

**OVERVIEW ON THALASSEMIAS: A REVIEW ARTICLE**

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**Abstract**

Thalassemia's are genetic disorders inherited from a person's parents. Thalassemia's are prevalent worldwide with 25,000 deaths in 2013. Highest rates are in the Mediterranean, Italy, Greece, Turkey, West Asia, North Africa, South Asian, and Southeast Asia. The  $\beta$ -thalassemia major is the most severe form and the affected children are dependent on regular blood transfusions for survival. One of the major complications in chronically transfused patients is development of irregular antibodies and in this situation; further transfusion of compatible red cell is difficult. Hemoglobinopathies imply abnormalities in the globin proteins themselves. Health complications are mostly found in thalassemia major and intermediate patients. Signs and symptoms include severe anemia, poor growth and skeletal abnormalities during infancy. Untreated thalassemia major eventually leads to death, usually by heart failure. Diagnosis by hematologic tests, hemoglobin electrophoresis, and DNA analysis. Individuals with severe thalassemia require blood transfusion, drug therapy i.e. deferoxamine, deferasirox, deferiprone, and bone marrow transplant. Bone Marrow Transplant (BMT) is still remains the only definitive cure available for patients with Thalassemia. Gene therapy for  $\beta$ - Thalassemia is still on trial and a hope for future. Genetic studies (DNA analysis) to investigate deletions and mutations in the alpha- and beta-globin-producing gene help in correct diagnosis and improved management in thalassemic patients. This topic will review the clinical features of thalassemia while focusing on pathophysiology, clinical features, complication, management, screening and diagnosis.

**Keywords - Thalassemia, Hemoglobinopathies, Bone Marrow Transplant, Gene Therapy.**

**Introduction**

The name thalassemia derived from a combination of two Greek words: *Thalassa* meaning the sea (Cooley *et al.*, 1925, 1927; Bradford and Dye, 1936) [1, 2, 3] that is the

Mediterranean and anemia (“weak blood”). Another term found in literature, although infrequently, is Cooley's anemia after the name of Prof. Cooley Thomas, a pediatrician in the USA who first described

the clinical characteristics of this disorder in patients of Italian origin 1925[1, 2]. Thalassemia is genetic blood disorders inherited from a person's parents that can result in the abnormal formation of hemoglobin [4, 5]. There are two main types, alpha and beta Thalassemia [4]. The severity of alpha and beta thalassemia depends on how many of four genes for alpha or two genes for beta globin are missing [5]. Thalassemia are widespread throughout the Mediterranean region, Africa, the Middle East, the Indian subcontinent and South-East Asia [6]. As of 2013 thalassemia occurs in about 208 million people with 4.7 million having severe disease [7]. It resulted in 25,000 deaths in 2013 down from 36,000 deaths in 1990[8]. Males and females have similar rates of disease [9]. Diagnosis is typically by blood tests including a complete blood count, special hemoglobin tests and genetic tests [10]. The current management of  $\beta$ -thalassemia major patient is based on regular transfusion of packed red cells and effective chelating therapy [11-14]. The aim of the transfusion therapy is to correct anemia and to maintain sufficient circulating level of hemoglobin (Hb) to suppress endogenous erythropoiesis [15]. Major complication in chronically transfused patients is iron overload [16]. Thirty years have passed since the first hemopoietic stem cell transplant (HSCT) in thalassemia and this procedure now stands today as a widely applied treatment for the definitive cure of thalassemia major, with more than 3000 HSCTs performed worldwide [17]. Even at a time when we are finally entering the long-awaited gene therapy era, to this day HSCT remains the only available curative option for thalassemia major [18] but It is not possible to manage and afford HSCT in each and every thalassemic patient in Indian subcontinent.

