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# Thalassemia: Current Situation in Pakistan

*Aisha Khalid*, Abdul Mueed Khalil Butt, Ruba Shahid, Amsha Hoor*

Knowledge Unit of Sciences, Department of Biochemistry, University of Management and Technology, Daska Road, Sialkot Campus, Pakistan.

*** Corresponding Author's Email ID: aisha.khalid@skt.umt.edu.pk**

**ABSTRACT:** *Thalassemia, inherited genetic disorder is among the main medical issues facing Pakistan like many other countries of the world. The main factor of thalassemia prevalence with frequent rate in Pakistan is consanguineous marriages causes misery not only to the patients but for their families also. The current treatment strategies such as blood transfusion, chelation therapy (Fe), bone marrow and stem cell transplantation are not compatible due to high iron load, development of alloantibodies, arthritis and severe agranulocytosis like side effects. In developed countries regular screening of pregnant women is done to control the prevalence of Beta-thalassemia but in Pakistan genetic counselling and parental diagnosis resources are limited to control the birth rate. Additionally, in the absence of coherent policy at national level creates more pressure on the health care system of the country. Thalassemia in Pakistan is managed by traditional diagnostic methods, such as chromatography, Hb electrophoresis and ARMS-PCR. The ARMS-PCR can only detect the commonly known mutations while the other ethnic specific, novel mutations remain obscure. Next-generation sequencing (NGS) offers advantages over standard PCR, including higher sensitivity and the ability to identify novel mutations. Health system and cultural issues creates hurdles to implement the policies of public health genomics in Pakistan. So, the government of Pakistan must take some measure to ensure the health quality of human and also make short and long term policies to overcome this genetic disorder.*

***Keywords:*** *Thalassemia, Inherited genetic disorder, Pakistan, Consanguineous marriages, Health system and Policies*

## INTRODUCTION

Thalassemia, a Greek word meaning "sea blood" is autosomal recessive disorder caused by less hemoglobin (Hb) production due to the presence of defective gene for the synthesis of alpha and beta globulin chain (Shakeel et al., 2016). Globally, it is the second most common hemoglobinopathy after sickle cell disease (Khalid et al., 2019). Pakistan unfortunately lies among the most thalassemia burdened countries of world and have high prevalence rate of alpha and beta type among the population (Zaheer et al., 2020). Alpha- thalassemia is caused by reduction of alpha-globulin chain of hemoglobin that leads to excess of beta-chains which form Hb Bart's (Khan et al., 2015). Cooley and Lee in 1925 first characterized the inherited disorder of Beta-thalassemia is due to reduced synthesis of globin chains leading to synthesis of hemoglobin with an impaired oxygen binding capacity (Adil et al., 2012). In Pakistan; this inherited hemoglobinopathy has 5-7% of gene carrier frequency so, the general population has roughly 9.8 million carriers pool (Ehsan et al., 2020).

### Beta-thalassemia

This type is further divided into Beta-thalassemia major, intermedia and minor as well. Beta-thalassemia major is also termed as Cooley's anemia / Mediterranean anemia causing patient to become transfusion dependent and occur if two persons carrying a single copy of defected Beta-globulin gene give birth to an offspring. However, those with Beta-thalassemia intermedia and minor show less severity in symptoms because of having one copy of gene and act as carrier. Moreover, 200 different types of mutations have been reported causing diverse level of Beta-globulin gene expression (Muhammad et al., 2017).

### Prevalence rate of Thalassemia

World Health Organization (WHO) reported that now thalassemia has most prevalence rate as inherited genetic disorder in the world due to the migration. Globally, it is estimated that around 30, 000 out of 56, 000 conceptions have been affected by the Beta-thalassemia (Khalid et al., 2019).

Thalassemia gene in Pakistani population is found in affected families only rather than distributed randomly (Ahmed et al., 2016). Pakistan has the highest prevalence of children infected with Beta- thalassemia in the world due to consanguineous marriages, disease gene frequency, high birth rate, large pedigree size and other social culture factors like low income and lack of awareness (Muhammad et al., 2017).

