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DIABETES MELLITUS IN β THALASSAEMIA MAJOR - PATHOGENESIS AND MANAGEMENT STRATEGIES

Shivani G. Varmani[1*], Kritika Mehta[1], Meenakshi Garg[2] and Susmita D. Sadhu[3]
Department of [1]Biomedical Science, [2]Food Technology, [3]Polymer Science, Bhaskaracharya College of Applied Sciences, Sector-2, Phase-I, Dwarka, New Delhi.

[*]Corresponding author: shivani.varmani@gmail.com

ABSTRACT

Thalassaemia an autosomal recessive genetic disorder is associated with a defect in the production of haemoglobin (Hb). It results in the imbalance of α and β globin chains due to reduced or lack of production of one of the globin chains. In particular, β thalassaemia results from defective synthesis of β globin. There is an accumulation of α globin. The most popular management strategy entails regular blood transfusion so that the haemoglobin levels are maintained in the normal range. The major drawback of transfusion therapy is chronic iron overload in the patients. Further, deposition of iron in the vital organs in these subjects leads to alterations in the functioning of various organs and organs systems. To overcome this major challenge iron chelation therapy is administered. Endocrine dysfunction is a major complication resulting from iron overload. Diabetes mellitus, being one of the major, results from the impairment in glucose homeostasis. Generally, it occurs during the second decade of life. The other reasons in addition to iron overload are β cell destruction, hepatitis C virus infections, autoimmunity etc. Various management and preventive strategies should be regularly employed. Dietary recommendations include low carbohydrate food, low iron intake, high calcium foods, etc to improve the quality of life in the patients. Assessment of diabetes should be aggressively and regularly done in these patients. Awareness should be created about this disease so as to curb its prevalence.

Key words: Thalassaemia (TM), β thalassaemia(BTM), Diabetes mellitus (DM), iron overload, haemoglobin (Hb).

INTRODUCTION

Thalassaemia is a rare congenital blood defect having lifelong implications in the life of the patients and their relatives. This hereditary condition results in defective production of the quaternary protein "haemoglobin-Hb". Haemoglobin, a component of red blood cells, carries oxygen from the lungs to different body organs and tissues and brings carbon dioxide back to the lungs. Hb is made up of a pair of α and β globin chains. Thus, the levels of both the globin chains should be equal (Galanello,1998). In thalassaemia, defect lies in the production of either of the two globin chains which results in ineffective synthesis of the haemoglobin. Thalassaemia is inherited as an autosomal recessive disorder at the genetic level due to some point mutation. According to the globin chain that is found to be defective thalssaemias are classified as α and β thalassaemia. The present article focuses on β thalassaemia and diabetes which is one of the major endocrine complications among these patients.

β thalassaemia is characterized by reduced or absent β globin chain synthesis. The gene encoding for β globin are located on chromosome 11. More than 200 point mutations and rarely some deletions can cause β thalassaemia (Higgs *et.al.,* 2001).

Due to this, there is an accumulation of α chain and further, it precipitates out. Finally, it leads to oxidative damage and ineffective erythropoiesis (Rund, 2005, Cao *et.al.,* 2005 and Olivieri, 2001). These patients producing reduced hemoglobin in red blood cells (RBC) and RBC production suffer from anemia. Patients become pale as their age progresses. The extent to which the production of globin chain synthesis is disturbed tells us the severity of the disease (Taher *et.al.,* 2006). Like for example, in thalassaemia intermedia anaemic conditions are there but it isn't that much severe (Cao, 2010).

According to the severity, β thalassaemia is classified as

- Thalassaemia major(homozygous recessive)
- Thalassaemia intermedia
- Thalassaemia minor(heterozygous)

Severity depends upon factors like foetal haemoglobin concentrations, coinheritance of α thalassaemia and coexistence of sickle cell trait (www.emedicine.medscape.com).