### **Prevalence**

The beta form of thalassemia is particularly prevalent among Mediterranean people, and this geographical association is

responsible for its naming [19]. In Europe, the highest concentrations of the disease are found in Greece, coastal regions of Turkey (particularly the Aegean Region such as Izmir, Balikesir, Aydin, Mugala, and Mediterranean Regions such as Antalya, Adna, Mersin), in parts of Italy, particularly southern Italy and the lower Povalley. The major Mediterranean islands (except Balearics) such as Sicily, Sardinia, Malta, Corsica, Cyprus, and Crete are heavily affected in particular. Other Mediterranean people, as well as those in the vicinity of the Mediterranean, also have high rates of thalassemia, including the people of West Asia and North Africa. Far from the Mediterranean, South Asian are also affected with World's highest concentrations of the carriers (30% of the population) being in the Maldives [20, 21]. Nowadays, it is found in populations living in Africa, the Americas, and Tharus people in the Terai region of Nepal and India [22]. It is believed to account for much lower malaria sickness and deaths [23], accounting for the historic ability of Tharus to survive in areas heavy malaria infestation, where other could not. Thalassemia are particularly associated with people of Mediterranean origin, Arabs (especially Palestinian and people of Palestinian descent), and Asians [24]. Maldives has the highest incidence of Thalassemia in the world with carrier rate of 18% of the population. The estimated prevalence is 16% in people from Cyprus, 1% in Thailand, and 5-10% in Iran, and 3-8% from Bangladesh, China, India, Malaysia, and Pakistan [25,26,27,28]. Thalassemia also occur in descendants of people from Latin America, Mediterranean countries (e.g. Greece, Italy, Spain, and others), and Portugal [25]. A biogeographic analysis with the aid of tools; such as Geographic Information System (GIS) may provide an insight into the non-biological factors influencing different loci in the  $\beta$  -globin gene in different geographical regions [29]

**Pathophysiology**

Normal adult hemoglobin is expressed as A2, A and F (fetal). Ninety-five to ninety-eight percent of adult hemoglobin is A, the major hemoglobin, which consists of two  $\alpha$  - and two  $\beta$  -chains ( $\alpha_2 \beta_2$ ). Hemoglobin A2 ( $\alpha_2, \delta_2$ ), the remainder of hemoglobin in adults is a minor component (less than 3.3%), and 1% or less of F ( $\alpha_2, \gamma_2$ ) [30], the gamma hemoglobin (Hb-F) is the predominant hemoglobin found only during fetal development. The equal production of  $\alpha$  and non-  $\alpha$  ( $\beta, \delta, \gamma$ ) globin chains is necessary for normal red blood cell (RBC) function.

The  $\beta$  globin chains are encoded by a single gene on chromosome 11;  $\alpha$  globin chains are encoded by two closely linked genes on chromosome 16 [31]. Thalassemia occurs when there is decreased or absent production of one of the types of globin chains (most commonly either  $\alpha$  or  $\beta$ ), that cause insufficient amount of normal structure of globin chains. This results in an imbalance between  $\alpha$  - and  $\beta$  -chains and causes the clinical features of Thalassemia [32]; it can be separated into two major types such as  $\alpha$  -thalassemia and  $\beta$  -thalassemia. Thalassemia Syndromes, Genotypes, and clinical features are summarized in table no. 1

