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Role of sclrostin (SOST) to predisposing for osteoporosis in β - thalassemia major patients

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Abstract--Sclrostin is a biomarker interrupted in bone resorption process by binding to LRP5 and/or LRP6 family, and prevent Wingless-type signaling (Wnt) which is important to both bone development and the maintain of bone mass. Sixty (60) patients with thalassemia major were enrolled from the period 2/5/2021 to 1/9/2021 in summer to assessment role of sclrostin to predisposing for osteoporosis in β -thalassemia major patients (β -TM). Patients ages were from (2-40 year) males and females they divided to children and adults had osteoporosis and/or osteopenia. All patients diagnosed by Hb electrophoresis and were receiving regular blood transfusions for anemia and chelation therapy for prevention of iron overload related complications. Detailed history and examination including height and weight were recorded on pre-designed questionnaire and blood samples were taken for measurement of serum sclrostin level. The results showed non-significant differences ($P>0.05$) of serum sclerostin (SOST) concentration between osteoporosis of beta thalassemia patients (β -TM) and osteopenia of beta thalassemia patients for both gender, but appeared increased significant ($P>0.05$) in male adults of osteopenia with progressive aged.

Keywords--Sclrostin (SOST), osteoporosis and beta-thalassemia.

Introduction

Osteoporosis is characterized by a decrease in bone mass and destruction. According to an internationally agreed definition, people with $BMD \leq -2.5$ have a standard deviation less than the average healthy young population with osteoporosis (1). β -thalassemia is an inherited disorders of hemoglobin (Hb) synthesis characterized by chronic anemia of varying severity , β -thalassemia major severe forms of β -thalassemia , commonly present in early childhood with severe anemia and require lifelong transfusion therapy for survival (2). The pathogenicity of osteopathy in β -TM is multifactorial comprising environmental (diet and lifestyle), iatrogenic (medicines), genetic and acquired factors (expansion of bone marrow, hemochromatosis, deficiency of GH or IGF-1, hepatitis and hypogonadism , cause severe problems in thalassemic patients (3). Sclerostin define as SOST gene encoded secreted glycoprotein 213-amino acid containing cysteine knot produced mainly by osteocytes, however, also produced by cementocytes and mineralized hypertrophic chondrocytes (4). Sclerostin have role to increase loss of bone mass in elderly, β -TM patients mostly have impaired bone density and imbalanced bone turnover and have high level of sclerostin in early age compared with healthy individuals (5). Serum sclerostin levels peak early in life with childhood and decline during the later stages of puberty towards a nadir at the end of puberty, and then increase over the remainder of adult life besides after age 30 year , there is a gradual and natural bone mass reduction that takes place over the ensuing decades into later life (6). Sclerostin binding to LRP5 and/or LRP6 family and prevent Wntless-type signaling (Wnt) that is important to both bone development and the maintain of bone mass (7,8). Additional, sclerostin also inhibiting the maturation of osteocytes and regulates the expression of genes involved in bone matrix mineralization (9).

Method

Across-sectional study was done on subjects in thalassemia center in Wasit province/ Iraq. All subjects received blood transfusion 15 mg every kilogram according to the weight of patients, demographic data including age, gender, and medical history were recorded through a comprehensive history from parents or guardians and from the patient's medical history. This study aim to detective role of sclrostin (SOST) to predisposing for osteoporosis in β - thalassemia major patients. The bone densitometry assayed by measured bone mineral density and classify to osteopenia or osteoporosis.

Patients subject

The samples tested were (60) samples which divided to children group and adult group . Children group were (30) samples (19 male and 13 female) their ages was from (2 to 15) years, adult group were (30) samples (11 male and 21 female) aged from (25 to 40) year, all patients divided to osteoporosis and/or osteopenia. Blood sample drawn from patients for measurement sclrostin concentration also all patients underwent DEXA scan using (Stratos – 393 France device) bone densitometer in AL-Zahraa Teaching hospital/ Wasit –Iraq. Clinical history was taken from each patient and their parents including: name, age , sex, sort of thalassemia, family history of thalassemia, age at diagnosis occupation.

Procedure for serum ferritin assay

- Prepare all reagents before beginning assay procedure. It is recommended that all standards and samples be added in duplicate for the micro-elisa strip-plate
- Add standard: Set the standard wells, testing sample wells. Add standard 50 μ l to standard well.
- Add Sample: Add the sample 10 μ l then add sample diluent 40 μ l to the testing sample wells; Blank well doesn't add anything.
- Add 100 μ l of HRP-conjugate reagent to each well, then cover with an adhesive strip and incubate for (60) minutes at (37°C).
- Aspirate each well and wash, repeating the process four times for a total of five washes. Wash by filling each well with (Wash Solution) (400 μ l) using a squirt bottle, manifold dispenser or Elisa Washer. Complete removal of liquid at each step is necessary to good performance. After the last wash, remove any remaining Wash Solution by aspirating or decanting. Invert the plate and blot it against clean paper towels.
- Add the chromogen solution A (50 μ l) and the chromogen solution B (50 μ l) to each well. Gently mix and incubate for (15) minutes at 37°C. keep away from light.
- Add (50 μ l) from stop solution to each well. The color in the wells should change from blue to yellow. If the color in the wells is green or the color change does not appear uniform, gently tapping the plate to ensure good mixing.
- Read the Optical Density (O.D.) at 450 nm using a microtiter plate reader within 15 minute.