β thalassaemia is the most common genetic variant among populations (Low, 2005). Generally, the disease seems to be more prevalent in the Mediterranean region, south East Asia and China. Thalassaemia is most prevalent in Cyprus (14%), Sardinia (12%), and South East

Asia (Flint et.al., 1998 and Weatherall *et.al.,* 2002). However, migration has changed the geographic spread and made it a worldwide health problem.

β thalassaemia has an incidence of about 1 in 100000 in the world annually. Average incidence in India is about 3.3%. In India, 1-2 out of every 1000 couples are at a risk of producing an affected offspring. Average incidence of β thalassaemia in various regions of India varies from 3% to 17% with an average prevalence of about 4% (Sood *et.al.,* 1993).

Thalassaemia requires a lifelong care and management as the disease can adversely affect vital organs and organ systems of the patient. The hyper transfusion and chelation therapy together have dramatically prolonged the life expectancy and quality of life among thalassaemic patients. However, the problem is further complexes by associated citrate toxicity and iron overload (Shamshirsaz, *et.al.,* 2003).

THALASSAEMIA AND DIABETES

Higher incidences of multi-endocrine abnormalities are reported in children, adolescents and young adults. Excessive iron gets deposited in most tissues primarily in the liver, heart and multiple endocrine glands. Endocrinopathies are now amongst the most common complications of thalassaemia with Diabetes mellitus (DM) and impaired glucose tolerance (IGT) as one of the major complication.

Glucose is critical for normal physiological functioning. It acts as a source of energy and also a starting material for all the biological reactions. Levels of glucose in blood are regulated by two endocrine hormones secreted by the organ pancreas: insulin and glucagon. Insulin is required to lower the blood glucose levels. Hence, it helps in the breakdown of glucose. Glucagon on the other hand is increasing the blood glucose levels. Both the hormones work together and maintain the normal glucose concentration in the blood.

Any impairment in homeostasis of glucose leads to a condition called Diabetes mellitus. It is classified as type 1 and type 2 diabetes mellitus. Type 1 occurs when there's deficiency of insulin in the blood. So, levels of blood glucose rise. While in type 2 diabetes mellitus insulin is there but cells develop an insulin resistance due to which there's an abnormality in the glucose homeostasis.

Diabetes mellitus is seen after the age of 10 years. The cause for DM in Thalassaemia is multi-factorial. The prevalence of impaired glucose tolerance and diabetes mellitus in β thalassaemia major (BTM) is variable and is up to 24% and 26% respectively. This variability in the prevalence relates to the difference in the age of introduction and application of effective iron chelation therapy and also to the ages of patients being studied, with lower rates in younger patients. It is believed that insulin resistance can be occurred in these patients before the onset of DM (Tong *et.al.,* 2002).

ETIOLOGY AND PATHOGENESIS

The etiology of DM in BTM is complex and multi-factorial. 'Figure 1' shows the etiological factors that can lead to diabetes mellitus in thalassaemia. The precise events attributing to the pathophysiology of IGT and DM in the patients remains to be clearly stated .Two kinds of situations are evident in the patients that lead to hyperglycemia are- insulin deficiency and insulin resistance.