**Table No. 1** Thalassemia Genotypes, Syndromes and clinical features

$\alpha$ Thalassemia	$\alpha$ Gene	Globins Chain	Hemoglobin	Clinical features
<b>Normal</b>	$\alpha\alpha / \alpha\alpha$	$\alpha_2 \beta_2$	A	Normal
<b>Silent carriers</b>	$\alpha\alpha / \alpha -$	$\alpha_2 \beta_2$	A	Asymptomatic
<b>Trait (minor)</b>	$\alpha - / \alpha -$ $- - / \alpha\alpha$	$\alpha_2 \beta_2$	A	Asymptomatic
<b>Hb H disease</b>	$- - / - \alpha$	$\alpha_2 \beta_2, \beta_4$	A, H	Jaundice, splenomegaly, occasionally need transfusion;
<b>Hydrops Fetalis</b>	$- - / - -$	$\gamma_4, \xi_2 \gamma_2$	Barts, Portland	Lethal, Death in utero or shortly after birth
$\beta$ Thalassemia	$\beta$ Gene	Globins Chain	Hemoglobin	Clinical features
<b>Normal</b>	$\beta / \beta$	$\alpha_2 \beta_2$	A	Normal
<b>Thalassemia minor (Trait)</b>	$\beta^+ / \beta$ $\beta^0 / \beta$	$\alpha_2 \beta_2, \alpha_2 \delta_2, \alpha_2 \gamma_2$	A, A <sub>2</sub> , F	Asymptomatic
<b>Thalassemia Intermediate</b>	$\beta^+ / \beta^0$ $\beta^+ / \beta^+$	$\alpha_2 \beta_2, \alpha_2 \delta_2, \alpha_2 \gamma_2$	A, F	clinical phenotype between thalassemia trait & thalassemia major
<b>Thalassemia Major</b>	$\beta^+ / \beta^+$ $\beta^0 / \beta^0$	$\alpha_2 \beta_2, \alpha_2 \delta_2, \alpha_2 \gamma_2$ $\alpha_2 \delta_2, \alpha_2 \gamma_2$	A, A <sub>2</sub> , F F, A <sub>2</sub>	Require chronic transfusion; iron overload in endocrine abnormalities and chronic organ damage
<b>HPFH</b>	$\gamma / \gamma$	$\alpha_2 \gamma_2$	F	Mild

The most common combination of  $\beta$ -thalassemia with abnormal Hb or structural Hb variant with thalassemic properties is Hb-E/ $\beta$ -thalassemia which is most prevalent in an area stretching from northern India and Bangladesh, through Laos, Cambodia, Thailand, Vietnam, Malaysia, the Philippines, and Indonesia [33]. These Hb-E/beta-Thalassemia may have mild to severe symptoms. In our previous study, we found that Hb-E/ $\beta$ -Thalassemia is the second most common cause of transfusion-dependent thalassemia in the Gwalior and Chambal region of central India [34].

The Pathophysiology of alpha thalassemia is different to that of beta Thalassemia. A deficiency of  $\alpha$  chain leads to the production of excess chains or  $\beta$  chains, which form Hb Bart's and Hb H respectively. These soluble tetramers do not precipitate in the bone marrow and hence erythropoiesis is more effective than in  $\beta$  Thalassemia [35]. Unlike the deletion that constitute most of the alpha thalassemia syndromes, beta thalassemia is caused by mutation on chromosome 11 that affect all aspect of beta globin production: transcription, translation, and the stability of the beta globin production [36]. Monitoring of the dose of iron chelator, according to the type of mutation in the beta globin gene, may help to improve the compliance of beta thalassemic to chelation therapy and prevent side-effects in patients with beta plus mutations [37]. Alpha hemoglobin stabilizing protein has a causal relationship with the severity of beta Thalassemia [38].

The molecular defects in  $\beta$  thalassemia result in absent or reduced  $\beta$  chain production. Alpha chain synthesis is unaffected and hence there is imbalanced globin chain production leading to an excess of  $\alpha$  chains. In the absence of their partners, they are unstable and precipitate in the red cell precursors, giving rise to large intracellular inclusions, which interfere with red cell maturation. Hence, there is a variable degree of intramedullary

destruction of red cell precursors (i.e. ineffective erythropoiesis). Those red cells that mature and enter the circulation contain  $\alpha$  chain inclusion, which interfere with their passage through the microcirculation, particularly in the spleen. These cells, which show a variety of abnormalities of membrane structure and permeability, are prematurely destroyed and thus the anemia of  $\beta$  thalassemia results from both ineffective erythropoiesis and a shortened cell survival. The anemia acts as a stimulus to erythropoietin production and this causes expansion of the bone marrow, which may lead to serious deformities of the skull and long bones. Because the spleen is being constantly bombarded with abnormal red cells, it hypertrophies [36].

