder increases in favor of osteoclasts [29]. It is suggested that the production of OPG primarily by human osteoblasts, antagonizes the osteoclast genetic activity of receptor activator of NFkB ligand ultimately increasing the BMD [30]. Moreover, bisphosphonates also increase the BMD by diminishing the markers of osteoclast function including tartrate-resistant acid phosphatase isoform 5b, N-telopeptide of collagen type I, OPG, and RANKL in thalassemia major-induced osteoporosis and postmenopausal women [31]. In our cohort we observed that there was a good correlation between the fall of BMD and corresponding fall in the alkaline phosphatase levels, along with an inverse correlation between the simultaneous corresponding increase in S. Calcium, and 25OH vitamin D levels.

TDTM patients often present with multiple endocrine dysfunctions including growth failure, hypogonadism, diabetes, hypothyroidism, hypoparathyroidism and, less frequently, hypoadrenalism [20,21]. Furthermore, significant differences have also been demonstrated in the mean SF levels between TDTM patients affected by primary amenorrhea and hypogonadism and TM patients without Endocrinopathies [21]. These abnormalities are closely related to iron overload, as shown by histology in different endocrine glands [32]. In our cohort, the prevalence of hypogonadism, osteoporosis, delayed puberty, diabetes mellitus, hypothyroidism and hypoparathyroidism were respectively 51.6%, 37.3%, 34%, 18.6%, 18.6% and 9.8% and are in keeping with other reported literature [20, 21]. Insulin dependent diabetes was seen in 10.9% patients and in none of these patients (and those with NIDDM also) have we seen reversal their abnormal glucose metabolism in spite of sustained efforts to treat iron overload as evident by a sustained fall in the average median SF from 3990ng/mL to 2094ng/mL in that cohort of 10 patients. This apparently is indicative of a more or less permanent loss of beta islet cells of the pancreas that produce insulin.

Vitamin D deficiency, hypogonadism, and hypothyroidism are all known to have significant deleterious effects on bone health [33,34]. They all can be easily and conveniently identified and corrected without much expense. Moreover, it needs to be emphasized that treatment of TDTM patients should also involve regular clinical screening for growth and endocrine dysfunction at the time of blood transfusions in addition to the regular monitoring of iron overload and blood chemistry. Regular supplementation of vitamin D and timely gonadal hormone replacement would also help improve and optimize bone mineral accumulation. Lastly an individually tailored treatment plan based on the patient's clinical disease profile, should be recommended to the TDTM patients with osteoporosis and bisphosphonates are effective in restoring the abnormal BMD along with the addition of calcium/vitamin D administration. Finally, patient education regarding the importance of compliance with chelation therapy is the most important factor that has a major significant role in decreasing several iron overload-related endocrine and metabolic complications. In conclusion, the study provides conclusive evidence of the impact of SF on BMD and endocrine gland dysfunction in TDTM patients.

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The authors report no conflicts of interest. The authors alone are responsible for the content and writing of this article.

Conflict of Interest:

The authors declare no conflict of Interest

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