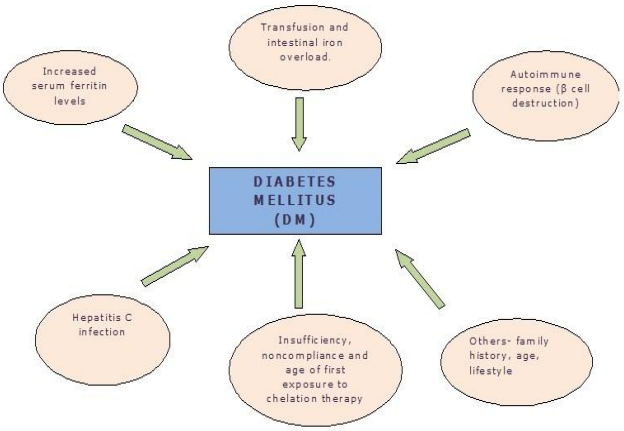

Figure 1 Etiological factors leading to diabetes mellitus in thalassaemics

Transfusional iron overload along with increased intestinal iron absorption appears to increase the iron load in Thalassaemia. Regular blood transfusions are the main line of treatment to overcome anaemia, but the ability to excrete iron form the body, however, remains limited. Once the body's ability to store iron is exceeded, free iron accumulates. Thus, over time transfusion therapy results in significant iron overload. Massive deposition of iron in the vital organs and its toxicity abrogates the functioning of these organs including liver and pancreas. The free Iron facilitates the formation of reactive hydroxyl radicals, which causes denaturation of proteins and membrane damage, thus, generating an oxidative stress in these organs. If untreated, it is fatal in the first or second decade of life. In β-thalassaemia, iron absorption adds to the transfusional iron overload. It is regulated by tissue hypoxia, erythropoietin excretion and ineffective erythropoiesis of an enormously expanded and active bone marrow. The latter leads to increase in the rate of iron absorption even in the presence of iron overload. Previous literature suggested accumulation of iron in the pancreas causes the defective insulin secretion and leads to insulin deficiency. However, other studies also showed the presence of hyperinsulinemia and IR (rather than insulin deficiency) suggesting the involvement of insulin resistance in producing impairment to glucose homeostasis. Hyperinsulinemia may result from reduced hepatic clearance, which may be associated to iron overload (Monge et.al, 2001). It is shown that insulin resistance appears quite early and leads to IGT. Although the studies are contradictory, progressive damage to β cells of the pancreas from hemosiderosis may appear later due

to impaired insulin secretion and results in the onset of overt diabetes.

Insulin dependent diabetes mellitus (IDDM) is also seen to occur due to the effect of an autoimmune response by the T lymphocytes which damage the β cells of pancreas. Insulin is one of the islet autoantigens, responsible for the activation of functions of T lymphocytes, inflammatory cytokines and development of insulin dependent DM. Pro- inflammatory Cytokines TNF and IL-6 play an important role in the pathogenesis of IDDM while TNF is also involved in promoting insulin resistance. Free iron provides an environment for autoimmune response (Labropoulou et.al., 1999). This is further supported by acute and rapid onset of diabetes causing ketosis and severe insulin deficiency in some of the thalassaemic cases. These individuals show selective β cell damage and severe insulin deficiency.

Serum ferritin when exceeds the value of 2500mg/ml are also associated with decrease in insulin sensitivity and appearance of insulin resistance.

Iron overload can be controlled and managed with the administration of chelation therapy. However, the dose and type of chelation therapy, compliance, sufficiency, side effect and age at the first exposure of Chelation therapy are some of the variables which can affect the situation to a greater extent.

The presence of hepatitis C infection has a pro-diabetic effect. Hepatitis C virus infection adds up to the iron overload causing harm to the liver and its function and also builds up insulin resistance hence leading to DM [17-22]. Glucose intolerance progresses with hepatic (liver) cirrhosis (Kwan et.al., 1995). It is seen that patients receiving regular blood transfusions are prone to these viral infections. However, the exact mechanism of how hepatitis virus leads to diabetes in thalassaemics can help in designing various therapeutic approaches and thus, can improve the treatment of thalassaemia leading to DM (Lecube et.al., 2006).

Diabetes mellitus itself is a common lifestyle disorder worldwide. This means that a person can develop DM irrespective of him being a thalassaemic. Family history of DM is a risk factor that person can develop thalassaemia. People with BTM and are into their old age have high probability of developing DM.