Results

Results in the table (1-1) was showed non-significant differences ($P>0.05$) of serum sclerostin (SOST) concentration (pmol/L) in all age ranges (2-8, 9-15, 25-32 and 33-40 year) between osteoporosis of beta thalassemia patients (β -TM) and osteopenia of beta thalassemia patients for both gender, also similar finding in the results of serum sclerostin (SOST) concentration (pmol/L) with progressive age, appeared non-significant differences ($P>0.05$) of sclerostin (SOST) regard to progressively with age in β -TM patients with osteoporosis, while in (33-40 year) of male thalassemia with osteopenia noted a significant increase ($P\leq 0.05$) in serum sclerostin (SOST) concentration when compared within male thalassemia with osteopenia for age ranges (9-15 and 25-32 year). Also there is no significant differences ($P>0.05$) of serum sclerostin (SOST) between male and female beta thalassemia major in both osteoporosis and osteopenia.

Table 1-1
The mean values of sclerostin (SOST) (pmol/L) concentration of the beta thalassemia major patients for both genders based on t-score in spine for adult patients and z- score in spine for children patients

Sclerostin (SOST) (pmol/L)				
Age range (Year)	Osteoporosis		Osteopenia	
	Male	Female	Male	Female
(2 - 8)	73.13±6.68 Aa	50.35±10.6 Aa	0.0	55.85±8.25 Aa
(9 -15)	76.83±8.76 Aa	43.50±0.5 Aa	62.18±11.11 Ab	68.88±10.9 Aa
(25-32)	53.50±0.50 Aa	38.66±4.72 Aa	43.00±5.28 Ab	51.67±8.23 Aa
(33-40)	66.50±3.50 Aa	65.00±11.42 Aa	75.70±9.63 Aa	74.87± Aa
LSD=29.32				

Data= Mean ±S. E. M.

Different capital letters denote to significant differences between groups ($P \leq 0.05$).

Different small letters denote to significant differences within groups ($P \leq 0.05$).

Similar capital and small letters denote to non-significant differences ($P > 0.05$).

LSD = Least significant difference.

Dissection

Sclerostin evaluated with aged, the bone loss is sustained with progressive age and then predisposes elderly patients to significant increase in risk of fracture and osteoporosis. The current study consider the first study to evaluate the biomarker for patients with β -TM in Iraq. So the findings may can be explained that absence of a significant difference in the level of serum sclerostin between thalassemia patients with osteopenia and/or with osteoporosis, depended on the lower in the bone mineral density at all ages, due to the bone marrow expansion beginning from a childhood to compensate for the severe deficiency in the blood and from anemia instead of building strength skeleton, therefore thalassemia patients have low bone mineral density starting with anemia. Also the deposition iron causes interferes in osteoid maturation and mineralization by the incorporation into crystals of calcium hydroxyapatite which consequently affects the growth of calcium hydroxyapatite crystals and increases osteoid in bone tissue (10). Moreover damaged bone with small size may simply contribute to the markedly low bone mineral density (BMD) seen in the thalassemic patients.

So, the present data an agreement with Palomo et al. that recorded there is no significant differences of sclerostin level between patients with BMD z- score (-2.1) (osteopenia) and patients with BMD z- score (-2.6) (osteoporosis) in patient X-linked hypophosphatemic rickets (XLH) and osteogenesis imperfecta (OI) they are of the most common heritable metabolic bone disorders in children and adolescents (11). As well as, the findings in the same line with study by voskaridou et al., (2012) they observed non statistically significant difference between baseline sclerostin levels of thalassemia men and thalassemia women (median 625 pg/ml, range 22-1 204 pg/ml vs. 576 pg/ml, 36-1 227 pg/ml,

respectively) (5). While the data of the current study were disagreement with many studies finding circulating sclerostin had been elevated in patients with postmenopausal osteoporosis (12-14), in patients with immobilization-induced bone loss (15) , with rheumatoid arthritis (16), with renal osteodystrophy (17) and in patients under hemodialysis (18). In fact sclerostin is a potential candidate as a biomarker of bone turnover due to its inhibitory action in osteoblast function, Sclerostin appeared rapidly as a potent inhibitor of Wnt canonical signaling (19). Involved in embryogenesis and morphogenesis, sclerostin directly inhibits the Wnt pathway by binding to LRP5/6 . The activation of the Wnt pathway triggers either the canonical signaling by the stabilization of β -catenin or the non-canonical signaling pathway independently of β -catenin (20).

Conclusion

It was concluded from current the study outcome that osteoporosis and osteopenia a common complications in β -thalassemia major patients they predisposed to low bone mineral density (BMD) by multifactorial such as defective of parathyroid gland (PTH) and excessive iron accumulated in bone tissues and various body organs. Sclerostin is a biomarker inhibit osteoblast function, our results showed no differences in sclerostin level between osteoporosis and osteopenia also the incidence of osteoporosis occur early among β -TM as a results of variation and imbalance of bone physiological biomarkers related to bone homeostasis.

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