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What We Learn from Bone Complications in Congenital Diseases? Thalassemia, an Example

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1. Introduction

The thalassemias, a group of inherited disorders of hemoglobin synthesis, are the most common monogenetic diseases worldwide and are curable by bone marrow transplantation (BMT). Many patients achieve a lifelong disease-free period after BMT. This has focused attentions on disease and treatment complications, for example bone complications. Some of bone disorders occur before and after transplantation and some of them (osteoporosis) and their complications are life threatening. For a better understanding of the bone complications in thalassemia, a brief review of normal bone is required. However, because thalassemia is a curable congenital disease and with an ethical background, the investigation of bone disorders in thalassemic patients (before and after transplantation), can provide a model of calcium and bone metabolism. This model, based on clinical and research findings before and after transplantation, can enlighten factors affecting bone and mineral metabolism throughout the life (disease period and cure period can be considered as periods of bone loss and bone gain through-out the normal life). This model can help in the understanding and management of bone disorders in other bone diseases and in primary osteoporosis. As a resident of a country with a large population of thalassemic patients (Iran), it is author's special interest that such studies help these patients achieve a better quality of life and decrease the burden of this disease not only in Iran but also in other countries worldwide.

2. What is thalassemia

2.1 Disease name and synonyms

The term thalassemia, has two components thalassa (sea) and haima (blood), both from Greek. Beta-thalassemia includes three main forms: thalassemia major ("Cooley's Anemia" or "Mediterranean Anemia"), Thalassemia Intermedia and Thalassemia Minor ("beta-thalassemia carrier", "beta-thalassemia trait" or "heterozygous beta-thalassemia") (Galanello & Origa, 2010). In this review the author's focus is on β -thalassemia major and its bone complications.

2.2 Definition

The thalassemias, hereditary hematologic disorders, are caused by defective synthesis of one or more of the hemoglobin (Hb) chains (Muncie & Campbell, 2009). Hb molecule is a

tetramer composed of 4 -globin polypeptide (2 alpha-globin and 2 beta-globin) plus a heme prosthetic group, to form the complete molecule. In the α -thalassemias, defective production of α -globin chains results in an unstable Hb causes and mild to moderate hemolytic and hypochromic anemia (Sankaran & Nathan, 2010). Beta thalassemia is caused by reduced or absent synthesis of beta globin chains. Hemolysis and impaired erythropoiesis is the result of this imbalance of globin chains. Fatal hydrops fetalis, is seen in cases of Alpha thalassemia major with hemoglobin Bart's (Muncie & Campbell, 2009).

Beta-thalassemia minor (carrier state) patients, are clinically asymptomatic (they are diagnosed, generally accidental by specific hematological features). Thalassemia major patients are severely transfusion-dependent. Thalassemia intermedia patients, ranging in severity from the asymptomatic carrier patients to the severe transfusion-dependent patients (Cao & Galanello, 2010).

Galanello and Origa, in their article (Galanello & Origa, 2010) suggested the following classification:

- Beta-thalassemia
 - Thalassemia major
 - Thalassemia intermedia
 - Thalassemia minor
- Beta-thalassemia with associated Hb anomalies
 - HbC/Beta-thalassemia
 - HbE/Beta-thalassemia
 - HbS/Beta-thalassemia (clinical condition more similar to sickle cell disease than to thalassemia major or intermedia)
- Hereditary persistence of fetal Hb and beta-thalassemia
- Autosomal dominant forms
- Beta-thalassemia associated with other manifestations
 - Beta-thalassemia-trichothiodystrophy
 - X-linked thrombocytopenia with thalassemia

2.3 Epidemiology of thalassemia

The total annual incidence of symptomatic individuals is estimated to be 1 in 100,000 worldwide and 1 in 10,000 in the European Union (Galanello & Origa, 2010). Approximately 5% of the world's population has a globin variant, and only 1.7% has the alpha or beta thalassemia trait. Thalassemia affects men and women equally and occurs in approximately 4.4 of every 10,000 live births. Alpha thalassemia is most common in persons of African and Southeast Asian descent, and beta thalassemia occurs most often in persons of Mediterranean, African, and Southeast Asian descent. The thalassemia trait affects 5-30% of persons in these ethnic groups (Muncie & Campbell, 2009).

2.4 Genetics of thalassemia

The extent of imbalance between the alpha and non-alpha globin chains, relates to the clinical severity of beta-thalassemia. Cao & Galanello suggest that the beta globin (HBB) gene maps in the short arm of chromosome 11, in a region also containing the delta globin gene, the embryonic epsilon gene, the fetal A-gamma and G-gamma genes, and a pseudogene (γ B1). Single nucleotide substitutions, deletions, or insertions of oligonucleotides that leads to frame shift, are the majority of mutations. Beta-thalassemia

rarely results from gross gene deletion. In addition to the variation in the phenotype resulting from allelic heterogeneity at the beta globin locus, the phenotype of beta-thalassemia can also be modified by the action of genetic factors mapping outside the globin gene cluster and not influencing fetal hemoglobin (Cao & Galanello, 2010).

2.5 Pathophysiology of thalassemia

Fessas (1963), as cited in Sankaran & Nathan, 2010, described unbalanced globin chain synthesis, as the cause of the β -thalassemia syndromes. Intraerythroblastic inclusions of unpaired α -globin molecules, results disease manifestations (Sankaran & Nathan, 2010).

Galanello & Origa explain two mechanisms for increase the clinical and hematological severity in beta-thalassemia heterozygote patients. In first mechanism, an excess of unassembled alpha chains (resulting in premature destruction of red blood cell precursors) is caused by the coinheritance of both heterozygous beta-thalassemia and triple or quadruple alpha globin gene arrangement, that increases the magnitude of the imbalance of alpha/non-alpha globin chain synthesis. In the other mechanism, premature destruction of red blood depends on the presence of a mutation in the beta globin gene, which causes extreme instability of the beta globin chains and the synthesis of truncated beta chain products (Galanello & Origa, 2010).

2.6 Diagnosis of thalassemia

Most individuals with the thalassemia trait are found incidentally when their complete blood count shows mild microcytic anemia. Hemoglobin electrophoresis with the beta thalassemia trait usually has elevated levels of HbA2.

Individuals with beta thalassemia major are diagnosed during infancy. Symptoms appear during the second six months of life. The most common symptoms are pallor, irritability, growth retardation, abdominal swelling, and jaundice. Beta thalassemia intermedia patients (with microcytic anemia, but milder symptoms) have start of disease later in their life (Muncie & Campbell, 2009). Genetic sideroblastic anemias, congenital dyserythropoietic anemias, and other conditions with high levels of HbF (such as juvenile myelomonocytic leukemia and aplastic anemia) are considered as differential diagnosis (Galanello & Origa, 2010).

2.7 Signs, symptoms and complications of thalassemia

Hemolytic anemia, poor growth, and skeletal abnormalities during infancy, are major sign and symptoms of beta thalassemia major (Muncie & Campbell, 2009). Growth retardation, pallor, jaundice, poor musculature, hepatosplenomegaly, leg ulcers, the development of masses from extramedullary hematopoiesis, and skeletal changes (results of the bone marrow expansion) are found in untreated or poorly transfused individuals with thalassemia major (Galanello & Origa, 2010). Thalassemia major patients are diagnosed within the first 2 years and require regular blood transfusions to survive (Sankaran & Nathan, 2010). Iron overload is the result of regular blood transfusions. Complications of iron over load includes endocrine complications (growth retardation, failure of sexual maturation, diabetes mellitus, and insufficiency of the parathyroid, thyroid, pituitary, and less commonly, adrenal glands), dilated cardiomyopathy, liver fibrosis and cirrhosis. Patients with thalassemia intermedia present later in life with moderate anemia and do not require regular transfusions. Though the thalassemia intermedia patients, come to medical attention later, may show an extended list of complications like hypertrophy of erythroid

marrow with medullary and extramedullary hematopoiesis and its complications (osteoporosis, masses of erythropoietic tissue that primarily affect the spleen, liver, lymph nodes, chest and spine, and bone deformities as well as typical facial changes), gallstones, painful leg ulcers and increased predisposition to thrombosis. Moderate anemia may be the only sign of thalassemia minor patients and they are in general, clinically asymptomatic (Galanello & Origa, 2010).

2.8 Genetic counseling and prenatal diagnosis in thalassemia

As there is big population of thalassemic patients in some countries and there is high carrier rate for thalassemic mutations in certain populations (explained before in part 2.3), population screening is ongoing in them. Availability of genetic counseling and prenatal diagnosis, makes such screening in these countries more useful (Cao & Galanello, 2010) and use of prenatal diagnosis may be stressed in such countries (Galanello & Origa, 2010).

Analysis of DNA extracted from fetal cells obtained by amniocentesis (at 15–18 weeks gestation), in high-risk pregnancies in which both members are defined carriers of beta-thalassemia, is possible for prenatal diagnosis. Chorionic villus sampling is useful and is performed at approximately 10–12 weeks gestation (Cao & Galanello, 2010).

2.9 Treatment of thalassemia

Many patients with b-thalassemia, and some patients with severe forms of a-thalassemia, require regular transfusions to survive. In the case of b-thalassemia, this therapy has an important effect on reducing the massive ineffective erythropoiesis and organ infiltration and bone destruction that is seen in β -thalassemia patients that are untreated. (Sankaran & Nathan, 2010). With multiple transfusions, iron overload and organ failure (particularly cardiac iron overload and heart failure) are the leading causes of death (Au, 2011). Therefore, after 10–12 transfusions, chelation therapy (an effective but non-absorbable iron chelator, such as desferrioxamine B (DFO) with a short plasma half-life) is initiated 5–7 days a week by 12-hour continuous subcutaneous infusion via a portable pump (Cao & Galanello, 2010).

2.9.1 Splenectomy

Splenectomy is recommended if the annual red cell requirement exceeds 180–200 ml/kg of RBC (assuming that the Hct of the unit of red cells is about 75%). Symptoms of splenic enlargement, leukopenia and/or thrombocytopenia and increasing iron overload despite good chelation, are considered as other indication for splenectomy (Galanello & Origa, 2010).

2.9.2 Bone marrow transplantation (BMT) in thalassemia

It is explained extensively in part 5.

2.9.3 Therapies under investigation in thalassemia

The potential of new chelation strategies, including combination or alternate treatment with available chelators, induction of HbF synthesis that can reduce the severity of beta-thalassemia by improving the imbalance between alpha and non-alpha globin chains, several pharmacologic compounds including 5-azacytidine, decytidine, butyrate derivatives and gene therapy in the management of beta-thalassemia syndromes are described by Cao and Galanello, Sankaran and Nathan as under investigation therapies (Cao & Galanello, 2010; Sankaran & Nathan, 2010).

2.9.4 Treatment of thalassemia in developed versus underdeveloped countries

In United States and Europe (as developed countries), there are approximately 10,000 homozygous patients with thalassemia. In such countries, due to effective prevention methods, the number of new cases is progressively decreasing. The result of high-quality medical care is longer life expectancy and a relatively good quality of life. BMT and gene therapy, is performed in such countries. The need of Western cultures is to develop improved support for patients with thalassemia and their families (Rund & Rachmilewitz, 2005). In a recent study by Hamidi et al, in Iran, low bone mass was significantly less prevalent in thalassemic patients in comparison to previous studies (Hamidi et al, 2010). Good bone health in patients may also be due to better and developing health network services in Iran and in other countries with high populations of these patients, thus providing a good health service. In Iran there are more than 300 transplanted thalassemic patients (Abolghasemi et al., 2007; Ghavamzadeh, 2009).

The treatment situation of thalassemia patients is different in less developed countries. It is very important because big population of thalassemic patients live there. Safe transfusion and chelation are not universally available. Consequently, many patients with thalassemia in underdeveloped nations die in childhood or adolescence (Rund & Rachmilewitz, 2005).

2.10 Prognosis in thalassemia

Following recent medical advances in transfusion, iron chelation and BMT therapy, prognosis in these patients has improved substantially in the last 20 years. However, the main cause of death in patients with iron overload, remains cardiac disease (Galanello & Origa, 2010).

- As a congenital disease, bone disorders in thalassemic patients are mainly due to bone growth problems and begin in childhood, thus a brief insight into normal bone growth and related matters are discussed in the following section.