#### **Clinical Manifestations**

Three main forms have been described thalassemia major, thalassemia intermediate and thalassemia minor. Alpha thalassemia silent carriers generally have no signs or symptoms of the disorder. People who have alpha or beta thalassemia trait can have mild anemia. However, many people with this type of thalassemia may be asymptomatic or experience very few symptoms. Symptoms may be worse in individuals that are pregnant, under stress, or malnourished. Symptoms may include: Fatigue. This may be the only symptom that an individual with beta thalassemia minor exhibits [39] (Satwani et al., 2005). People with beta thalassemia intermedia have mild to moderate anemia. In the beta thalassemia intermedia, the patients with Hb of much below 7 or 8 gm/dl excess energy consumption due to the profound hemolysis can produce small stature, poor weight gain, poor energy levels, susceptibility to infection and yellow discoloration (jaundice) of the skin, eyes, and mucous membranes caused by increased amount of bilirubin in the blood. Beta Thalassemia major (also called Cooley's anemia) has severe form of Thalassemia and symptoms appears in first two years of life. Affected infants fail to thrive and gain weight normally and

become progressively pale. Feeding problems, diarrhea, irritability, fever and progressive enlargement of the abdomen due to splenomegaly and prominence of the cheek bones tends to obscure the base of the nose and to expose the upper teeth, puffiness of the eyelid and a tendency to a Mongoloid slant of the eyes are common presenting symptoms [40]. People with hemoglobin H disease have severe thalassemia. Signs and symptoms occur within the first 2 years of life. They may include severe anemia and other serious health problems, such as: Pale and listless appearance, Poor appetite, Dark urine. The Hydrops Fetalis Syndrome is recognized by the finding of a hydropic infant with a severe anemia, a thalassemic blood picture, and the presence of 80% or more Hb Barts on hemoglobin electrophoresis [41].

Complication of  $\beta$ -thalassemia includes iron over load, infections, bone marrow deformities, enlarged spleen, and slow growth rate and heart problems. People with  $\beta$ -thalassemia can get an overload of iron in their bodies, either from the disease itself or from frequent blood transfusions. Too much iron can result in damage to the heart, liver, and endocrine system, which includes glands that produce hormones that regulate processes throughout the body [42]. People with thalassemia have an increased risk of infection. This is especially true if the spleen has been removed [43]. Thalassemia can make the bone marrow expand, which causes bones to widen. This can result in abnormal bone structure, especially in the face and skull. Bone marrow expansion also makes bones thin and brittle, increasing the risk of broken bones [44]. The spleen aids in fighting infection and filters unwanted material, such as old or damaged blood cells. Splenomegaly can make anemia worse, and it can reduce the life of transfused red blood cells. Severe enlargement of the spleen may necessitate its removal [45]. Anemia can cause a child's growth to slow. Puberty also may be delayed in children with Thalassemia [46].

Heart Diseases, such as congestive heart failure and abnormal heart rhythms, may be associated with severe Thalassemia [47].

### **Diagnosis**

Several laboratory tests may be used to help detect and diagnose Thalassemia like: Complete blood count (CBC), Blood smear, Iron studies, Hemoglobinopathy (Hb) DNA analysis (Genetic testing) [48], and prenatal testing (Genetic testing of amniotic fluid) [49]. The step in the diagnosis of the different forms of thalassemia include the initial recognition of the disease as thalassemic disorder and its differentiation from other congenital and acquired disorder of hemoglobin synthesis which can mimic the thalassemia syndromes [39]. In silent carrier state Thalassemic Patients are essentially asymptomatic and the CBC, hemoglobin electrophoresis, and peripheral smear are usually normal. Slight hypochromia and microcytosis may be evident by microscopic evaluation. In alpha thalassemia minor the red cell is abnormal with microcytosis, hypochromia, and elevated amount of Hb Bart noted (3%-8%) [39].

