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The Circulating Levels of Osteoprotegerin and RANKL in Transfusion-dependent Beta-thalassemia Patients

Transfüzyona Bağımlı Beta Talasemi Hastalarında Dolaşımdaki Osteoprotegerin ve RANKL Düzeyleri

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Abstract

Objective: β-thalassemia is a lifelong blood disorder with anemia and systemic effects. One of the complications commonly encountered in β-thalassemia, particularly with advancing age, includes weakened bones. The roles of osteoprotegerin (OPG) and receptor activator for nuclear factor B ligand (RANKL) in age-related osteoporosis, as well as β-thalassemia-related bone disease, have been studied. This study aimed to compare the levels of OPG and RANKL in transfusion-dependent β-thalassemia (TDT) patients with healthy controls (HCs).

Materials and Methods: This study comprised 120 TDT and 60 HCs, whose blood counts and biochemical profiles were assessed, followed by ELISA for OPG and RANKL according to the manufacturer's guidelines. Data were analysed using the Mann-Whitney U test and Spearman's correlation, with a p-value of ≤0.05 considered statistically significant.

Results: The median age was slightly higher in HCs, with overall more male representation. Blood counts were comparable in both groups, except slightly higher WBC count. High serum ferritin, suggestive of iron overload, was noted in TDT. Findings suggest a reduced OPG and RANKL level in TDT patients compared to HCs. OPG was reduced in both male and female TDT patients, while RANKL was reduced in male TDT patients only. A very weak to no correlation of OPG or RANKL was determined with age and serum ferritin.

Conclusion: Our results show reduced OPG and RANKL levels in TDT patients, particularly in males, with a very weak correlation with age and serum ferritin. However, further studies to explore their role in bone metabolism and association with bone density are needed.

Keywords: Beta-thalassemia, transfusion dependent β-thalassemia, TDT, OPG, RANKL, bone disease

Öz

Amaç: β-talasemi, anemi ve sistemik etkilerle seyreden, yaşam boyu devam eden bir kan hastalığıdır. Özellikle yaş ilerledikçe, β-talasemide sık karşılaşılan komplikasyonlardan biri kemik zayıflığıdır. Osteoprotegerin (OPG) ve RANKL'nin yaşa bağlı osteoporozdaki ve β-talasemiye bağlı kemik hastalığındaki rolleri daha önce incelenmiştir. Bu çalışma, transfüzyona bağımlı β-talasemi (TDT) hastaları ile sağlıklı kontrollerde (SK) OPG ve nükleer faktör B ligandı için reseptör aktivatörü (RANKL) düzeylerini karşılaştırmayı amaçlamıştır.

Gereç ve Yöntem: Bu çalışmaya kan sayımları ve biyokimyasal profilleri değerlendirilen, ardından üretici talimatlarına göre OPG ve RANKL için ELISA yapılan 120 TDT hastası ve 60 SK dahil edilmiştir. Veriler Mann-Whitney U testi ve Spearman korelasyonu ile analiz edilmiş; p≤0,05 istatistiksel olarak anlamlı kabul edilmiştir.

Bulgular: Sağlıklı kontrollerin medyan yaşı biraz daha yüksek olup, genel olarak erkek oranı daha fazlaydı. Her iki grubun kan sayımları karşılaştırılabilir düzeydeydi, ancak beyaz kan hücresi sayısı SK'da biraz daha yüksekti. TDT grubunda demir yüklenmesini düşündüren yüksek

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serum ferritin düzeyleri saptandı. Bulgular, TDT hastalarında SK'lara kıyasla OPG ve RANKL düzeylerinin azaldığını göstermektedir. OPG düzeyi hem erkek hem kadın TDT hastalarında düşükken, RANKL düzeyi yalnızca erkek TDT hastalarında düşüktü. OPG ve RANKL'nin yaş ve serum ferritin ile çok zayıf ya da hiç korelasyon göstermediği belirlendi.

Sonuç: Sonuçlarımız, TDT hastalarında özellikle erkeklerde OPG ve RANKL düzeylerinin azaldığını ve bu parametrelerin yaş ile serum ferritinle çok zayıf bir ilişki gösterdiğini ortaya koymaktadır. Bununla birlikte, bu moleküllerin kemik metabolizmasındaki rollerini ve kemik yoğunluğu ile ilişkilerini araştırmak için ileri çalışmalara ihtiyaç vardır.