3. Normal bone growth

3.1 Normal bone development

Schonau, explains the first phase of bone development so: in development period of embryo, the axial skeleton and extremities are initially in the form of cartilage. The first spontaneous mineralization occurs in the diaphysis. As a result of the activities of osteoclasts and osteoblasts, this mentioned tissue will be replaced by the mature bone matrix. Bones' longitudinal growth take place in the specialized epiphyseal growth plates in which chondrocytes synthesize cartilage matrix, that will be changed to primary and secondary spongiosa in the metaphyseal junction. The growth of The axial skeleton thickness happens due to periosteal and endosteal growth (Schonau, 1998). Turn-over of the bones is necessary for either normal mineralized bone matrix maintenance or bone's growth. In healthy adults, resorption and formation of bones take place together in the remodeling process. Though this process is important for maintaining normal skeletal integrity, it does not have any role in changes in bone shape. Diversely, growth of childhood skeletal takes place in bone modeling, a process in which increased bone mass and changes in bone shape, happens. If bone resorption exceeds bone formation a problem occurred named Osteopenia. Which can occur in 2 different ways. It happens when bone resorption exceeds bone formation or when bone formation diminishes, but resorption is normal. (von Scheven, 2007). When muscular strength and parallel biomechanical usage increase, an increase in cortical thickness and area must be happened. The ratio of cortical thickness to bone

diameter (corticalis index) increases as child grows up (Schonau, 1998). The velocity of increase of bone density in children, mostly mimics height growth velocity. It means, a first gradual phase of bone acquisition happens in early childhood and a more accelerated phase of accumulation, approximately 8% per year, occurs during adolescence. (von Scheven, 2007). A decrease phase of bone density happens after 20 or 30 years old, before that, bones mass increases to peak bone mass (PBM). Schonau, suggests that the percentage of ash weight of the individual skeletal sections however does not change significantly with age. On the other hand, physiological content of mature bone tissue (matrix plus minerals) does not change essentially with age and represents a kind of "constant." Morogulis (1931) as cited in Schonau, 1998, also showed that the calcium and phosphate contents of the of very different animal species's skeletal systems were nearly the same. In contrast the water content does change. Up to years 20 the water content in bone tissue decreases. It is because of the high vascularity of the bones during the elevated phase of remodeling and modeling processes in growth time. It decreases later. (Schonau, 1998).

3.2 How peak bone mass is gained

The increase of total skeletal calcium (from approximately 25 g at birth to 900 and 1200 g in adult females and males, respectively), is gotten through bone growth, modeling and remodeling, which proceed at different rates at various skeletal sites. (Rabinovich, 2004). During childhood and adolescence, changes in size and shape of the skeleton happens together. And also bone grow up in width and cortical thickness. Genetic, hormonal and environmental factors influence all these processes. (Bianchi, 2007). Bone mass increase is faster in adolescence, 25% of the PBM acquired during the two-year period close to peak height velocity. Rabinovich suggests that maximal rates of bone mineral accrual lag behind peak height velocity by 6–12 months, resulting in relatively undermineralized bone and increased fracture risk in the peri-pubertal years. At peak height velocity, males and females have reached 90% of their adult stature but have acquired only 57% of their adult total body bone mineral content (BMC). Bone mineral accrual continues after linear growth is complete, but the timing of PBM remains debatable (Rabinovich, 2004). About 85% of human skeleton is cortical bone and 15% is trabecular. The bone gain and loss during growth or in later age affects these 2 parts, in different ways. Hormonal/metabolic factors influence strongly the trabecular bone density throughout the sexual maturation. Cortical bone consolidates slower. Bianchi states that Although the timing of peak values has not been precisely determined, the PBM is probably reached at the end of the second decade in the axial skeleton (predominantly trabecular bone), but only later in the appendicular skeleton (predominantly cortical bone) (Bianchi, 2007). Rabinovich says that is suggested that, though at least 90% of PBM is achieved by age 18, 5–12% of bone mineral density is reached during the third decade (Rabinovich, 2004). Heritable factors is supposed to attribute to approximately 60–80% of the variations in peak bone mass (Bachrach, 2001), Bianchi results that these changes are not only continuous, but also subject to great individual variation, mostly related to the variability of pubertal development, and this is essential for the correct evaluation of BMD in young subjects (Bianchi, 2007).

3.3 Gender differences

Rabinovich explains difference between girls and boys in growing bone: during puberty, estrogen in girls inhibits periosteal formation while stimulating endocortical bone

formation, thus limiting the medullary space. In contrast, in boys, androgens stimulate periosteal formation, bone diameter, and cortical thickness (Rabinovich, 2004). Also, van Kuijk suggests that, both the starting age of the pubertal spurt and the growth process happens earlier in girls, but the duration of the growth spurt and the maximal peak of growth are greater in boys. Increase in bone density starts around the age of 10 in girls and around the age of 12 in boys. (Van Kuijk, 2010).

3.4 Genetics of low bone mass

As Marini and Brandi categorized in their 2010 article (Marini & Brandi, 2010), the main osteoporosis candidate genes are: Calciotrophic and sex hormones and their receptors ((i) Vitamin D receptor (VDR), (ii) Parathyroid hormone (PTH) and PTH receptor (PTHrP), (iii) Estrogen Receptor Alpha and Beta (ER α and ER β), (iv) Calcitonin (CT) and its receptor (CTR), (v) Aromatase (CYP19A1), (vi) Androgen receptor (AR), (vii) Calcium-sensing receptor (CaSR), (viii) Glucocorticoid receptor (GR)), cytokines, growth factors and local regulators ((i) Interleukin-6 (IL6), (ii) Insulin-like growth factor 1 (IGF-I), (iii) Transforming growth factor β 1 (TGF β -1), (iv) Bone morphogenetic protein 7 (BMP7, OP1), (v) Bone morphogenetic protein 4 (BMP4), (vi) Bone morphogenetic protein 2 (BMP2)), Bone matrix proteins ((i) Collagen type I alpha1 (COL1A1), (ii) Collagen type I alpha2 (COL1A2), (iii) Osteopontin (OPN, SPP1), (iv) Osteocalcin (OCN, BGLAP), (v) Osteonectin (ON, SPARC)) and miscellaneous genes such as (i) Low-density lipoprotein receptor-related protein 5 (LRP5), (ii) Low-density lipoprotein receptor-related protein 6 (LRP6), (iii) Receptor activator of nuclear factor kappa B (RANK), (iv) RANK ligand (RANKL), (v) Osteoprotegerin (OPG), (vi) Sclerotin (SOST), (vii) Chloride channel 7 (CLCN7) and (viii) Methylenetetrahydrofolate reductase (MTHFR) (Marini & Brandi, 2010).

3.5 Low bone mass in pediatrics

Congenital connective tissue disorders such as osteogenesis imperfecta and Ehler-Danlos syndrome are important causes of pediatric osteoporosis. Neuromuscular disorders (cerebral palsy and Duchenne muscular dystrophy), childhood cancer, endocrine disorders (Turner Syndrome and juvenile diabetes mellitus), and inborn errors of metabolism (Gaucher disease) and chronic diseases like thalassemia are secondary causes of pediatric osteoporosis include. Don't forget pharmacological treatment, that are used for treatment of common pediatric conditions (iatrogenic causes. Among these, Glucocorticoids and anticonvulsants are known causes. Some add various forms of chemotherapy to this list (Bogunovic et al., 2009). However idiopathic juvenile osteoporosis is an acknowledged cause of osteoporosis in children and may it is the cause of a higher than expected prevalence of inadequate BMD in the pediatric population.

3.6 Problems with DXA in pediatrics

Bone density measurement by dual energy X-ray absorptiometry (DEXA) the standard method for bone mineral Densitometry. It is also one of most non-invasive techniques for the assessment of bone mass (Hamidi et al., 2008). Not surprising, it is used for many pediatric studies that produced many papers in the field of bone densitometry and in body composition (Van Kuijk, 2010). The WHO based the diagnosis of postmenopausal osteoporosis on the presence of a BMD T-score of 2.5 or greater below the mean for young women (Hamidi et al., 2008). The term "low bone mineral density for age" was mentioned

at the "2007 ISCD Pediatric Position Development Conference" as a criterion for low bone mass in children, and is described as a child with a Z-score below -2.0. The difference between adult and pediatric criterion for low bone mass is that children have not reached PBM, yet. Instead, a child's Z-score (comparison of BMD of patient to age and sex matched normal children in reference data of pediatric software) must be noticed. (Daniels et al., 2003). However, must not forget that DXA has challenging aspects in pediatrics densitometry. True bone density is defined as BMC (g) divided by volume (cm³). Bogunovic explains that as DXA is a 2-dimensional projectional technique. In DXA, a two-dimensional projection, measures a three-dimensional object, bone. As a result, the BMD measured by DXA is defined as BMC (g) divided by the projected area (cm²) not divided by the projected volume (cm³). As a consequence of this area measurement of density, smaller bones appear to have a lower BMD than larger bones (Bogunovic et al., 2009). Van Kuijk, reminds us that in adults, bone size does not change over time. In contrast, bone size changes in growing children in 3 dimensions. When measuring children using DXA and following them over time, growth is measured more than actual changes in bone density (Van Kuijk, 2010). Another challenge, as Bogunovic believes is that the assignment of DXA Z-scores is dependent on the comparison of the patient's BMD to normative childhood data for age and sex. The wide variation in height, and, therefore, of bone size in children complicates the interpretation of BMD results especially in short children. Longitudinal evaluation of a given patient over time is complicated by the ever-changing size of the growing skeleton. Furthermore, the rates of skeletal growth vary with each bony dimension (Bogunovic et al., 2009). All these problems, pose a question: To Do or Not to Do DXA for the measurement of bone density and fracture risk in children? In response we must remember some points related to DXA, 1) patients are exposed to less radiation when measuring BMD by DXA, which is very important in children, 2) it is less fearful for children (less noisy with no tunnel) 3) DEXA is used worldwide and many pediatric studies have been published in the field of bone densitometry and in body composition studies, by using this method and 4) Studies suggest that bone mass may contribute to fracture risk in childhood (Van Kuijk, 2010). Therefore, the answer may be that carrying out DXA for the measurement of bone density and fracture risk in children, is a helpful method, although, it must be remembered, as Bogunovic reminds us, that bone fragility in children extends beyond a single BMD measurement and is influenced by bone geometry and body size and the diagnosis of osteoporosis requires the presence of both a clinically significant fracture history and low bone mass (Bogunovic et al., 2009).

3.6.1 Special considerations in the comparison of normal children and children with chronic disease, some points on the BMD of chronically ill children

As explained above, the measurement of BMC (g/cm) and BMD (g/cm²) are not only dependent on the mineral density of cortical and spongy bone, but also on the geometric configuration. This situation is of great importance in pediatrics. Schonau concludes that if BMC or BMD measurement results in decreased values for children with short stature (e. g., with "smaller bones"), this does not necessarily describe a mineral deficiency or a mineralization disorder, as is often thought (Schonau, 1998). Wide variation in age at onset and progression of puberty is another problem. It means a wide variation in the age at attainment of PBM. Some diseases, like juvenile arthritis, is thought to delay pubertal onset

and development. As it is believed that one-third to one-half of the total mineralization in the lumbar spine in adult women is accumulated during the 3 years around the onset of puberty. Therefore Rabinovich concludes that, comparing the BMD of a well-grown 13-year-old girl who is in mid-puberty with that of a small pre-pubertal 13-year-old with juvenile arthritis is fraught with problems. She suggests that a DXA scan is not needed to tell who has the lower BMD. The question then is, is the BMD finding in this small pre-pubertal girl normal? (Rabinovich, 2004). As van Kuijk suggested, children with chronic disorders or medication, should never be compared with age-matched reference (normal) values. They should be compared with children with the same maturation status (skeletal age) (Van Kuijk, 2010).