### Public and Private Sector Organization

In Pakistan management program of thalassemia poses great challenge as the ideal management program should accomplish the multidisciplinary team to address the all aspects. However, In Pakistan more than 40 public and private/Non-Government organizations

(NGO) including Ganaga Ram hospital Lahore, Fatimid Foundation Multan Center, Pakistan Thalassemia Center, Islamabad, Kashif Iqbal Thalassemia Care Center, Karachi and Sundas Foundation Lahore etc. are working for cure and eradication of thalassemia (Asif and Hassan, 2016).

Globally, many countries such as Italy, Iran and Greece have successfully managed and eradicate the thalassemia from their population via establishment of excellent healthcare program. Developing countries like Pakistan need more platforms at national level and more efforts are required for future management and prevention of thalassemia in population. The government should also establish the Technical Advisory Group (TAG) at district level of Pakistan for the complete guidance of the effected families (Zaheer et al., 2020). The other responsibilities of these TAG are to conduct awareness program about the thalassemia at local level even in school and colleges for future eradication objective.

**Treatment Measures and their Complications**

Currently, this heterozygous disorder in Pakistan is coped by repeating the blood transfusion, chelation therapy and transplantation (bone marrow or stem cell) (Muhammad et al., 2017). Thalassemia major patients in Pakistan suffering a severe myocardial iron load due to repeated blood transfusion cycles (Alvi et al., 2016). The multiple blood transfusions in thalassemia patient cause the production of alloantibodies against the foreign red blood cells as a most common side effect (Zaheer et al., 2020). The immunity status and antigenic variation between the recipient and donor's blood originated the phenomena of alloimmunization in thalassemia patient. This complication further creates serious difficulty in matching the compatible blood for recipient and leads to life-threatening condition (Qidwai et al., 2018).

The developing countries including Pakistan are at high risk of getting transfusion transmitted viral infections such as human immunodeficiency syndrome (HIV), hepatitis C virus (HCV) and hepatitis B virus (HBV) due to repeated blood transfusion (Ahmed et al., 2016). The other factors which caused high prevalence of viral infection in thalassemia patient in Pakistan are inadequacy of blood banks, poorly managed transfusion safety standards, limited and costly medical facilities etc. The frequency of HCV spread in thalassemia patients (32.1%) is 6 times greater as compared to non-thalassemia ones (6.2%). Research studies also revealed that in Pakistan, the prevalence of HCV infection in β-thalassemia patients is higher in Punjab (45.98%) as compared to Sindh (31.81%) and Khyber Pakhtunkhwa (28.04%) (Sabiha et al., 2020).

Hemochromatosis (Iron overload) in β-thalassemia patients is another worst

form of complication due to frequent blood transfusion (Ahmed et al., 2016). Excess iron gets accumulated in different organs like liver, pancreas, kidney and hearts and caused oxidative stress by converting the molecular oxygen into reactive radical species.

In β-thalassemia patients, there is an abnormal regulation of ferritin protein is also recorded which basically control the regulation of iron in human body. Renal dysfunction in patients with β-thalassemia is caused by iron overload, long-lasting anemia, toxicity of defroxamine (an iron chelating agent) and chronic hypoxia (Rasool et al., 2016). The uric acid level in β-thalassemia patients is significantly higher as compared to non-thalassemia patients. Similarly, abnormality of enzymes like serum alanine transaminase, alkaline phosphatase and aspartate aminotransferase suggests that the thalassemia patients have developed the chronic malfunction. Patients with Beta-thalassemia also have high level of lipid peroxidation products like Malondialdehyde (MDA). It is usually suggested that MDA (a biomarker) and serum ferritin has a strong association with each other and these two parameters play a vital role to estimate the cellular damage in thalassemia (Rasool et al., 2016).