The Hydrops Fetalis syndrome is recognized by the finding of a hydropic infant with a severe anemia, a thalassemic blood picture, and the presence of 80% or more Hb Barts on hemoglobin electrophoresis [40]. The homozygous for the severe form of beta thalassemia are easily recognized by the hematological change with very high level of Hb F; Hb A<sub>2</sub> values. The heterozygous states are recognized by microcytic hypochromic red cells and elevated level of Hb A<sub>2</sub> [41].

DNA analysis tests are used to help confirm mutations in the alpha and beta globin-producing genes. DNA testing is not routinely done but can be used to help diagnose thalassemia and to determine carrier status, if indicated. More than 250 mutations have been associated with beta thalassemia, though some cause no signs or symptoms. However, others decrease the amount of beta globin

production and some prevent it completely. The presence of one of those mutations confirms a diagnosis of beta thalassemia. The primary molecular test available for alpha thalassemia detects common mutations (e.g., deletions) in the two alpha genes HBA1 and HBA2. Each person has two copies of each of these genes, called alleles, in their cells, one from their mother and one from their father. These alleles govern alpha globin production and if mutations lead to functional loss of one or more of alpha genes, alpha thalassemia occurs. Genetic testing of amniotic fluid is issued in the rare instances a fetus is at increased risk for thalassemia. This is especially important if both parents likely carry a mutation because that increases the risk that their child may inherit a combination of abnormal genes, causing a more severe form of Thalassemia [50].

#### **Treatment**

Most individuals with mild thalassemia traits require no treatment. They may want to consider genetic counseling, however, because they may pass the mutant gene on to their children [51]. People with hemoglobin H disease or beta thalassemia intermedia will experience variable amounts of anemia throughout their life. They can live relatively normal lives but will require regular monitoring and may occasionally need blood transfusion. Folic acid supplementation is often given, but iron supplementation is not recommended. [52]. Hb Bart hydrops Fetalis syndrome or alpha thalassemia major currently has no effective treatment and babies are usually miscarried, stillborn, or die shortly after birth. Attempts at intrauterine transfusions, after early prenatal detection with Doppler ultra-sonography of this condition, have been conducted, but most survivors experienced a high prevalence of congenital malformations [53, 54] and attempts should be discouraged until more effective therapies (e.g., somatic gene therapy) are available [51].

Treatment of individuals with thalassemia intermedia is symptomatic. As

hypersplenism may cause worsening anemia, retarded growth and mechanical disturbance from the large spleen, splenectomy is a relevant aspect of the management of thalassemia intermedia [55-57].

Presently, till today the Bone Marrow Transplant (BMT) is still remains the only definitive cure available for patients with Thalassemia. Gene therapy for  $\beta$ -Thalassemia is still on trial and a hope for future [58, 59]. First successful BMT was done in 1980s by Prof. Guido Lucarelli. In low risk young patients, the thalassemia-free survival is 87%, the mortality is 3 %. The drawback is that this curative method required an HLA (Human leukocyte Antigen)-matched compatible donor [60]. If the patient does not have an HLA-matched donor such as the first curative method requires, there is another curative method called Bone Marrow Transplantation(BMT) from haploidentical mother to child (mismatched donor), in which donor is the mother. It was invented in 2002 by Doctor Pietro Sodani. The results are: thalassemia free survival rate 70%, rejection 23 %, and mortality 7%. The best results are with very young patients [61]. BMT treatment for thalassemia is still not available for all patients in Indian perspective, at our center out of 120 patients only one patient has gone for successful bone marrow transplant [62].