3.7 Fractures in pediatrics

Fragility fractures are raising in pediatric population. This may be due to growing number of chronic disease in this population. It caused the increase of use of DXA in children. Healthy children with frequent fragility fracture, have been the focus of research. This is changing, may be because escalating of children with chronic diseases and fragility fractures. When an atraumatic event, cause fracture, fragility fracture come true. The difficulty looms here because as Bogunovic et al state, in young children especially, distinction between traumatic and atraumatic fractures may prove to be a challenge (Bogunovic et al., 2009). Other side of this problem, appear there, when there are many papers on fractures in childhood, but very few of these focus to identify fragility fractures, and fewer focused on the concept of osteoporosis in the young in relation to fractures. Bianchi reminds us that fractures, especially in infants, and especially if multiple or repeated, may be the consequence of violence and child abuse. However, fractures are common events in children. Landin, 1997, as cited in Bianchi, 2007, estimated that 42% of boys and 27% of girls sustain a fracture between 0 and 16 years of age. The most fractures in them, occurs between 10 and 15 years and forearm is the most common site (Bianchi, 2007). Is low BMD a risk factor for fractures? Bone mass may contribute to fracture risk in childhood (Bogunovic et al., 2009). Adverse reactions to cow milk, low dietary calcium intake, early age at first fracture, asthma and overweight (Goulding et al., 2005), and low physical activity are suggested as risk factors for fractures in children. Others suggested that lower BMD for body size, lower milk intake and lower physical activity related with recurrent fractures (Manias et al., 2006). Carbonated beverages also had some relations to fragility fractures. In children with chronic diseases, no systematically collected data is available. Bianchi reviewed that and suggested that some studies found no significant differences in the fracture rate between patients and controls. In contrast, many studies found an increased fracture risk in children affected by various diseases such as acute lymphoblastic leukemia, cerebral palsy, celiac disease, organ transplantation and glucocorticoids users (Bianchi, 2007).

3.8 Treatment of low bone mass in children

Unfortunately, though general measures (optimizing the intake of calories, vitamin D and calcium; providing appropriate weight-bearing activity; replacing GH or sex steroids; and minimizing doses of glucocorticoids) are recommended for better acquisition and maintaining of bone mass in children, they may not be sufficient to prevent or restore deficits in bone mass. Anti-resorptive agents (eg. Bisphosphonates), found valuable in treating some disorders, such as steroid-induced osteoporosis. In steroid-induced

osteoporosis, increased bone loss also contributes to the deficit, so anti-resorptive agents, seem affective. The ideal is treatment children to improve the failure of bone mineral acquisition, but they are not recommended yet (Bachrach, 2001). However, the use of different anti-osteoporotic agents (anabolic or anti-resorptive) in pediatric patients is not very common or recommended, especially in young children, due to a lack of large and systematic studies and comprehensive data supporting their efficacy or addressing their adverse effects in pediatric patients.

4. Bone and thalassemia

Osteopenia and are observed in 40–50% of beta-thalassemia Major patients, and so osteoporosis can be considered prominent causes of co-morbidity in this population, which significantly increases fracture risk (Gaudio et al., 2010).

Before discussing bone disorders in thalassemia patients, it is necessary to understand normal bone function and remodeling.

4.1 Bone in normal individuals

Voskaridou & Terpos, explain the role of skeleton, bone properties and BMU as so: the skeleton provides mechanical support for the body and is a reservoir for normal mineral metabolism. Bone is an active tissue constantly being remodeled and changing metabolically through the balanced activity of osteoclasts and osteoblasts on trabecular surfaces. On a microscopic level, bone metabolism always occurs on the surface of the bone at focused sites, each of which is termed a bone metabolism unit (BMU) (Voskaridou & Terpos, 2004). Mundy suggests that the sequence is always the same, osteoclastic bone resorption followed by osteoblastic bone formation to repair the defect. The resorptive phase of the remodeling process has been estimated to last 10 days. This period is followed by repair of the defect by osteoblasts attracted to the site of the resorption defect which then presumably proceed to make new bone. This part of the process takes approximately 3 months (Mundy, 1999). After the lacunae are filled with osteoids, Voskaridou & Terpos state that this newly formed matrix is mineralized with hydroxyapatite, giving the BMU tensile strength (Voskaridou & Terpos, 2004).

4.1.1 Osteoclasts

Hodge et al, describe Osteoclasts as multinucleated cells which differentiate from early myelomonocytic progenitors rather than more differentiated monocyte/macrophage progenitors (Hodge et al., 2004). Roodman describes their function as they reabsorb bone by secreting proteases which dissolve the matrix and produce acid that releases bone mineral into the extracellular space under the ruffled border of the plasma membrane of osteoclasts (Roodman, 2004). Voskaridou & Terpos say osteoclastogenesis requires contact between osteoclast precursors and stromal cells or osteoblasts. They say the adherence of osteoclasts to the bone surface is critical for the bone resorptive process, since agents that interfere with osteoclast attachment, such as cathepsin K, block bone resorption (Voskaridou & Terpos, 2004).

Wittrant et al, state the role of colony-stimulating factor-1 (CSF-1), released by osteoblasts, as it stimulates the proliferation of osteoclast progenitors via the c-fms receptor (CSF-1R) and,

in combination with the receptor activator of nuclear factor- κ B ligand (RANKL), leads to the formation of mature osteoclasts (Wittrant et al., 2009).

These two molecules are expressed by bone marrow stromal cells, also (Voskaridou & Terpos, 2004). Wittrant et al names the cells of the mononuclear phagocytic lineage including osteoclast progenitors and mature osteoclasts as well as placental trophoblasts, uterine decidual cells, smooth muscle cells, microglia, renal mesangial cells and osteoblasts, as other sites that express CSF-1R (Wittrant et al., 2009). PTH administration in 7-14 first days, to enhances RANKL- and M-CSF-stimulated osteoclast formation and bone resorption was shown in vivo (Jacome-Galarza et al., 2011). Thyroxine, 1,25-dihydroxyvitamin D3, and cytokines that use gp130 as part of their receptor, such as interleukin-6 (IL-6) and oncostatin M, are named as other factors which enhance RANKL expression (Voskaridou & Terpos, 2004).

Rankle/OPG system has a characteristic position in osteoporosis and metabolic bone disease. Osteoprotegerin (OPG), a secreted member of the tumor necrosis factor receptor superfamily, has been identified as an osteoblast-derived regulator of bone resorption. OPG neutralizes RANK that is essential for osteoclast formation and activation (Morabito et al., 2004). Alteration in the Rank/Rankl/OPG system may favors osteoclasts and osteoporosis formation (Toumba & Skordis, 2010).

4.1.2 Osteoblasts

Marie & Kassem explain in detail that bone formation is dependent on the recruitment of a sufficient number of osteoblasts as well as the activity of individual osteoblasts. They suggest that osteoblastic cells are recruited to bone forming surfaces mainly from a group of skeletal stem cells with osteogenic differentiation potential (referred to as skeletal, mesenchymal stem cells (MSC), or stromal stem cells. Some believe that some of these cells are pericytes located on the outer surface of blood vessels and sinusoids in the bone marrow, though, the exact location of mesenchymal stem cells in vivo is still debatable (Marie & Kassem, 2011).

Wnt signaling pathway is named as a key pathway involved in the regulation of bone mass. Johnson et al in an article in 2004, explained that Wnt signaling is also required for a diverse number of developmental events including mesoderm induction, organogenesis, CNS organization and limb patterning. In addition, a number of Wnt's have been implicated in vertebrate skeletal development. For example, there is evidence that Wnt3a, Wnt4, Wnt5a, Wnt5b, and Wnt7a all have important roles in chondrogenesis. Another member of the Wnt family, Wnt9A (formerly Wnt14), can induce morphological and molecular signs of joint formation when inappropriately expressed, indicating that Wnt9A plays a crucial role in the initiation of synovial joint development. Wnt9A expression can also lead to the arrest and reversal of chondrogenic differentiation in vitro (Johnson et al., 2004). We explained before, the PTH role in resorption. PTH also have anabolic effects and Marie & Kassem explain that the anabolic effects of PTH on bone formation are mediated through PTH receptor-dependent mechanisms. PTH enhances osteoblastic cell proliferation and function, extends the lifespan of mature osteoblasts through antiapoptotic effects, enhances Wnt signaling through inhibition of the Wnt antagonist, sclerostin, and enhances the local production of bone anabolic growth factors such as insulin-like growth factor 1 (IGF1) (Marie & Kassem, 2011). Though the differentiation of osteoblasts is less well understood than the differentiation of osteoclasts (Voskaridou & Terpos, 2004), bone morphogenetic proteins (BMPs) are critical factors that stimulate the growth and differentiation of osteoblasts (Marie

& Kassem, 2011). Voskaridou & Terpos name several factors such as Basic fibroblast growth factor (bFGF), Insulin-like growth factors (IGF, type I and II), Transforming growth factors (TGF, beta 1 and beta 2) and platelet-derived growth factor (PDGF) and a number of hormones, such as PTH, thyroxine, oestrogen, cortisol, insulin, and calcitonin, as well as vitamin D, are involved in the regulation of bone metabolism, effecting both progenitors and mature osteoblastic cells and osteoclasts (Voskaridou & Terpos, 2004).

4.2 Bone complications in thalassemic patients

Peculiar mongoloid appearance, caused by enlargement of the cranial and facial bones, combined with skin discoloration, anemia, splenomegaly and some enlargement of the liver were included in the first description of thalassemia by Cooley & Lee (Wonke, 1998). Galanello & Origa explain Skeletal changes include typical craniofacial changes such as bossing of the skull, prominent malar eminence, depression of the bridge of the nose, tendency for a mongoloid slant of the eye, and hypertrophy of the maxillae, which tend to expose the upper teeth (Galanello & Origa, 2010).

Some experts suggest that, the thalassemic anemia and the need for transfusion, as earlier as appear in the disease course, the facial changes are more prominent, and all agree that the disease course changes are only seen or are more prominent in untreated patients or in those with no regular transfusion program (Cao & Galanello, 2010). Tyler et al suggest that the skeletal changes in untreated thalassemia are due to ineffective erythropoiesis and expansion of the bone marrow which affect every part of the skeleton. These changes include osteoporosis, growth retardation, platyspondyly and kyphosis (Tyler et al., 2006). Anemia, hemosiderosis, iron chelation therapy, and associated hormonal disorders, are described as main causes of spinal deformity (Haidar et al., 2011). Salehi et al. , suggest that expanded erythropoiesis occurs at extra-medullary sites, most commonly resulting in a para-spinal mass but occasionally affecting organs containing pluripotential stem cells (Salehi et al., 2004). Tyler et al., state that skeletal dysplasia, predominantly affects the rapidly growing long bones, in particular the distal ulna, causing irregularity and sclerosis of the physeal-metaphyseal junction and causing splaying of the metaphysis. They say , Deferoxamine (DFX) also exacerbates the observed growth retardation. DFX-induced skeletal dysplasia, may cause toxicity, which is associated with visual and auditory impairment (Tyler et al., 2006).

Among the spinal deformities observed, Papanastasiou et al suggest that an increased prevalence of frontal curves was reported of at least, 5° in 67% of patients with TM. However, scoliosis curvatures of more than 10° and less than 14° were observed in 21.7% of examined patients. It seemed that location, direction, and pattern of the curvatures, age of onset, gender, and rate of progression of this type of scoliosis associated with TM, differed those in patients with idiopathic scoliosis. They, in their greater than 10-year study reported that the prevalence of frontal curves of at least 5° in 43 TM patients was approximately 80%. Scoliosis of at least 10° and not more than 19° was revealed in 28% to 35% of patients. The most common scoliosis curve pattern was the S-shaped (right thoracic, left lumbar). The prevalence of scoliosis was not gender related, irrespective of age and curve magnitude. Progression of scoliosis in the 10-year period was only detected in four (12%) of 34 patients with scoliosis of 5° to 14°, a rate much lower than that reported in patients with idiopathic scoliosis. Only one patient (2.9%) developed scoliosis of 65° that progressed to 85°, and no other patient developed scoliosis curves that required bracing or operative treatment. No correlation was shown between scoliosis progression and (remaining) growth potential, curve pattern, gender, or curve

magnitude (Papanastasiou et al., 2002). As Haidar et al., mention around 24% of curves showed spontaneous resolution, this was equally distributed among all but the right thoracic curve patterns. Left lumbar and thoraco-lumbar scoliosis improved at a rate of 22% and 33%, respectively. However, most of the curves showed a magnitude of less than 10°. This remarkable absence of progression and spontaneous resolution in small curves depicts the unique etiology of scoliosis in this hematologic condition. Of note, thoracic kyphosis increased with patient age, whereas lumbar lordosis decreased with age and followed the changes of thoracic kyphosis. The 'junction' thoracolumbar kyphosis increased with patient age, but independently from thoracic kyphosis and lumbar lordosis. However, neither scoliosis magnitude nor progression was correlated to thoracic kyphosis (Haidar et al., 2011).