Anahtar kelimeler: Beta-talasemi, transfüzyona bağımlı β-talasemi, TDT, OPG, RANKL, kemik hastalığı

Introduction

Beta-thalassemia (β-thalassemia) is an inherited blood disorder due to defective β-globin chains resulting in anemia and systemic effects (1). β-thalassemia is clinically classified into transfusion dependent (TDT) and non-transfusion dependent β-thalassemia (NTDT) based mainly on the transfusion frequency. Systemic complications include organomegaly, endocrine problems and skeletal changes (2,3). β-thalassemia is the most common hemoglobinopathy worldwide and in Pakistan, though the exact prevalence remains unknown, ~5000 births per annum are reported (4).

Patients are treated with regular blood transfusions or drugs with potential to induce fetal hemoglobin (HbF) production to ameliorate the anemia and related complications (5). In the recent years, improved healthcare facilities have increased the lifespan of β-thalassemia patients, however, the long-term consequences remain a challenge (6-8). One of the major complications include bone disease which comprises of weakened bones, skeletal changes and increased risk of fractures (9-14). The pathogenesis of bone disease in β-thalassemia is complex with several risk factors which includes low calcium and vitamin D, endocrine problems, iron overload and the use of iron chelation therapy (15-18). Bone remodeling is a tightly regulated process with a balance between bone formation and resorption (19). Any dysregulation in this process results in bone diseases resulting in osteopenia and osteoporosis as debilitating illnesses. The pathway involving osteoprotegerin (OPG) and receptor activator for nuclear factor B ligand (RANKL) has been associated with bone disease (20,21). The OPG/RANKL ratio has been found to be a key regulator of bone mass and bone homeostasis (20,22). Similar to other conditions associated with bone disease, the role of OPG/RANKL ratio has also been studied in β-thalassemia (23-25). Dysregulated OPG/RANKL with increased osteoclastic activity results in bone weakening and increases the risk of bone related complications. The objective of this study was to determine the circulating levels of OPG and RANKL in TDT β-thalassemia patients. The findings of this study would be beneficial in understanding the role of OPG and RANKL in TDT who are at risk of bone related complications.

Materials and Methods

Study Participants

This study included 120 TDT patients and 60 healthy controls (HCs) of age ≥1 years regardless of gender and ethnicity, after informed consent from participants or their parents/guardians. NTDT and hemoglobinopathies other than β-thalassemia were excluded. This study was conducted at the Thalassemia Center Al-Khidmat Hospital, Peshawar and Blood Diseases Clinic, Peshawar Institute of Medical Sciences, Peshawar after ethical approval from the Institutional Ethical Committee of Institute of Pathology and Diagnostic Medicine, Khyber Medical University, Peshawar, Pakistan (ref: # KMU/IPDM/IEC/2024/27; dated: 12.12.2024).

Laboratory Parameters

Serum samples were collected from TDT patients and HCs and stored at -80 °C freezer for later use. Sandwich ELISA was done for the estimation of OPG and RANKL levels as per the manufacturer protocols (IDEAL company). Serum ferritin levels were determined as per standard protocol. Were also determined as per standard protocol (Cobas® c311 analyser, Roche Diagnostics International Ltd, Switzerland). Complete blood counts were performed on each blood sample collected in EDTA tube using Automated Hematology Sysmex analyser XP-100.

Statistical Analysis

Data were statistically analysed using Graph Pad Prism (version 10.6.0). Categorical variables are represented as frequency and percentages while numerical variable as median and interquartile range or range. Data normality was determined by Shapiro-Wilk test and Mann-Whitney U test was applied for comparison between two groups. Spearman's correlation analysis was done to determine the association of age and serum ferritin with serum OPG and RANKL levels. A p-value of ≤0.05 was considered as statistically significant.

Results

Demographic and Clinical Characteristics

This study included TDT (n=120) and HCs (n=60) with median age of eight and ten years, respectively, with male preponderance. Splenomegaly was noted in 20% of TDT patients with 10.83% had splenectomy done prior to inclusion in this study. Serum ferritin was higher in TDT patients compared to HCs (median: 2636 vs. 56.50 ng/mL, p<0.0001). Hb and platelet count were lower in TDT patients while WBC count was comparable between TDT patients and HCs. Data are summarized in Table 1.