The current management available for majority of  $\beta$ -thalassemia major patient in low socio-economic countries like India is regular transfusion of packed red cells; effective chelating therapy and management of complications of iron overload [16]. The aim of the transfusion therapy is to correct anemia and to maintain circulating level of hemoglobin (Hb) sufficient to suppress endogenous erythropoiesis [15]. In transfusion dependent Thalassemia, the superiority of regularly repeated transfusions, as compared to transfusions only for symptomatic anemia, was first recognized

by Orsini in France and later by Wolman and Piomelli in US, who suggested a transfusion program aimed at monitoring a basal Hb level sufficient to eliminate hypoxia [63, 64]. Several different regimens like hyper transfusion regimen (the pre-transfusion Hb is maintained as >10 gm/dl with mean Hb of about 12 gm/dl, immediate post transfusion Hb rising to 14 gm/dl and returning to baseline after 3–4 weeks) , Super transfusion regimen (the pre-transfusion Hb is maintained at  $\geq 11$  gm/dl or a hematocrit of more than 35% with a mean Hb of about 14 gm/dl), while in moderate transfusion regimen the pre-transfusion Hb is maintained at the values between 9 and 10 gm/dl and to reach a post-transfusion level of 13 to 14 gm/dl have been proposed over the years. This prevents growth impairment, organ damage and bone deformities, allowing normal activity and quality of life, and is associated with relatively low rates of blood requirement and of iron accumulation [65]. The amount of blood to be transfused depends on several factors including the weight of the patient, and the target increase in Hb level. Appropriate graphs and formulae to calculate the amount of blood to be transfused are available [66, 67]. In general, the amount of transfused RBC should not exceed 15 to 20 ml/kg/day, infused at a maximum rate of 5 ml/kg/hour to avoid a fast increase in blood volume.

**Characteristics of blood products for transfusion:** Careful selection of healthy voluntary donors is a prerequisite for obtaining safe blood units for patients with thalassemia. To avoid transfusion reactions from anti-leukocyte and anti-platelet antibodies and transmission of viral agents present in leukocytes such as cytomegalovirus, patients with thalassemia should receive leukoreduced packed red cells [68, 69]. In the patients sensitized to plasma proteins washed red cells may be beneficial. Extended red cell antigen typing including at least Rh antigens, Duffy, Kidd and Kell is recommended before starting

transfusions to avoid alloimmunization against red cells. Prevalence of Alloimmunization at our center was 3.3% [61]. Author(s) has also used other blood components like Neocytes concentrate/pooled Neocytes and whole umbilical cord blood to the thalassemic patients in his previous studies and results are fruitful [70,71].

Iron overload is the most relevant complication associated with transfusion therapy. When Patient is on a regular transfusion regimen progressively develop clinical manifestations of iron overload: hypogonadism (35-55% of the patients), hypothyroidism (9-11%), hypoparathyroidism (4%), diabetes (6-10%), liver fibrosis, and heart dysfunction (33%) [40, 41]. A unit processed from 420 ml of donor blood contains approximately 200 mg of iron, or 0.47 mg/ml of whole donor blood. Normal intestinal iron absorption is about 1-2mg/day. In patients with thalassemia who do not receive any transfusion, iron absorption increases several-fold. It has been estimated that iron absorption exceeds iron loss when expansion of red cell precursors in the bone marrow exceeds five times that of healthy individuals [72]. Iron status should be accurately assessed in order to evaluate its clinical relevance, the need for treatment, and the timing and monitoring of chelation therapy. The iron status of multi-transfused patients can be assessed by several methods. Serum ferritin has in general been found to correlate with body iron stores [73]. In recent years, nuclear magnetic resonance imaging (MRI) techniques for assessing iron loading in the liver and heart have been introduced [74-75]. As the body has no effective means for removing iron, the only way to remove excess iron is to use iron binders (chelator), which allow iron excretion through the urine and/or stool. As a general rule, patients should start iron chelation treatment once they have had 10-20 transfusions or when ferritin levels rise above 1000 ng/ml [76].