4.2.1 Bone and joint pain

Bone or joint pain, reported in 34% of participants during the 30 days before enrollment, in one study in all thalassemic patients. Vogiatzi et al., state that 6 percent required prescription pain medication and an additional 12.2% used analgesics as over-the-counter. They report that age, sex, and thalassemia syndrome were all independent predictors of the presence and severity of bone and joint pain and the odds of more severe pain, increased 47% for each 5-yr age increase. 40% of females, but only twenty-eight percent of males complained of recent pain. Bone pain was reported more frequently among b TM participants (40%) compared with b TI and E-b participants (16% and 19%, respectively) (Vogiatzi et al., 2009). As Haidar et al suggested, though arthralgia has been mainly attributed to iron overload or use of iron chelators, back pain is mainly associated with osteoporosis, compression fractures, and intervertebral disc degeneration. They report that in one study by the Thalassemia Clinical Research Network (TCRN), young adults with thalassemia experienced pain comparable to the general population, whereas older adults (aged 35+) experienced greater pain. There was an association between pain and low vitamin D level. (Haidar et al., 2011). Vogiatzi et al report that GH-deficient patients were reported to have more severe bone pain, as did those with a history of medicated heart disease, cirrhosis, or hepatitis C (Vogiatzi et al., 2009).

4.2.2 Intervertebral disc changes

Haidar et al. In an extended report about bone disease and skeletal complications in patients with β thalassemia major, suggest that a significant difference in disc degeneration severity has been demonstrated between TM patients and controls on MRI and radiographs. The pattern of disc degeneration was different in TM patients as they exhibited multilevel disease with all levels of the lumbar spine involved. Although no clear mechanism has been suggested for the development of disc changes in TM patients, an underlying metabolic basis has been suggested. They say that the degeneration of intervertebral discs results, in part, from weakening of the annulus fibrosus. The chelating agent, deferoxamine, commonly used in patients with TM, is thought to deleteriously affect the integrity and strength of the annulus fibrosus fibers. Alternatively, the injurious effect of iron overload is also postulated as a factor (Haidar et al., 2011).

4.2.3 Osteoporosis

Several sensitive techniques are available for the quantitative assessment of the degree of total bone mass. Bone density measurement by dual energy X-ray absorptiometry (DEXA)

of the lumbar spine and femoral neck is recommended as one of the most reliable non-invasive techniques for the assessment of bone mass (Kanis, 1994).

According to the World Health Organization (WHO, 1994), osteoporosis is a disease characterized by low bone mass and micro-architectural deterioration of bone tissue, leading to enhanced bone fragility and a consequential increase in fracture risk. The WHO based the diagnosis of postmenopausal osteoporosis on the presence of a BMD T-score of 2.5 SD or greater below the mean for young women (Hamidi et al., 2008). The term "low bone mineral density for age" was mentioned at the "2007 ISCD Pediatric Position Development Conference" as a criterion for low bone mass in children, and is described as a child with a Z-score below -2.0 (Daniels et al., 2003).

In spite of adequate transfusion and iron chelation, Thalassemia-induced osteoporosis (TIO) is seen in 30–50% of TM patients, that can cause substantially compromised quality of life in thalassemic patients (Mamtani & Kulkarni, 2010).

4.2.3.1 Genetics of bone density in thalassemic patients

Voskaridou and Terpos, reported that polymorphism at the Sp1 site of the collagen type Ia1 (COLIA 1) gene (collagen type I is the major bone matrix protein) was found in approximately 30% of TM patients who were heterozygotes (Ss) and in 4% who were homozygotes (SS) for the Sp1 polymorphism. They reported the female to male ratio was 2:1. This means that male patients with TM carrying the Sp1 mutation may develop severe osteoporosis of the spine and the hip more frequently than patients who do not carry this mutation. The COLIA 1 polymorphism has been also associated with reduced BMD in postmenopausal osteoporosis, and predisposes women to osteoporotic fractures (Voskaridou & Terpos, 2004). Marini & Brandi reported a similarity between this finding and genetic findings in non-thalassemic patients (Marini & Brandi, 2010).

A possible beneficial effect of BsmI on patient response to alendronate therapy should be emphasized (Gaudio et al., 2010). Haidar et al report the vitamin D receptor (VDR) BsmI and FokI polymorphisms to constitute risk factors for bone mineral damage, low BMD, and short stature in pre-pubertal and pubertal patients with TM, (Haidar et al., 2011).

As Gaudio et al say, it should be remembered that the pathogenesis of osteoporosis is multifactorial, and includes environmental (diet, lifestyle, and drugs) as well as acquired (bone marrow expansion, hemochromatosis, chelation therapy, hepatitis, deficiency of growth hormone or insulin growth factor I, and hypogonadism) and genetic factors (Gaudio et al., 2010).

4.2.3.2 Altered modeling/remodeling in thalassemic patients

Haidar et al, believe that most acquired factors act mainly through the inhibition of osteoblastic activity. They suggest that histomorphometry studies have revealed that increased osteoid thickness, increased osteoid maturation and mineralization lag time, and defective mineralization are common in TM pediatric patients (Haidar et al., 2011). Mildly increased resorption found in adult patients with beta TM (Vogiatzi et al., 2010). Baldini et al explain an interesting hypothesis that the chronic request for blood cell production can play a role in the etiology of osteoporosis through overstimulation of the hematopoietic system, increasing the number of osteoclasts and osteoblasts resulting in accelerated bone turnover (Baldini et al., 2010). However, Domrongkitchaiporn et al., suggest that increased resorption may be a cause of hypogonadism in these patients (Domrongkitchaiporn et al., 2003).

4.2.3.3 Gender differences in bone density in thalassemic patients

Some studies support that gender of thalassemic patients affects not only the prevalence, but also the severity of osteoporosis syndrome in TM. However the results are contradicted and some studies showed no gender differences in patients with TM, when they were hypogonadal (Toumba & Skordis, 2010).

4.2.3.4 Acquired factors contributing to reduced BMD in beta-thalassemia

4.2.3.4.1 Bone marrow expansion

Expansion of hematopoiesis and bone marrow expansion, caused severe bone deformities with marked facial and limb changes that were originally described by Cooley et al in 1927 in untreated thalassemia major patients (Jensen et al., 1998). As Wonke, also suggests, the bone marrow expansion due to ineffective erythropoiesis is a typical finding in patients with TM and is considered a major cause of bone destruction. The commonest sites for extramedullary hematopoiesis are the spleen, liver and chest; less common sites are para-vertebral masses and brain lesions. As the ribs contain hematopoietic marrow at all ages, overactive marrow results in, osteoporosis of the ribs, localized lucencies, cortical erosions, and 'rib within rib' deformities (Wonke, 1998). Mechanical interruption of bone formation, leading to cortical thinning, increased distortion and fragility of the bones, occurs due to Marrow expansion (Voskaridou & Terpos, 2004). Tyler et al. refer to ineffective hematopoiesis as a cause of severe anemia and increased erythropoietin production, resulting in expansion of the bone marrow by a factor of 15 to 30. They suggest that even with an optimal transfusion regimen, the bone marrow remains hyperactive. The appearance of "cob-webbing" in the pelvis is the reason of the expanded bone marrow that destroys the medullary trabeculae with initial cortical and trabecular thinning and subsequent trabecular coarsening (Tyler et al., 2006).

Salehi et al., even reported spinal cord compression that is seen in these patients, which can cause neurologic compromise and is, in part, due to extramedullary hematopoiesis (Salehi et al., 2004).

4.2.3.4.2 Endocrine complications

4.2.3.4.2.1 General

Idiopathic hemochromatosis (Iron overload), are commonly associated with hypogonadism and diabetes, while the other endocrinopathies seen in patients with β -thalassemia major and Iron overload, are less common in them. As Perera et al. suggest, a significant predictor of endocrine failure is the duration of transfusion therapy (Perera et al., 2010). In below, we explain endocrine disorders in thalassemic patients, more extensively, as these disorders are major and important causes of bone complication in thalassemic patients.

4.2.3.4.2.2 Growth failure

Homozygous β -thalassemias, have almost invariably growth retardation. Soliman et al. describe these changes as significant size retardation that is observed in stature, sitting height, weight, biacromial (shoulder), and bicristal (iliac crest) breadths (Soliman et al., 2009). All studies do not show such results (Cao & Galanello, 2010). Soliman et al., state that after the age of 4 years, the longitudinal growth patterns, display rates consistently below those of normal controls and the bone age is frequently delayed after the age of 6-7 years. Growth retardation becomes markedly severe with failure of the pubertal growth spurt

(Soliman et al., 2009). Though hemosiderosis-induced damage of the endocrine glands is one of the main causes for their growth failure, Cao & Galanello, Muncie & Campbell, Toumba & Skordis and Soliman et al, state that other factors could considerably contribute to the etiology of this growth delay including (i) chronic anemic hypoxia secondary to low hemoglobin concentration (Muncie & Campbell, 2009) (ii) toxicity of desferrioxamine treatment (Cao & Galanello, 2010); (iii) increased energy expenditure due to high erythropoietic turnover and cardiac work; (iv) nutritional deficiencies including calories, folic-acid, zinc, and vitamin A (Soliman et al., 2009); (v) disturbed calcium homeostasis and bone disease (Toumba & Skordis, 2010) (vi) hepatic and pancreatic dysfunction (Soliman et al., 2009).

Perera et al., emphasize that normal stature is rarely attained, even in the well-managed patient. They report the administration of GH in some centers internationally at the judgment of individual clinicians, but the role or response to GH is not clearly understood in these patients and probably has no clear benefit unless GH deficiency is confirmed by formal testing (generally as a consequence of early childhood pituitary failure) (Perera et al., 2010).

4.2.3.4.2.3 Delayed puberty/hypogonadism in thalassemia

Both primary and secondary sexual development are usually delayed in both genders in β -thalassemia major (Vogiatzi et al., 2005). An association between hypogonadotrophic hypogonadism and osteoporosis in adult patients with TM has been reported in the past. Jensen et al (1998), found that hypogonadotrophic hypogonadism is a substantial contributor to the development of osteoporosis. Hypogonadotrophic hypogonadism is the commonest endocrinological complication in β -thalassaemia major and is present in 42% of patients (Jensen et al., 1998). Perera et al. describe the finding in these patients as menarche is frequently delayed by an average of 1-2 years, breast development is poor and female patients frequently have oligomenorrhoea/amenorrhoea even if menarche occurs. Men frequently have poor or absent virilization, reduced libido and oligo/azospermia. They report both genders less fertile and commonly require reproductive assistance to achieve a successful pregnancy (Perera et al., 2010). Toumba & Skordis explains the complication as disruption of gonadotrophin production (due to iron deposition in gonadotrophic cells) and delayed puberty and hypogonadotrophic hypogonadism. They say secondary amenorrhea will invariably develop with time, especially in patients poorly compliant with chelation therapy. Also primary is common. Men also develop hypogonadotrophic hypogonadism and secondary gonadal failure. So low testosterone secretion is common. They report also primary gonadal failure due to iron deposition in the testes and ovaries. (Toumba & Skordis, 2010).

Perera et al., in an overview of endocrinopathies associated with β -thalassemia major, (2010), highlighted the high prevalence of hypogonadism with resultant growth failure and infertility, and suggested the following approach and management protocol in these patients:

1. Formal surveillance from the age of 10-12 years to identify changes associated with puberty, including the development of primary or secondary sexual characteristics. Consideration of an endocrine consultation in cases of suspected delayed puberty.
2. In adults, in addition to regular clinical review, annual monitoring of gonadotropin levels and sex hormone levels for both men and women should be organized. If clinically indicated, use of appropriate hormone replacement therapy in cases of hypogonadism.
3. Regular monitoring (1-3 times/year) of zinc levels, especially if patient is on deferiprone. In cases of zinc deficiency, supplementation to normal levels would also be

reasonable until further clarification of the relationship between zinc deficiency and hypogonadism becomes available (Perera et al., 2010).

4.2.3.4.2.4 Fertility in thalassemia

Pregnancy reported generally safe if baseline cardiac function is good (Rund & Rachmilewitz, 2005). Psihogios et al., suggested that with optimal therapy, most young adults with homozygous β -thalassemia can achieve reproductive, sexual, and social experiences similar to those of their healthy peers (Psihogios et al., 2002).

4.2.3.4.2.5 Impaired glucose tolerance and diabetes mellitus in thalassemia

There are different reports on the prevalence of diabetes in thalassemia major, however, Holger Cario reported that the prevalence is about 5%, while impaired glucose tolerance is found in up to 27% of patients (Cario et al., 2003).