Serum OPG and RANKL Levels

In this study, the median serum OPG levels were lower in TDT patients compared to HCs (204.3 vs. 277.5; p<0.0001), shown in Figure 1a. Similarly, the median serum RANKL levels were also

Table 1. Demographic and clinical characteristics of study participants			
Characteristics	**TDT patients (n=120)**	**HCs (n=60)**	**p-value (Mann-Whitney U test)**
Age in years Median (range)	8.0 (2-19)	10.0 (4-17)	0.001
Gender Females, n (%) Males, n (%)	52 (43.33) 68 (56.67)	23 (38.34) 37 (61.66)	-
Spleen status Splenomegaly, n (%) Splenectomy, n (%)	24 (20.0) 13 (10.83)	N/A	-
Serum ferritin (ng/mL) Median (range)	2636 (41.4-10595)	56.50 (28-104)	<0.0001
Hb (g/dL) Median (range)	7.4 (2-10.6)	12.75 (10.2-15.6)	<0.0001
WBC count Median (range)	7.3 (1.5-123.5)	8.45 (4.1-11)	0.408
Platelet count Median (range)	258.5 (31-791)	310.0 (152-672)	0.020
TDT: Transfusion-dependent β-thalassemia, Hb: Hemoglobin, WBC: White blood cell, N/A: Not applicable			

lower in TDT patients as compared to HCs (319.0 vs. 392.3; p<0.0001), as in Figure 1b. In addition, the levels of OPG and RANKL were lower in TDT patients and HCs in both female and male participants except RANKL in females (Figure 1c-f). No to weak correlation was determined between OPG or RANKL and serum ferritin or age. Data shown in Table 2.

Discussion

β-thalassemia is a lifelong blood disorder with multiorgan involvement including weakened bones and risk of fractures (26,27). The pathogenesis of bone disease in β-thalassemia is complex with several proposed mechanisms, ranging from nutritional deficiencies to disrupted bone metabolism pathways. Transfusion frequency, chronic anemia, iron overload and the use of iron chelation have been associated with reduced bone density (18,28). Despite nutritional supplementation with calcium, zinc, phosphorus, vitamin D and use of drugs to strengthen bones such as bisphosphonates, the risk of bone related complications remain a challenge (29,30). In order to improve the bone health and minimise the risk of complications, it is critical to understand the pathogenesis of bone disease in β-thalassemia. The role of OPG and RANKL mediated impaired bone metabolism have been shown to play an important role in age-related and β-thalassemia related bone disease (21,24,25). Alterations in the OPG and RANKL have been associated with increased osteoclastic activity resulting in weakened bones (31). To determine the OPG and RANKL levels in TDT patients, this study was conducted comprising of 120 TDT patients and 60 HCs. The median age of TDT patients and HCs were eight and ten years, respectively and slightly more male representation. Anemia, iron overload, splenomegaly and history of splenectomy was present in TDT patients similar to previously published studies (32). Overall, the serum OPG and RANKL levels were

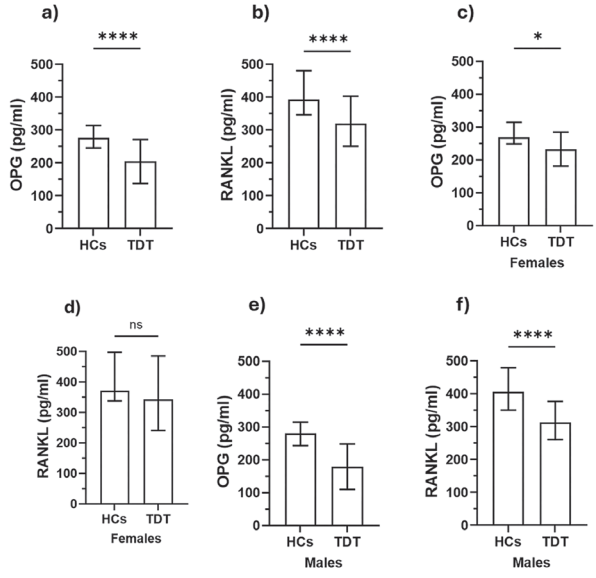

Figure 1. Serum OPG and RANKL levels in TDT patients and HCs. Serum OPG (a) and serum RANKL (b) levels were compared between TDT patients (n=120) and HCs (n=60) using Mann-Whitney U test. Serum OPG and RANKL were compared between female (c, d) and male (e, f) participants of each group using Mann-Whitney U test
*Data are represented as median with interquartile range using Box and Whisker plots and p-value denoted as ns: Non-significant, *: <0.05, ****: <0.0001, OPG: Osteoprotegerin, RANKL: Receptor activator for nuclear factor B ligand, TDT: Transfusion-dependent β-thalassemia, HCs: Healthy controls*

reduced in TDT patients compared to HCs in this study. Previous studies have shown reduced OPG in TDT patients, however, an increased level of RANKL (23,25,31). In contrast, increased levels of OPG and RANKL were determined in TDT patients in a study by Pietrapertosa et al. (33). Additionally, previous studies have