Mainly three chelation drugs available in the market are deferoxamine (DFO), deferiprone (DFP) and Deferasirox (DFX). The first drug available for treatment of iron overload was deferoxamine (DFO), an hexadentate iron chelator that is not orally absorbed and thus needs parenteral administration, usually as a subcutaneous 8- to 12-hour nightly infusion, 5-7 nights a week. Average dosage is 20-40 mg/kg body weight for children and 30-50 mg/kg body weight for adults [76, 77]. Second drug deferiprone (DFP), orphan drug is an orally active iron chelator which has emerged from an extensive search for new treatment of iron overload. Comparative studies have shown that this chelator, at doses of 75-100 mg/kg/day may be as effective as DFO in removing body iron [78]. Third drug, Deferasirox (DFX) is a once-daily, orally administered iron chelator that a large program of clinical trials has shown to be effective in adults and children [79, 80]. It received European Union marketing authorization as an orphan drug from the EMEA in 2002 and was authorized for marketing in most countries in 2006.

### **Complications**

In developed countries, patients are given routine transfusion therapy, which has lengthened survival and altered the clinical course of the disease. To prevent alloimmunization extended blood grouping including Complete Rh, Kell, Duffy, Kidd along with ABO grouping should be done and identical blood is transfused after proper cross matching to the transfusion dependent thalassemic patients [62]. Patients maintained on a regular transfusion regimen progressively develop clinical manifestations of iron overload: hypogonadism (35-55% of the patients), hypothyroidism (9-11%), hypoparathyroidism (4%), diabetes (6-10%), liver fibrosis, and heart dysfunction (33%) [40,41]. Iron overload of tissue with or without transfusion is fatal, which is the most important complication of  $\beta$ -thalassemia if not prevented or adequately

treated, now it is a major focus of management [81]. Serum ferritin has in general been found to correlate with body iron stores [82]. After approximately one year of transfusions, iron begins to be deposited in parenchymal tissues [83]. Morbidity and mortality are now the result of chronic transfusion induced iron overload and most patients die of heart dysfunction of iron deposition [84]. Iron accumulation in the liver causes fibrosis and cirrhosis [85]. Endocrine abnormalities related to iron overload include diabetes mellitus and impaired glucose tolerance, adrenal insufficiency, hypothyroidism, osteoporosis, hypoparathyroidism and hypogonadism [85]. In most studies, bone density is markedly reduced (cause osteoporosis) in patients with  $\beta$ -thalassemia, particularly those with hypogonadism. Osteopenia may be related to marrow expansion, even in patients who receive transfusions, [86] or to iron induced osteoblast dysfunction, diabetes, hypoparathyroidism, or hypogonadism [87]. Indications for splenectomy are symptoms of splenic enlargement, leukopenia and/or thrombocytopenia and increasing iron overload despite good chelation [88].

### **Conclusion**

Thalassemia are inherited disorder; beta thalassemia has high severity, presented by mild to severe anemia. Diagnosis by Complete blood count (CBC), Blood smear, Iron studies, Hemoglobinopathy, DNA analysis (Genetic testing), and Prenatal testing (Genetic testing of amniotic fluid). Treatment of Individuals with severe anemia is via regular blood transfusion, iron chelation, splenectomy, and bone marrow transplant. Prevention is by premarital screening, carrier detection and prenatal testing. The prognosis of  $\beta$  thalassemia major was very grim with no treatment; the natural history was for death by age five from infections and cachexia. Survival was prolonged by transfusion and chelation therapy into the second decade, but it is evident that the



treatment that saved lives in children caused death from cardiac disease in adolescence or early childhood. Bone Marrow Transplant (BMT) is still remains the only definitive cure available for patients with Thalassemia. Gene therapy for  $\beta$ - Thalassemia is still on trial and a hope for future. Genetic studies (DNA analysis) to investigate deletions and mutations in the alpha- and beta-globin-producing gene help in correct diagnosis and improved management in thalassemic patients.

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#### Conflict of Interest

Authors have declared that there are no Conflict of interests.

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