Immune system activation against pancreatic beta cells in beta-thalassemia patients, is reported and pancreatic iron deposition is considered as factors that triggers the autoimmune response (iron depositions act as environmental factor) and immune response, in turn, contributes to selective beta-cell damage (Najafipour et al., 2008). Perera et al., did not report family history as a risk factor in thalassemic patient (Perera et al., 2010). In the study by Najafipour et al., risk factors reported for impaired glucose metabolism were, age, amount of blood transfused and duration of blood transfusion. Because not all of the patients with thalassemia major could be correctly diagnosed by fasting glucose alone, the authors preferred to use the oral glucose tolerance test (OGTT) rather than fasting blood glucose levels (BGLs) for the diagnosis of abnormal glucose tolerance in thalassemic patients (Najafipour et al., 2008).

Duration of transfusion therapy, in some studies was the strongest predictor for the development of diabetes (every decade of transfusion exposure further increasing the odds of developing diabetes by 2.5 times). The fact that diabetes mellitus is generally seen in the 3rd or 4th decade, may be explainable by these findings.. Perera et al state that it is prudent to begin screening for diabetes after the 1st decade of transfusions (regular 6th monthly or annual) by assessing fasting BGLs followed by a 75-g 2-h OGTT if fasting results are abnormal (Perera et al., 2010).

Glyburide treatment and antidiabetic compounds improve insulin sensitivity. Treatment with basal-bolus insulin therapy is also used in these patients. However must not forget that effective iron chelation may improve glucose tolerance (Perera et al., 2010; Cario et al., 2003). Some believe that HbA1c is not a good tool for measuring glycemic control because of reduced red cell lifespan, ineffective hematopoiesis and frequent blood transfusions (affect the validity of HbA1c results). They propose serum fructosamine as an alternative way of monitoring glycemic control, though there is some limitations in its use. Blood glucose self monitoring and regular pre-transfusion venous blood glucose measurements may be use for measuring glycemic control, as an alternative ways in these patinets (Perera et al., 2010).

4.2.3.4.2.6 Hypothyroidism in thalassemia

The severity of thyroid dysfunction is variable in thalassemic patients and the reports of prevalence are very different. Najafipour et al, reported the prevalence of hypothyroidism in their patients 16%, but found the prevalence of 13% to 60% in different studies of patients with thalassemia. However they believe that milder forms of thyroid dysfunction are much more common in thalassemic patients (Najafipour et al., 2008). Primary thyroid damage (from iron

infiltration) or secondary problems (due to pituitary dysfunction due to hemosiderosis of thyrotroph cells) are reported in these patients. Duration of transfusion therapy, has been the strongest predictor for development of hypothyroidism (Perera et al., 2010).

4.2.3.4.2.7 Short stature in thalassemia

As an important complication of thalassemia major, we discuss short stature in an independent section, not attached to growth failure. Najafipour et al, reported that 49% of thalassemic patients had a height standard deviation score less than -2 and 83% of thalassemic patients had a height standard deviation score less than -1. Normal stature is rare even in optimally treated patients. (Najafipour et al., 2008).

Even in well treated patients, it is prevalent and this is may be due to endocrine disorders, lifestyle, iron overload and high doses of desferrioxamine (DFX) when tissue iron burden is not very high (Ferrara et al., 2002).

4.2.3.4.2.8 Hypopituitarism in thalassemia

Hypogonadotropic hypogonadism occurs in a large proportion of patients, because pituitary gland is one of the most vulnerable target organs to the early toxic effects of iron overload (Cao et al., 2011). Pan-hypopituitarism is a rare (especial in patients with good chelation therapy). Perera et al, describe the usual sequence for onset of pituitary dysfunction as begins with FSH, LH, GH and follows by ACTH and TSH (Perera et al., 2010).

4.2.3.4.2.9 The RANKL/OPG system in thalassemia

The increase in RANKL, followed by unmodified OPG levels, with the consequent increase in the RANKL/OPG ratio may represent the cause of uncoupling in bone turnover observed in thalassemia patients (Toumba & Skordis, 2010). Haidar et al, report a negative correlation between 17- β estradiol in female and the RANKL and RANKL and free testosterone in male thalassemia patients. They reason that there is a role for the RANKL/OPG system on the action of sex steroids on bone (Haidar et al., 2011).

4.2.3.4.2.10 GH and IGF1 axis in thalassemia

According to the importance of the GH and IGF1 axis, we investigate this axis in detail in the following:

Despite normal response to provocation, some studies have shown that spontaneous GH secretion is defective in some short patients with TM. Soliman et al, emphasize that these data means the GH-IGF-I-IGFBP-3 axis in thalassemic children is defective. Structural abnormalities of their pituitary glands is also reported in association with defective GH secretion in thalassemic children. Impaired liver functions (secondary to siderosis and/or chronic viral hepatitis) may cause low IGF-I synthesis. Interestingly, Soliman et al, suggest that increased caloric dietary intake significantly increased IGF-I levels in thalassemic pediatric patients (Soliman et al., 2009).

4.2.3.4.2.11 Parathyroid gland dysfunction in thalassemia

Hypoparathyroidism is another factor contributes to osteopenia and subsequently osteoporosis. It is believed that this complication develops more in late adolescence A recent study reported a prevalence of up to 13.5% with no sex differences (Angelopoulos et al., 2006 (a)). Main causes of hypoparathyroidism, are iron deposition on parathyroid cells (Galanello & Origa, 2010). Typical biochemical picture of hypoparathyroidism with low calcium and high phosphate levels, is seen in these patients. Low calcium and phosphorus

are found in 24-hour urine collection. Bone X-rays are characteristic for osteoporosis. Abnormal cerebral CT findings are reported to be related to hypoparathyroidism in thalassemics (Karimi et al., 2009; Angelopoulos et al., 2006 (a)).

4.2.3.4.3 Nutrition, Vitamins, Calcium, minerals and calorie intake in thalassemia

Vitamin C deficiency in iron-overloaded patients, is seen with increases the risk of osteoporotic fractures at the level of epiphyseal lines (Wonke, 1998). Vitamin D deficiency (although it is not reported in all studies in thalassemic patients) is also implicated in the pathogenesis of osteoporosis in TM patients due to the regulatory effect of vitamin D in both osteoclasts and osteoblasts. Adequate calcium intake during skeletal development can increase bone mass in adolescents (Voskaridou & Terpos, 2004). It was shown that increased caloric dietary intake significantly increased IGF-I levels in thalassemic children. Soliman et al., emphasized that aggressive nutritional therapy and/or GH/IGF-I therapy with vitamin D supplementation and/or calcium may improve bone growth and mineralization and prevent the development of osteoporosis and consequent fractures in these patients. They report that many studies, have also shown that improving caloric intake and supplying micronutrients including vitamin D, zinc, and carnitine have a positive effect on linear growth that can be mediated through increasing IGF-I synthesis (Soliman et al., 2009).

4.2.3.4.4 Liver disease in thalassemia

Liver diseases is a known risk factor for osteoporosis (Toumba & Skordis, 2010). The effect of iron overload in the liver is so huge and prominent that determination of liver iron concentration in a liver biopsy specimen shows a high correlation with total body iron accumulation and is considered the gold standard for the evaluation of iron overload (Galanello & Origa, 2010). Complications of iron overload include involvement of the liver (chronic hepatitis, fibrosis, and cirrhosis) (Cao & Galanello, 2010). Several factors are implicated in the reduction of bone mass in TM as well as liver disease (La Rosa et al., 2005). Growth retardation and short stature in these patients and low vitamin D are described as complications of liver disease (Baldini et al., 2010).

4.2.3.4.5 Iron overload in thalassemia

As described, iron overload causes many complications in thalassemic disease which affect bone. However, there are some bone complications that are related to iron overload directly. Some authors suggest direct iron toxicity on osteoblasts (Origa et al., 2005; Galanello & Origa, 2010). Mahachoklertwattana et al, suggest that iron deposition in bone may impair osteoid maturation and inhibit mineralization locally, resulting in focal osteomalacia (Mahachoklertwattana et al., 2003). Although all studies do not agree with these findings (Domrongkitchaiporn et al., 2003), the mechanism by which iron interferes with osteoid maturation and mineralization is explained by Toumba & Skordis as the incorporation of iron into crystals of calcium hydroxyapatite, which consequently affects the growth of calcium hydroxyapatite crystals and increases osteoids in bone tissue (Toumba & Skordis, 2010). Mahachoklertwattana reported a study on the effect of iron overload on bone remodeling in animals showed decreased osteoblast recruitment and collagen synthesis, resulting in a decreased rate of bone formation. Iron deposits in bone and low circulating IGF-I levels may partly contribute to the above findings (Mahachoklertwattana et al., 2003). Domrongkitchaiporn et al., described extensive iron staining on trabecular surfaces and a marked reduction in trabecular bone volume without significant alteration in bone

formation and bone resorption rates, as well as a significant reduction in BMD in 18 thalassemic patients (Domrongkitchaiporn et al., 2003). Thus, it seems that further studies are needed to address the effect of iron toxicity on bone metabolism in thalassemia.

4.2.3.4.6 Chelation therapy in thalassemia

Chelation therapy is a known risk factor for bone problem in thalassemia patients (Origa et al., 2005; Vogiatzi et al., 2010). Growth failure and bone abnormalities, and cartilage alterations are reported as chelating therapy complication (Toumba & Skordis, 2010). Wonke et al., described the role of desferrioxamine in osteoporosis of thalassemic patients as follows: Desferrioxamine inhibits DNA synthesis, fibroblast proliferation and collagen formation, and may also cause zinc deficiency. Growth arrest and a reduction in growth velocity, difficulty in walking, frequently complain of pain in the hips and lower back is seen in patients who receive inappropriately high doses of desferrioxamine, specially when the iron burden is low, (Wonke, 1998).

4.2.3.4.7 Physical activity in thalassemia

As Haidar et al. Suggest, the association between mechanical stress and bone mass was first recorded by Galileo in 1683, who noted the relationship between body weight and bone size. They say that the low bone mass in TM patients is associated with reduced physical activity due to complications of the disease and overprotective parents, who do not encourage muscle activity (Haidar et al., 2011). However, bone disease management in these patients now includes increased physical activity (Rund & Rachmilewitz, 2005; Haidar et al., 2011; Wonke, 1998; Toumba & Skordis, 2010). What must not forget is that there is some conditions requiring special attention in recommending physical activity like severe heart disease, splenomegaly, and osteoporosis (Galanello & Origa, 2010).

4.2.3.5 Fractures in thalassemia

From self-reporting and a review of medical records, fractures occur in 36% of thalassemic patients, with 8.9% reporting three or more lifetime fractures. Extremity fractures are most common at 33%, followed by back and hip fractures at 3.6% (in one study, 10% of all fractures were reported in the spine, hip and pelvis). Low bone mass, sex hormone replacement therapy, and at least one iron overload-related endocrinopathy, was related to the prevalence of fracture. Multiple fractures are also a problem in TM patients (Haidar et al., 2011). Vogiatzi et al found The cumulative risk of fractures increased almost linearly with age. Overallly, they didn't find,sex difference ; though among participants <20 years of age, males were more likely to have a fracture compared with females. Whites participants had reports of fracture rates more than Asian. Other their findings was that spine and femur BMD Z-score and total body BMC were negatively associated with fracture rate. For a 1-SD decrease in spine or femur BMD Z-score, the mean fracture rate increased by 37% or 47%, respectively ($p < 0.001$ for both) (Vogiatzi et al., 2009).

The peak age of fracture was the mid to late 30s. Interestingly, the percentage of subjects who remained fracture-free by the age of 18 years was significantly higher than population estimates of healthy children without hemoglobinopathies. There did not appear to be an increase in fracture prevalence during the adolescent growth spurt or surrounding the initiation of menstruation, as is typically observed in healthy reference cohorts. This may be attributed to anemia which leads to decreased physical activity and fewer opportunities for recreational fractures. There is decreased time available for sports and physical activity as

these patients spend a significant amount of their time at health care centers, or overprotected by parents and caregivers. In summary, these findings confirm that the epidemiology of fractures in TM remains unique, as it is not correlated with risk taking behavior but is mainly due to vitamin D deficiency or low BMD which become more severe with age in this cohort of patients. (Haidar et al., 2011).