Table 2. Correlation analysis of age and serum ferritin with serum OPG and RANKL levels

Characteristics	TDT patients (n=120)		HCs (n=60)	
	OPG	RANKL	OPG	RANKL
Age in years				
Coefficient of correlation	0.173	0.153	-0.011	-0.052
p-value	0.058	0.093	0.933	0.693
Serum ferritin (ng/mL)				
Coefficient of correlation	0.012	-0.083	-0.109	-0.179
p-value	0.896	0.370	0.404	0.171

TDT: Transfusion-dependent β-thalassemia, OPG: Osteoprotegerin, RANKL: Receptor activator for nuclear factor B ligand, HCs: Healthy controls

not found any difference in the levels of OPG and RANKL in TDT and HCs based on the gender (31). However, our results show a significantly reduced OPG and RANKL levels in male TDT patients compared to male HCs ($p<0.0001$) while slightly reduced OPG in female TDT patients ($p<0.05$) and no difference in RANKL compared to HCs ($p>0.05$). The effect of gender, endocrine profile, vitamin D and calcium have been shown to modulate OPG/RANKL mediated bone metabolism (21). Although the factors affecting bone health in TDT were not determined in this study, it is not uncommon to have bone related complications in these patients (16,34). In β-thalassemia, the bone related complications such as osteopenia and osteoporosis increase with advancing age, our study found weak to no correlation of age with serum levels of OPG and RANKL. Moreover, a very weak to no correlation was found between serum ferritin and serum levels of OPG and RANKL.

Limited data are available on the effect of iron overload on the levels of OPG or RANKL. However, studies have shown an association of iron overload and iron chelating drugs with reduced bone density in TDT (18).

Interestingly, the role of OPG and RANKL are not limited to bone metabolism but shown to regulate several physiological and pathological mechanisms including immunity, cancers, cardiomyopathies and oral health (35-37). TDT is a complex disease with multisystem involvement and the possible systemic involvement of OPG and RANKL such as cardiomyopathy along with bone metabolism (38). Keeping in view the variations noted in OPG and RANKL levels in TDT among ours and previous studies, several factors such as transfusion frequency, bone density and use of bisphosphonate, vitamin D, corticosteroid or HbF inducing drugs could influence the levels. Furthermore, the role of the endocrine profile particularly thyroid and parathyroid hormones on bone metabolism needs consideration. Therefore, further studies are needed to understand the pathogenesis of bone disease in TDT including the role of OPG and RANKL mediated bone metabolism and systemic effects with above mentioned limitations taken into account.

Conclusion

Overall, the level of OPG and RANKL were reduced in TDT patients compared to HCs. OPG levels were reduced in both female and male TDT patients compared to HCs while RANKL was only reduced in TDT males. Age and serum ferritin levels had a very weak to no correlation with OPG or RANKL levels.

Ethics

Ethics Committee Approval: This study was conducted at the Thalassemia Center Al-Khidmat Hospital, Peshawar and Blood Diseases Clinic, Peshawar Institute of Medical Sciences, Peshawar after ethical approval from the Institutional Ethical Committee of Institute of Pathology and Diagnostic Medicine, Khyber Medical University, Peshawar, Pakistan (ref: #KMU/IPDM/IEC/2024/27; dated: 12.12.2024).

Informed Consent: Informed consent was taken from participants or their parents/guardians.

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Footnotes

Authorship Contributions

Surgical and Medical Practices: N.S., M.I.K., G.F.R., Concept: A.H., G.F.R., Design: K.S., A.H., G.F.R., Data Collection or Processing: K.S., N.S., G.F.R., Analysis or Interpretation: A.H., A.J.M., Q.A., M.I.K., Literature Search: K.S., A.H., A.J.M., Q.A., N.S., G.F.R., Writing: K.S., A.H., A.J.M., Q.A., N.S., M.I.K., G.F.R.

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