Iron chelating drugs with various mode of administration are used for beta-thalassemia patients but it has side effects such as arthritis 5-20%, severe agranulocytosis 0.5% and neutropenia 5% were observed (Olivieri and Brittenham, 1997; Ejaz et al., 2015). Pakistan which is considered as low income country has limited resources of bone marrow transplantation for the β-thalassemia patient besides its significant result (Riaz et al., 2019). The supply of safe blood transfusion and iron chelation therapy is another hurdle due to poor medical and high cost facilities.

In developed countries of the world the screening of pregnant women for beta-thalassemia is routinely performed but in Pakistan the situation is different because of large population mostly living in remote areas. So, it is not advisable to screen the whole population with limited national resources. In developing countries of the world like Pakistan most of the pregnancies segregate beta-thalassemia due to lake of awareness program about prenatal screening at national level. Recently, screening of affected families is considered as more practical, feasible and cost effective strategy (Muhammad et al., 2017).

**Diagnostic Methods**

The study of prevalence of β-thalassemia mutations in Mardan Division of Khyber Pakhtunkhwa (KPK) province, Pakistan, gave valuable information which can be used in thalassemia prevention programs such as genetic counselling and prenatal diagnosis (PND) to control the population of affected births (Shakeel et al., 2016). So far, in Pakistan, thalassemia is managed by traditional

diagnostic methods, such as chromatography, Hb electrophoresis and ARMS-PCR. These methods cannot always detect serious thalassemic condition resulting from deletions. The ARMS-PCR can only detect the commonly known mutations, while the ethnic specific, novel mutations remain obscure. Next-generation sequencing (NGS) offers advantages over standard PCR, including higher sensitivity and the ability to identify novel mutations. Next-generation sequencing is considered as a competitive screening method capable of detecting thalassemia carrier rates of 49.5% in contrast to traditional molecular methods identifying only 22.0% in the Chinese population. For the first time, this study attempted to use high throughput sequencing technology in diagnosis of beta-thalassemia in a Pakistani family of Pashtun ethnicity. The application of this high-throughput sequencing approach led to the identification of a pathogenic frameshift variant A>A/AC (rs35699606) on the HBB gene (Sabiha et al., 2020).

**Factors and Economic Cost on Thalassemia in Pakistan:**

There are two possible risk factors behind thalassemia, one is family history, in which the genes for thalassemia are inherited from parents to offspring and other is ancestry, which shows high prevalent rate among people of Greek, Middle Eastern, Italian, Southern Asian (Dhanya et al., 2020). In Pakistan, families of the thalassemia patients required approximately 8-10k per month amount for the regular blood transfusion and medication. Ishfaq (2016) did a research study on 500 major thalassemia patients from The Children's Hospital & the Institute of Child Health Multan. Results revealed that Saraiki background families are more affected among the other ethnic groups in Pakistan as shown in below table 1. The data also evaluate that 59.12% of the families have monthly income of around 10,000 PKR which create more critical condition for the respondent families.

**Table 1: Representing the Thalassemia patient frequency among the different ethnic groups from "The Children's Hospital & the Institute of Child Health" Multan, Pakistan.**

| Sr. No. | Ethnic Groups | Frequency |
|---|---|---|
| **1.** | Saraiki | 43.0% |
| **2.** | Urdu | 21.6% |
| **3.** | Balouchi | 19.0% |
| **4.** | Pathan | 5.8% |
| **5.** | Punjabi | 5.8% |
| **6.** | Sindhi | 0.6% |

Economically, the huge amount of cost is required for treatment of thalassemia. Comprehensive treatment of 60,000 registered patients cost 7.8 billion rupees per year. On an average, blood transfusion cost is Rs 30,000 per year per child and cost of iron chelation is Rs 150,000 per year per child. Major part of this mentioned cost is covered by the effected families themselves or in collaboration with NGOs. Journal of Pakistan Medical association in 2020 reported that around 3.5 billion rupees would be saved via managing the 40 to 50% of thalassemia patient blood requirements.