4.2.3.6 Management of thalassemia-induced osteoporosis

Prevention is essential for the effective control of this potentially debilitating morbidity in TM. Annual follow-up of BMD, starting in adolescence, is considered crucial. Haidar et al., recommend that Physical activity must always be encouraged and smoking should be discouraged. Adequate iron chelation, adequate calcium and zinc intake in combination with the administration of vitamin D, may prevent bone loss and fractures later and in adulthood. Hypogonadism and its prevention and treatment in thalassemic patients is very important in management of bone complication in thalassemia (Haidar et al., 2011). Despite the aforementioned measures, patients with TM still continue to lose bone mass and require treatment. Hormonal replacement, Calcitonin, Hydroxyurea, Bisphosphonates (clodronate, alendronate, pamidronate, and zoledronic) are used in the management of osteoporosis in thalassemic patients. Calcitonin, may decrease bone pain. (Voskaridou & Terpos, 2004 and Haidar et al., 2011).

Of course, it must be remembered that the use of these agents in pediatric patients is not very common or recommended, especially in young children, due to a lack of large systematic studies and comprehensive data supporting their efficacy or address their adverse effects in pediatric patients.

4.2.3.7 Bone mineral density in adult thalassemic patients

The thalassemic patients live longer now. Therefore, it is necessary to assess the bone problems in adult thalassemic patients. The increased survival of these patients during the last decade is due to regular transfusion associated with adequate iron chelation. Specific bone deformities are more rare but osteopenia and osteoporosis are more common. Low bone mass occurs despite transfusions, effective chelation, calcium, and vitamin D supplementation and hormonal deficiency replacement (Baldini et al., 2010). Though hypogonadism is important in low bone mass in TM patients, it may not be overt. Even in eugonadal women, as a delay of menarche which is common, a subtle deficiency in ovarian function cannot be ruled out (Carmina et al, 2004). Napoli et al demonstrated, at least in women with thalassemia major, that hormone replacement therapy was unable to prevent bone loss. This suggests that several mechanisms potentially contribute to low bone mass. One of these mechanisms may be vitamin D deficiency. It should be noted that TM patients progressively develop iron overload, and it is possible that a deficiency in liver hydroxylation of vitamin D, or in vitamin D absorption, can appear in older thalassemic patients (Napoli et al., 2006). However, all studies are not agree with high prevalence of low Vit-D in thalassemic patients. Another problem in these patients is GH-IGF1 axis. It was demonstrated that the GH-IGF-I-IGFBP-3 axis in thalassemic children is defective (Soliman et al., 2009) and it is shown that GH is important in adult life and that replacement therapy should not be ignored in adults with hypopituitarism (La Rosa et al., 2005).

Baldini et al., found that the femoral site is more influenced (by biochemical and clinical factors) than the spinal site. (Baldini et al., 2010). Christoforidis et al., suggested that optimal conventional treatment in β -thalassemia major can help to achieve normal bone mass

acquisition. They stated major contributors to this, as the regression of marrow expansion due to regular transfusions, the prevention of endocrine complications following adequate chelation therapy, and the reduction in deferioxamine-induced bone toxicity with the additional administration of deferiprone. As patients with thalassemia are in greater danger of developing predisposing factors for osteoporosis, optimal bone acquisition, comparable to the normal population, is essential in order to reduce future risks of osteoporosis in adult life. They recommend close surveillance with regular screening, preventive intervention and early management of possible endocrine complications are important in order to secure normal bone health. Life prolongation for patients with thalassemia major also requires improvement in quality of life (Christoforidis et al., 2006). In addition, Baldini et al. suggested that transfusion and chelation treatment can prevent bone demineralization only when applied early in childhood (Baldini et al., 2010).

5. Bone and thalassemia after bone marrow transplantation

5.1 General

Osteoporosis is increased in recipients of heart, kidney, lung, and liver transplants (Petropoulou et al., 2010). Patients undergone bone marrow transplantation have some difference with other transplant recipients. Their underlying disease, organ dysfunction, age, and the median interval between diagnosis and transplantation is different. That interval is usually shorter for BMT. Kerschan-Schindl et al., conclude that BMT recipients may receive less pre-treatment impairing bone metabolism, experience fewer restrictions in mobility, and have a more normal nutritional status. Additionally, BMT recipients generally receive less subsequent immunosuppressive therapy which may induce osteopenia (Kerschan-Schindl et al., 2004).

Thalassemic patients are in an increased risk of accelerated bone loss and thus osteoporosis, because BMT is a curative treatment for thalassemia, and many patients achieve a lifelong disease-free period after BMT. Several factors enhance bone loss in them, including gonadal failure, prolonged immobility, decreased osteoprogenitor cells, conditioning regimens, vitamin D deficiency, secondary hyperparathyroidism, cyclosporine and high-corticosteroid use for graft-versus-host disease (D'Souza et al., 2006). Though some of them are not uncommon before transplantation (Angelopoulos et al., 2006 (b)).

Many investigators such as D'Souza et al. (D'Souza et al., 2006) and Schulte et al. (Schulte & Beelen, 2004) reported the significant lowering effect of corticosteroids on BMD in transplanted patients. However, their studies were not specifically on pediatric thalassemic patients, and a study by Daneils et al. did not find a statistically significant correlation between glucocorticoid exposure and BMD in transplanted children.

Kerschan-Schindl et al., suggest the amount of bone loss and the pattern of loss are controversial. The amount of bone loss within 1 year after transplantation varied and was approximately 2% for the lumbar spine and 12% for the femoral neck. At 5 years after allogeneic BMT, the lumbar spine BMD was within normal limits, but the femoral neck BMD was decreased; osteopenia was present in 43% and osteoporosis in 7% of patients (Kerschan-Schindl et al., 2004). Schulte & Beelen, demonstrated data of rapid bone loss during the first 6 months after transplantation (5.7% at the lumbar spine and 6.9% to 8.7% at the femoral neck sites) with no further decline between months 6 and 12, and recovery of bone mass during further follow-up (Schulte & Beelen, 2004).

As stated by Klopfenstein et al. in the study by Petryk et al., the incidence of osteopenia was 18% and the incidence of osteoporosis was 16% prior to BMT, which increased to 33% and 18%, respectively, 1 year after transplantation (Klopfenstein et al., 1999). In the study by Schulte et al., the lowest BMD in the femoral neck was seen 24 months after transplantation (Schulte & Beelen, 2004). However, as BMT is the only curative treatment for thalassemia, some investigators showed that the changes in BMD after transplantation may change in a positive direction (Leung et al., 2005).

5.2 Special considerations

5.2.1 Special consideration in children (Short stature)

Short stature is present in a significant number of transplanted thalassemic children. A close correlation between age at transplant and subsequent growth rate has been demonstrated (subjects who received BMT after 7 years of age, failed to achieve their full genetic potential), however, growth impairment in these subjects is due to multifactorial deranged function of the hypothalamic-pituitary-gonadal axis, abnormal hepatic conversion of steroid hormones to their active metabolites and defective hepatic biosynthesis of insulin-like growth factor (IGF-I). It is possible that iron overload is primarily involved in this phenomenon. Chronically transfused, inadequately chelated patients develop hepatocellular injury and late growth failure within the first decade of life. This is followed in adolescence by pubertal failure and dysfunction of various endocrine organs (De Simone et al., 2001).

5.2.2 Special consideration in older recipients

It must be remembered that early experience suggested that the results of transplantation for thalassemia were particularly poor for patients older than 16 years. However, Lucarelli et al., found that when the revised regimen for class 3 pediatric patients was used for older class 3 patients, the results were much improved (Lucarelli et al., 1999). However, Kaste, et al., recommend routine screening of BMD for all alloBMT patients. They suggest that patients should be advised to evaluate all behaviors which adversely affect bone health eg. avoid smoking, limit intake of caffeine and carbonated beverages, establish a weight-bearing exercise regimen after orthopedic consultation, and ensure adequate dietary intake of calcium and vitamin D. Patients should also be treated for other conditions that affect BMD such as hypogonadism and hypothyroidism (Kaste, et al., 2004).

In Iran, there is a large population of thalassemic patients and after Italy, the largest population of transplanted thalassemic patients. Thus, special attention to bone diseases before and after transplantation is necessary in these patients, and such studies may be helpful in improving life quality in affected individuals.

6. What we have learned about bone and thalassemia

The thalassemias, a group of inherited disorders of hemoglobin synthesis, are the most common monogenetic diseases worldwide and these diseases are curable by BMT. Many patients achieve a lifelong disease-free period after BMT. Thus, special attention to bone diseases before and after transplantation in these patients is necessary, and such studies may be helpful in improving life quality in affected individuals. Coping with huge problems related to the main disease and during and after BMT, the provision of a normal and safe

life for these patients is a humanitarian problem. Some special points on the prevention, diagnosis, management and monitoring of bone disease in thalassemic patients are listed below:

- Assessment of bone conditions in thalassemic patients before and after transplantation is ethical and many assessments are routine.
- As a multifactorial disease (ineffective erythropoiesis and bone marrow expansion, endocrine complications, iron overload and iron chelation therapy (deferoxamine), vitamin deficiencies, and decreased physical activity all affect bone in thalassemic patients), the assessment of any of these risk factors and factors effecting them, are grounds for research which can be used to provide a better life for these patients. This is true for bone diseases following BMT.
- As a congenital disease that affects bone from an early age and is completely curable, the assessment of patients in a cohort before and after transplantation, provides an opportunity to investigate factors which affect bone in a positive or negative way, when bone is being destroyed by the main disease and when the main disease is cured.
- Genetic studies provide a way of identifying the genes responsible for low bone mass in non-thalassemic and normal individuals, especially when there are similarities in genes which cause low bone mass in thalassemic patients and non-thalassemic osteoporotic patients.
- It is questionable whether the international criteria for defining osteopenia and osteoporosis are relevant to patients with TM; also the diagnostic methods used for osteoporosis in thalassemic patients are questionable as multiple factors and micro-structural characteristics are involved in the pathogenesis of osteoporosis.
- Progression from childhood to puberty and adulthood in these patients provides ground for extended and ethical research on cohort changes in bone density and bone metabolism between these periods. As screening for low bone mass is ethical and routine in pediatrics and adults, there is a unique opportunity to assess the correlation between the diagnostic criteria for low BMD in adult and children.
- Assessment of the effects of different preventive and treatment methods and drugs on bone and different risk factors that affect bone in these patients.
- With an ethical background for investigating bone problems in thalassemic patients, providing a model of calcium and bone metabolism, and factors affecting this metabolism, throughout the life (in periods of bone gain and bone loss), is possible. This is possible by using clinical and research findings in these patients. As thalassemia is a congenital disease which is also curable, finding ways for understanding and management of bone disease in other bone disorders and in primary osteoporosis is possible.

7. Conclusion

With the expanding number of thalassemia and transplanted thalassemic patients worldwide, a better understanding of bone diseases is necessary to provide a better and safer life for these patients. The findings from these studies can be used in a model to better understand human bone diseases and help in the management of these conditions.

8. Acknowledgements

The author thanks Dr. B. Larijani (the director of EMRI-TUMS), Dr. F. Mohseni, Dr. MR. Mohajeri Tehrani, Dr. AA. Hamidieh, Mrs. A. Oojaghi and the Special Medical Center of Charity Foundation for Special Disease of Iran for their valuable assistance in this study.

9. References

- Abolghasemi, Hassan. Amid, Ali. Zeinali, Sirous. Radfar, Mohammad H. Eshghi, Peyman. Rahiminejad, Mohammad S. Ehsani, Mohammad A. Najmabadi, Hossein. Akbari, Mohammad T. Afrasiabi, Abdolreza. Akhavan-Niaki, Haleh. Hoorfar, Hamid. (2007). Thalassemia in Iran: epidemiology, prevention, and management. *Journal of Pediatric Hematology/Oncology*. Vol. 29, No. 4, (Apr 2007), pp. 233-238, 1077-4114 (Print)
- Angelopoulos (a), Nicholas G. Goula, Anastasia. Ombopoulos, Grigorios. Kaltzidou, Victoria. Katounda, Eugenia. Kaltsas, Dimitrios. Tolis, George. (2006). Hypoparathyroidism in transfusion-dependent patients with beta-thalassemia. *Journal of Bone and Mineral Metabolism*. Vol. 24, No. 2, (2006), pp. 138-145, 0914-8779 (Print)
- Angelopoulos (b), Nicholas G. Katounda, Eugenia. Rombopoulos, Grigorios. Goula, Anastasia. Kaltzidou, Victoria. Kaltsas, Dimitrios. Ioannis, Pappas, Tolis, George. (2006). Evaluation of bone mineral density of the lumbar spine in patients with beta-thalassemia major with dual-energy x-ray absorptiometry and quantitative computed tomography: a comparison study. *Journal of Pediatric Hematology/Oncology*. Vol. 28, No. 2, (Feb 2006), pp.73-78, 1077-4114 (Print)
- Au, W Y. Lee, V. Lau, C W. Yau, J. Chan, D. Chan, E Y T. Cheung, W W W. Ha, S Y. Kho, B. Lee, C Y. Li, R C H. Li, C K. Lin, S Y. Ling, A S C. Mak, V. Sun, L. Wong, K H F. Wong, R. Yuen, H L. (2011), A synopsis of current care of thalassaemia major patients in Hong Kong. *Hong Kong Medical Journal*. Vol. 17, No. 4, Aug 2011, pp. 261-6, 1024-2708 (Print)
- Bachrach, L K. (2001). Acquisition of optimal bone mass in childhood and adolescence. *Trends in Endocrinology and Metabolism: TEM*, Vol. 12, No. 1, (Jan-Feb 2001), pp. 22-28, 1043-2760 (Print)
- Baldini, Marina. Forti, Stella. Marcon, Alessia. Ulivieri, Fabio Massimo. Orsatti, Alessandra. Tampieri, Benedetta. Airaghi, Lorena. Zanaboni, Laura. Cappellini, Maria Domenica. (2010). Endocrine and bone disease in appropriately treated adult patients with beta-thalassemia major. *Annals of Hematology*, Vol. 89, No. 12, (Dec 2010), pp. 1207-1213, 1432-0584 (Electronic)
- Bianchi, Maria Luisa. (2007). Osteoporosis in children and adolescents. *Bone*, Vol. 41, No. 4, (Oct 2007), pp. 486-495, 8756-3282 (Print)
- Bogunovic, Ljiljana. Doyle, Shevaun M. Vogiatzi, Maria G. (2009). Measurement of bone density in the pediatric population. *Current Opinion in Pediatrics*, Vol. 21, No. 1, (Feb 2009), pp. 77-82, 1531-698X (Electronic)
- Cao, Antonio, Moi, Paolo. Galanello, Renzo. (2011). Recent advances in beta-thalassemias. *Pediatric Reports*, Vol. 3, No. 2, (Jun 2011), p. e17, 2036-7503 (Electronic)
- Cao, Antonio. Galanello, Renzo. (2010). Beta-thalassemia. *Genetics in Medicine*, Vol. 12, No. 2, (Feb 2010), pp. 61-76, 1530-0366 (Electronic)

- Cario, Holger. Holl, Reinhard W. Debatin, Klaus-Michael M. Kohne, Elisabeth. (2003). Insulin sensitivity and beta-cell secretion in thalassaemia major with secondary haemochromatosis: assessment by oral glucose tolerance test. *European Journal of Pediatrics*, Vol. 162, No. 3, (Mar 2003), pp. 139-146, 0340-6199 (Print)
- Carmina, E. Di Fede, G. Napoli, N. Renda, G. Vitale, G. Lo Pinto, C. Bruno, D. Malizia, R. Rini, G B. (2004). Hypogonadism and hormone replacement therapy on bone mass of adult women with thalassemia major. *Calcified Tissue International*, Vol. 74, No.1 (Jan 2004). pp. 68-71. 0171-967X (Print)
- Christoforidis, Athanasios. Hatzipantelis, Emmanouil. Tsatra, Ioanna. Kazantzidou, Eirini. Katzos George. Athanassiou-Metaxa, Miranda. (2006). Bone mineral density in children and young adults with beta-thalassemia major conventionally treated. *Pediatric Blood & Cancer*, Vol 47, No. 1, (Jul 2006). pp.113-114, 1545-5009 (Print)
- Daniels, Mark W. Wilson, Darrell M. Paguntalan, Helen G. Hoffman, Andrew R. Bachrach, Laura K. (2003). Bone mineral density in pediatric transplant recipients. *Transplantation*. Vol. 76, No. 4, (Aug 2003), pp. 673-678, 0041-1337 (Print)
- D'Souza, A B. Grigg, A P. Szer, J. Ebeling, P R. (2006). Zoledronic acid prevents bone loss after allogeneic haemopoietic stem cell Transplantation. *Internal Medicine Journal*, Vol. 36, No. 9, (Sep 2006), pp. 600-603, 1445-5994 (Electronic)
- De Simone, M. Verrotti, A. Iughetti, L. Palumbo, M. Di Bartolomeo, P. Oliosio, P. Rosato, T. (2001). Final height of thalassemic patients who underwent bone marrow transplantation during childhood. *Bone Marrow Transplantation*. Vol. 28, No. 2, (Jul 2001), pp. 201-205, 0268-3369 (Print)
- Domrongkitchaiporn, Somnuek. Sirikulchayanonta, Vorachai. Angchaisuksiri, Pantep. Stitchantrakul, Wasana. Kanokkantapong, Chavasak. Rajatanavin, Rajata. (2003). Abnormalities in bone mineral density and bone histology in thalassemia. *Journal of Bone and Mineral Research*, Vol. 18, No. 9, (Sep 2003), pp. 1682-1688, 0884-0431 (Print)
- Ferrara, Mara. Matarese, Sofia M R. Francese, Matteo. Borrelli, Barbara. Coppola, Antonietta. Coppola, Lina. Esposito, Luigi. (2002). Effect of VDR polymorphisms on growth and bone mineral density in homozygous beta tlassaemia. *British Journal of Haematology*, Vol. 117, No. 2, (May 2002), pp. 436-340, 0007-1048 (Print)
- Galanello, R. Origa, R. (2010). Beta-thalassemia. *Orphanet Journal of Rare Disease* , Vol. 5:11, May 2010, 1750-1172 (Electronic)
- Gaudio, Agostino. Morabito, Nancy. Xourafa, Anastasia, Curro, Monica. Caccamo, Daniela. Ferlazzo, Nadia. Macri, Ilaria. La Rosa, Maria Angela. Meo, Anna. Ientile, Riccardo. (2010). Role of genetic pattern on bone mineral density in thalassemic patients. *Clinical Biochemistry*. Vol. 43, No. 10-11, (Jul 2010), pp. 805-807, 1873-2933 (Electronic)
- Ghavamzadeh, Ardeshir. Alimoghaddam, Kamran. Jahani, Mohammad. Mousavi, Seied Asadollah. Iravani, Masood. Bahar, Babak. Khodabandeh, Ali. Khatami, Farnaz. Gaffari, Fatemeh. Jalali, Arash. (2009). Stem cell transplantation; Iranian experience. *Archives of Iranian Medicine*, Vol. 12, No. 1, (Jan 2009), pp. 69-72, 1029-2977 (Print)
- Goulding, Ailsa. Grant, Andrea M. Williams, Sheila M. (2005). Bone and body composition of children and adolescents with repeated forearm fractures. *Journal of Bone and Mineral Research*. Vol. 20, No. 12, (Dec 2005), pp. 2090-2096, 0884-0431 (Print)
- Haidar, Rachid. Musallam, Khaled M. Taher, Ali T. (2011). Bone disease and skeletal complications in patients with beta thalassemia major. *Bone*, Vol. 38, No. 3, (Mar 2011), pp. 425-32, 1873-2763 (Electronic)

- Hamidi, Zohreh. Sedaghat, Mojtaba. Hejri, Soroosh Mortaz. Larijani, Bagher. (2008). Defining cut-off values for the diagnosis of osteoporosis in postmenopausal women by quantitative ultrasonography of the phalanx. *Gynecological Endocrinology*, Vol. 24, No. 10, (Oct 2008), pp. 546-8, 1473-0766 (Electronic)
- Hamidi, Zohreh. Hamidieh, Amir Ali. Mohajeri, Mohammad Reza. Nedaeifard, Leila. Heshmat, Ramin. Alimoghaddam, Kamran. Ghavamzadeh, Ardeshtir. Larijani, Bagher. (2010). Affects Of allogenic hematopoietic stem cell transplantation on bone density of pediatric patients with beta thalassemia major. *Proceedings of ASBMR 2010 Annual Meeting*, ISBN: 1523-4681 (Electronic), Toronto, October 2010. DOI: 10.1002/jbmr.5650251305(p S363-S502)
- Hodge, Jason M. Kirkland, Mark A. Aitken, Cathy J. Waugh, Caryll M. Myers, Damian E. Lopez, Carolina M. Adams, Brendan E. Nicholson, Geoffrey C. (2004), Osteoclastic potential of human CFU-GM: biphasic effect of GM-CSF. *Journal of Bone and Mineral Research*. Vol. 19, No. 2, (Feb 2004), pp. 190-199, 0884-0431 (Print)
- Jacome-Galarza, Christian E, Lee, Sun-Kyeong. Lorenzo, Joseph A. Aguila, Hector Leonardo, (2011), Parathyroid hormone regulates the distribution and osteoclastogenic potential of hematopoietic progenitors in the bone marrow. *Journal of Bone and Mineral Research*. Vol. 26, No. 6, (Jun 2011), pp. 207-16, 1523-4681 (Electronic)
- Jensen, C E. Tuck, S M. Agnew, J E. Koneru, S. Morris, R W. Yardumian, A. Prescott, E. Hoffbrand, A V. Wonke, B. (1998). High prevalence of low bone mass in thalassaemia major. *British Journal of Haematology*, Vol. 103, No. 4, (Dec 1998), pp. 911-915, 0007-1048 (Print)
- Johnson, Mark L. Harnish, Kimberley. Nusse, Roel. Van Hul, Wim. (2004). LRP5 and Wnt signaling: a union made for bone. *Journal of Bone and Mineral Research*. Vol. 19, No. 11, (Nov 2004), pp. 1749-1757, 0884-0431 (Print)
- Kanis, J A. (1994). Assessment of fracture risk and its application to screening for postmenopausal osteoporosis: synopsis of a WHO report. WHO Study Group. *Osteoporosis International*. Vol. 4, No. 6, (Nov 1994), pp. 368-381, 0937-941X (Print)
- Karimi, M. Rasekhi, A R. Rasekh, M. Nabavizadeh, S A. Assadsangabi, R. Amirhakimi, G H. (2009). Hypoparathyroidism and intracerebral calcification in patients with beta-thalassemia major. *European Journal of Radiology*. Vol. 70, No. 3, (Jun 2009), pp. 481-484, 1872-7727 (Electronic)
- Kaste, S C. Shidler, T J. Tong, X. Srivastava, D K. Rochester, R. Hudson, M M. Shearer, P D. Hale, G A(2004). Bone mineral density and osteonecrosis in survivors of childhood allogeneic bone marrow transplantation. *Bone Marrow Transplantation*, Vol. 33, No. 4, (Feb 2004), pp. 435-441, 0268-3369 (Print)
- Kerschan-Schindl, K. Mitterbauer, M. Mitterbauer M. Fureder, W. Kudlacek, S. Grampp, S. Bieglmayer, C. Fialka-Moser, V, Pietschmann, P, Kalhs, P. (2004), Bone metabolism in patients more than five years after bone marrow transplantation. *Bone Marrow Transplantation*. Vol. 34, No. 6, (Sep 2004), pp. 491-496, 0268-3369 (Print)
- Klopfenstein, Kathryn J. Clayton, Julie. Rosselet, Robin. Kerlin, Bryce. Termuhlen, Amanda, Gross, Thomas. (1999). Prevalence of abnormal bone density of pediatric patients prior to blood or marrow transplant. *Pediatric Blood & Cancer*, Vol 53, No. 4, (Oct 2009), pp. 675-677. 1545-5017 (Electronic)
- La Rosa, Clementina. De Sanctis, Vincenzo. Mangiagli, Antonino. Mancuso, Michele. Guardabasso, Vincenzo. Galati, Maria Concetta. Caruso-Nicoletti, Manuela. (2005).