**Social Obstacle**

Unfortunately in Pakistan social and cultural issues such as inter-family marriages (46–62%), home birth rate (80%), limited literacy ratio, increasing population with low level of health care resources especially in the rural areas resist the implementation of public health policy (Zaheer et al., 2020). The researcher investigation revealed the five major mutations such as IVS 1–5(G→C), Fr 8/9 (+G), Fr 41/42(-CTTT), IVS 1–1 and Del 619 in major ethnic group including Punjabi, Pathan, Sindhi and Balochi from different district of Karachi, Pakistan. Further analysis also explore that the frequency of IVS 1-5 (G→C) was around 44.4% in thalassemia patient of Pakistan among the other type of mutations (Usman et al., 2009).

**Recommendations**

According to WHO in developing countries, genetic testing services at early stage potentially lower the 70% of birth defects ratio in general population. In countries like Pakistan, prevention is least expensive and most effective means to deal with beta-thalassemia. It is therefore prerequisite to investigate the molecular basis and natural history of these disorders to establish the most cost effective methods for their control and management (Ahmed et al., 1996; Mu and Lodhi, 2014; Hoodbhoy et al., 2019). The data from the low income countries also revealed that clinical services for the Thalassemia major patients were significantly improved due to the government support over the last few years (Allen et al., 2016).Now there is need to strengthened the clinical care services not only at national level but also at the community level via establishing the program for awareness (Riaz et al., 2019). Government should take initiatives like population based education programs based on health belief programs and Government should also implement mass screening for carrier detection to tackle this hazardous issue. To stop the spreading of this disorder, there is a challenge that should be accepted by our Government to prevent this issue and the challenge is the establishment of national preventive program with joint efforts of Government, NGOs (Non-Government Organizations), legislations and thalassemia societies (Khalid et al., 2019).

**Future Perspectives**

The management of monogenic disease of thalassemia just like other disorders such as sickle cell anemia is majorly hampered due to lack of adequate knowledge as compared to the developed countries of the world (Weatherall, 2010). Government should have to take some major steps to improve and ensure the quality health of Pakistani people. Public Health Genomics (PGH) is an organization that provides health benefits across a wide range of clinical setting and provide health benefits at the population level. The goal of genomics is to improve public health outcomes, including treatment and prevention of various diseases at population level but Pakistan is a developing country, here genetic services are still unavailable to most of the people. There are multiple opportunities which are not provided properly to the people in Pakistan like National newborn screening program, public health genomics, framework and various clinical genetic testing services (Riaz et al., 2019).

In this study, there is a proposal of some short-term (3-5 years) and long-term (10-15 years) public health genomic goals in Pakistan, so that Pakistan can overcome this genetic disorder.

1. Pakistan should invest in professional trainings so people get knowledge and can aware others.
2. NBS (New born screening program) should be established in Pakistan to diagnose genetic disorder that can be treated at the time of birth.
3. Establishment of advisory panel of expert Pakistani researchers, who have enough knowledge to advise Government on various relevant issues related to genomic in Pakistan.
4. Development of a national public health genomics policy framework.
5. Government should invest national funds in clinical genetic testing and genomic research (Riaz et al., 2019).
6. A platform known as "Technical Advisory Group (TAG) on thalassemia" should develop narrative consultations at the national level, which include experts, NGOs, parents, patients and other stakeholders. The result of this platform should be comprehensive National Thalassemia Policy with the consent to control the aspects of thalassemia (Zaheer et al., 2020).
7. In a study, it is said that the patients with β-thalassemia intermedia trait are at the risk of converting into β-thalassemia major. That is why to prevent it genetic testing and clinical analysis should be performed (Khan et al., 2015).
8. Future investigations should include large scale sample sizing for the better findings of β-thalassemia mutations (Shakeel et al., 2016).
9. For the long term control and to prevent the β-thalassemia, characterization at molecular level and the genetic counselling are the most important implementation.
10. Effective screening is needed for the prevention of TTIs in the patients of β-thalassemia (Ahmed et al., 2016).

## CONCLUSION

This manuscript elaborates the importance of establishment of community level program for the counseling of effected families and completes eradication of thalassemia in Pakistani population along with national scale prevention program. The government should specify the reasonable budget amount for the financial support, treatment of thalassemia patients and its future prevention from Pakistan.

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