- Growth hormone secretion in adult patients with thalassaemia. *Clinical Endocrinology*. Vol. 62, No. 6, (Jun 2005), pp. 667-671, 0300-0664 (Print)
- Leung, T F. Hung, E C W. Lam, C W K. Li, C K. Chu, Y. Chik, K W. Shing, M M K. Lee, V. Yuen, P M P. (2005). Bone Marrow Transplantation, Vol. 36, No. 4, (Aug 2005), pp. 331-336, 0268-3369 (Print)
- Lucarelli, G. Clift, R A. Galimberti, M. Angelucci, E. Giardini, C. Baronciani, D. Polchi, P. Andreani, M. Gaziev, D. Erer, B. Ciaroni, A. D'Adamo, F. Albertini, F. Muretto, P. (1999). Bone marrow transplantation in adult thalassemic patients. *Blood*, Vol. 93, No. 4, (Feb 1999), 0006-4971 (Print)
- Mahachoklertwattana, Pat. Sirikulchayanonta, Vorachai. Chuansumrit, Ampaiwan. Karnsombat, Patcharee. Choubtum, Lulin. Sriphraprang, Arporn. Domrongkitchaiporn, Somnuek. Sirisriro, Rojana. Rajatanavin, Rajata. (2003). Bone histomorphometry in children and adolescents with beta-thalassemia disease: iron-associated focal osteomalacia. *The Journal of Clinical Endocrinology and Metabolism*. Vol. 88, No. 8, (Aug 2003). pp. 3966-3972, 0021-972X (Print)
- Mamtani, M. Kulkarni, H. (2010), Bone recovery after zoledronate therapy in thalassemia-induced osteoporosis: a meta-analysis and systematic review. *Osteoporosis International*, Vol. 21, No. 1, (Jan 2010), pp. 183-7, 1433-2965 (Electronic)
- Manca, Laura. Masala, Bruno. (2008). Disorders of the synthesis of human fetal hemoglobin. *IUBMB Life*. Vol. 60, No. 2, (Feb 2008), pp. 94-111, 1521-6543 (Print)
- Manias, Karen. McCabe, Debbie. Bishop, Nick. (2006). Fractures and recurrent fractures in children; varying effects of environmental factors as well as bone size and mass. *Bone*. Vol. 39, No. 3, (Sep 2006), pp. 652-657, 8756-3282 (Print)
- Marie, Pierre J. Kassem, Moustapha. (2011). Osteoblasts in osteoporosis: past, emerging, and future anabolic targets. *European Journal of Endocrinology*. Vol. 165, No. 1, (Jul 2011), pp. 1-10, 1479-683X (Electronic)
- Marini, Francesca. Brandi, Maria Luisa. (2010). Genetic determinants of osteoporosis: common bases to cardiovascular diseases? *International Journal of Hypertension*, Vol. 2010, (2010), LID - 394579 [pii], 2090-0392 (Electronic)
- Morabito, Nunziata. Gaudio, Agostino. Lasco, Antonino. Atteritano, Marco. Pizzoleo, Maria Antonia. Cincotta, Maria. La Rosa, Mariangela. Guarino, Roberta. Meo, Anna. Frisina, Nicola. (2004). Osteoprotegerin and RANKL in the pathogenesis of thalassemia-induced osteoporosis: new pieces of the puzzle. *Journal of Bone and Mineral Research*. Vol. 19. No. 5, (May 2004), pp. 722-727, 0884-0431 (Print)
- Muncie, HL Jr. Campbell, J. (2009). Alpha and Beta Thalassemia, *American Family Physician*, Vol. 80, No. 4, Aug 2009, pp. 339-44, 0002-838X (Print)
- Mundy, G R. (1999). Cellular and molecular regulation of bone turnover. *Bone*. Vol. 24, No. 5 supply, (May 1999), 8756-3282 (Print)
- Najafipour, Farzad. Aliasgarzadeh, Akbar. Aghamohamadzadeh, Naser. Bahrami, Amir. Mobasri, Majid. Niafar, Mitra. Khoshbaten, Manouchehr. A cross-sectional study of metabolic and endocrine complications in beta-thalassemia major. *Annals of Saudi Medicine*, Vol. 28, No. 5, (Sep-Oct 2008), pp. 361-366, 0256-4947 (Print)
- Napoli, N. Carmina, Enrico. Bucchieri, Salvatore. Sferrazza, C. Rini, G B. Di Fede, G. (2006). Low serum levels of 25-hydroxy vitamin D in adults affected by thalassemia major or intermedia. *Bone*, Vol. 38, No. 6, (Jun 2006). pp. 888-892, 8756-3282 (Print)
- Orig, R. Fiumana, E. Gamberini, M R. Armari, S. Mottes, M. Sangalli, A. Paglietti, E. Galanello, R. Borgna-Pignatti, C. (2005). Osteoporosis in beta-thalassemia: Clinical

- and genetic aspects. *Annals of the New York Academy of Sciences*, Vol. 1054, (2005), pp. 451-456, 0077-8923 (Print)
- Papanastasiou, Dimitris A. Ellina, Aikaterini. Baikousis, Andreas. Pastromas, Basilis. Iliopoulos, Panos. Korovessis, Panagiotis. (2002). Natural History of Untreated Scoliosis in beta-Thalassemia. *Spine*, Vol. 27, No. 11, (Jun 2002), pp. 1186-1890, 1528-1159 (Electronic)
- Perera, N J. Lau, N S. Mathews, S. Waite, C. Ho, P J. Catterson, I D. (2010). Overview of endocrinopathies associated with beta-thalassaemia major. *Internal Medicine Journal*, Vol. 40, No. 10, (Oct 2010), pp. 689-696, 1445-5994 (Electronic)
- Petropoulou, Anna D. Porcher, Raphael. Herr, Andree-Laure. Devergie, Agnes. Brentano, Thomas Funck. Ribaud, Patricia. Pinto, Fernando O. Rocha, Vanderson. Peffault de Latour, Regis. Orcel, Philippe. Socie, Gerard. Robin, Marie. (2010). Prospective assessment of bone turnover and clinical bone diseases after allogeneic hematopoietic stem-cell transplantation. *Transplantation*. Vol. 89, No. 11, (Jun 2010), pp. 1354-1361. 1534-6080 (Electronic)
- Psihogios, Vicki, Rodda, Christine, Reid, Elizabeth, Clark, Malcolm, Clarke, Caroline, Bowden, Donald. (2002). Reproductive health in individuals with homozygous beta-thalassemia: knowledge, attitudes, and behavior. *Fertility and Sterility*, Vol. 77, No. 1, (Jan 2002), pp. 119-127, 0015-0282 (Print)
- Rabinovich, C. Eglar. (2004). Osteoporosis: a pediatric perspective. *Arthritis and Rheumatism*. Vol. 50, No. 4, (Apr 2004), 0004-3591 (Print)
- Roodman, G David. (2004). Mechanisms of bone metastasis. *The New England Journal of Medicine*. Vol. 350, No. 16, (Apr 2004), pp. 1655-1664, 1533-4406 (Electronic)
- Rund, Deborah. Rachmilewitz, Eliezer. (2005). (MEDICAL PROGRESS)Beta-thalassemia. *The New England Journal of Medicine*. Vol. 353, No. 11, (Sep 2005). pp. 1135-46, 1533-4406 (Electronic)
- Salehi, S A. Koski, T. Ondra, S L. (2004). Spinal cord compression in beta-thalassemia: case report and review of the literature. *Spinal Cord*. Vol. 42, No. 2, (Feb 2004), pp. 117-123, 1362-4393 (Print)
- Sankaran, VG. Nathan, DG. (2010). Thalassemia: an overview of 50 years of clinical research. *Hematology/Oncology Clinics of North America*, Vol. 24, No. 4, (Dec 2010), pp. 1005-1020, 0889-8588 (Print)
- Schonau, E. (1998). Problems of bone analysis in childhood and adolescence. *Pediatric Nephrology (Berlin, Germany)*, Vol 12, No. 5, (Jun 1998), pp. 420-429, 0931-041X (Print)
- Schulte, Claudia M S. Beelen, Dietrich W. (2004). Bone loss following hematopoietic stem cell transplantation: a long-term follow-up. *Blood*, Vol. 103, No. 10, (May 2004), pp. 3635-3643, 0006-4971 (Print)
- Soliman, Ashraf T. Khalafallah, Hany. Ashour, Rasha. (2009). Growth and factors affecting it in thalassemia major. *Hemoglobin*. Vol. 33, No. Suppl 1, (2009), pp. S116-S126, 1532-432X (Electronic)
- Toumba, Meropi. Skordis, Nicos. (2010). Osteoporosis syndrome in thalassaemia major: an overview. *Journal of Osteoporosis*, Vol. 2010, p. 537673, 2042-0064 (Electronic)
- Tyler, P A. Madani, G. Chaudhuri, R. Wilson, L F. Dick, E A. (2006). The radiological appearances of thalassaemia. *Clinical Radiology*, Vol. 61, No. 1, (Jan 2006), pp.40-52, 0009-9260 (Print)
- van Kuijk, Cornelis. (2010). Pediatric bone densitometry. *Radiologic Clinics of North America*. Vol. 48, No. 3, (May 2010), pp. 623-627, 1557-8275 (Electronic)

- Vogiatzi, Maria G. Macklin, Eric A. Fung, Ellen B. Cheung, Angela M. Vichinsky, Elliot. Olivieri, Nancy. Kirby, Melanie. Kwiatkowski, Janet L. Cunningham, Melody. Holm, Ingrid A. Lane, Joseph. Schneider, Robert. Fleisher, Martin. Grady, Robert W. Peterson, Charles C. Giardina, Patricia J. (2009). Bone disease in thalassemia: a frequent and still unresolved problem. *Journal of Bone and Mineral Research*. Vol. 24, No. 3, (Mar 2009), pp. 543-557, 1523-4681 (Electronic)
- Vogiatzi, Maria G, Tsay, Jaime, Verdelis, Kostas, Rivella, Stefano. Grady, Robert W. Doty, Stephen. Giardina, Patricia J. Boskey, Adele L. (2010). Changes in bone microarchitecture and biomechanical properties in the th3 thalassemia mouse are associated with decreased bone turnover and occur during the period of bone accrual. *Calcified tissue international*. Vol. 86, No. 6, (Jun 2010), pp. 484-94, 1432-0827 (Electronic)
- Vogiatzi, Maria G. Autio, Karen A. Mait, Jeffrey E. Schneider, Robert. Lesser, Martin. Giardina, Patricia J. (2005). Low bone mineral density in adolescents with beta-thalassemia. *Annals of the New York Academy of Sciences*. Vol. 1054. (2005), pp. 462-466, 0077-8923 (Print)
- von Scheven, Emily. (2007). Pediatric bone density and fracture. *Current Osteoporosis Reports*. Vol. 5, No. 3, (Sep 2007), pp. 128-34, 1544-1873 (Print)
- Voskaridou, Ersi. Terpos, Evangelos. (2004). New insights into the pathophysiology and management of osteoporosis in patients with beta thalassaemia. *British Journal of Haematology*, Vol. 127, No. 2, (Oct 2004), pp. 127-39, 0007-1048 (Print)
- Wittrant, Y. Gorin, Y. Mohan, S. Wagner, B. Abboud-Werner, S L. (2009). Colony-stimulating factor-1 (CSF-1) directly inhibits receptor activator of nuclear factor- κ B ligand (RANKL) expression by osteoblasts. *Endocrinology*. Vol. 150, No. 11, (Nov 2009), pp. 4977-88, 1945-7170 (Electronic)
- Wonke, B. (1998). Bone disease in beta-thalassaemia major. *British Journal of Haematology*, Vol. 103, No. 4, (Dec 1998), pp. 897-901, 0007-1048 (Print)

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Osteoporosis

Edited by PhD. Yannis Dionyssiotis

ISBN 978-953-51-0026-3

Hard cover, 864 pages

Publisher InTech

Published online 24, February, 2012

Published in print edition February, 2012

Osteoporosis is a public health issue worldwide. During the last few years, progress has been made concerning the knowledge of the pathophysiological mechanism of the disease. Sophisticated technologies have added important information in bone mineral density measurements and, additionally, geometrical and mechanical properties of bone. New bone indices have been developed from biochemical and hormonal measurements in order to investigate bone metabolism. Although it is clear that drugs are an essential element of the therapy, beyond medication there are other interventions in the management of the disease. Prevention of osteoporosis starts in young ages and continues during aging in order to prevent fractures associated with impaired quality of life, physical decline, mortality, and high cost for the health system. A number of different specialties are holding the scientific knowledge in osteoporosis. For this reason, we have collected papers from scientific departments all over the world for this book. The book includes up-to-date information about basics of bones, epidemiological data, diagnosis and assessment of osteoporosis, secondary osteoporosis, pediatric issues, prevention and treatment strategies, and research papers from osteoporotic fields.

How to reference

In order to correctly reference this scholarly work, feel free to copy and paste the following:

Zohreh Hamidi (2012). What We Learn from Bone Complications in Congenital Diseases? Thalassemia, an Example, Osteoporosis, PhD. Yannis Dionyssiotis (Ed.), ISBN: 978-953-51-0026-3, InTech, Available from: <http://www.intechopen.com/books/osteoporosis/what-we-learn-from-bone-complications-in-congenital-diseases-thalassemia-an-example>

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