DIET AND LIFESTYLE MANAGEMENT OF DIABETES IN THALASSAEMICS

1. The patient has an iron overload due to repeated transfusions. Therefore, dietary iron should be restricted. Meat iron, soy protein should be excluded from the diet as 35% of red meat iron is absorbed in the body. White chicken can be included into the diet, as it doesn't have myoglobin. Non-meat iron should also be avoided.
2. Beer and other alcoholic beverages increase iron absorption from the dietary source. Therefore, it should be avoided.
3. Wheat, bran, maize and oats decrease the iron absorption in the body and therefore should be introduced into the diet.
4. Tea, coffee, milk products and some spices like oregano decrease iron absorption. Drinking black tea after meals reduces iron absorption through the GI tract in the intestinal area. Tea has antioxidants like polyphenols that bind to ferric ions and reduce oxidative stress and thus, protect erythrocytes form damage.
5. Reactive oxygen species (ROS) are produced in thalassaemics and play an important role in the pathogenesis of diabetes mellitus in general and thalssaemics, so antioxidants can prove to be effective in treatment (Rachmilewitz, 2001). Some thalassaemics show enhanced effects with antioxidants if they are given as combination of antioxidants like for example, vitamin E which is a lipid soluble antioxidant when given with N-acetylcysteine which is a protein antioxidant provide better results (Pace et.al., 2003).
6. Plant flavonoids like rutin and curcumin also are effective antioxidants that have the potential to produce effect in reducing oxidative stress in thalassaemics (Rund, 2001).
7. Milk being calcium enriched is crucial in diet as it prevents osteoporosis. Low fat milk should be consumed wherever it is indicated.
8. Vitamin C uptake in the diet improves excretion of iron in patients receiving chelation therapy.
9. To delay and prevent the development of glucose intolerance to a great extent, low carbohydrate diet is preferred for the thalassaemics when they are into their adolescence. This is because chances of getting aberrations in glucose metabolism are higher during this age. Intake of complex carbohydrates should be promoted. Low glycemic index (GI) food should be taken more. Simple sugars should be avoided. High fibre diet should be consumed (Sachdeva, 2006).
10. TM patients with diabetes and IGT should be monitored and managed accordingly to the severity of the problem. Patients are put on to dietary modifications or insulin therapy and/or to hypoglycemic drugs to achieve desired glucose levels in the blood (Sachdeva, 2006).
11. Regular dietary patterns are promoted. Compliance to these dietary regimens is monitored. Meal timing, quantities, quality and balance is advocated among the patients (Sachdeva, 2006).
12. Lifestyle modifications: Regular exercise and active lifestyle is promoted in light of patient's health status (Sachdeva, 2006).

TREATMENT OF THALASSAEMIA

Since disease is actually a genetic defect so it can't be cured as such. But management strategies are thought off to improve the quality of life of the patients as much possible. Chronic transfusion therapy ensures that

the haemoglobin levels don't fall below 9-10g/dL of blood volume.

A wider approach is also involved to treat the adverseness of thalassaemia. Induced foetal haemoglobin production in the patients is carried out which rectifies the imbalance of amount of α and β chains as foetal Hb requires gamma globin with α globin. Gene therapy is given which aims to deliver β globin gene to the cells with the help of viral vectors (Persons, 2003 and Puthenveetil, 2004).

Antisense technology is also taken into thought to correct the defect at the level of nucleotide where point mutation has occurred. It can also correct the splicing defects seen in thalassaemia (Vacek et.al., 2003). Also hematopoietic stem cell transplantation has proved to be beneficial in thalassaemics to quite an extent. But limit to this method of cure is due to its high cost and trouble in finding a suitable donor. It involves problems like problems like graft rejection.

The best way to get rid of this genetic disease is to detect at the stage that it doesn't becomes a problem afterwards. Polymerase chain reaction is used to detect the mutations in the DNA of the foetus at the first trimester stage. Technique of pre-implantation genetic diagnosis is used nowadays as an approach in which the affected cells are selected and removed at the blastomere stage of the developing embryo but such a technique can lead to errors as well although being a useful technique undoubtedly (Braude et.al., 2003 and Piyamongkol *et.al.,* 2003). Future strategies focus on the detection of mutation at the prenatal levels by isolating foetal DNA or foetal cells from mother's blood (Di, 2000 and Ding *et.al.,* 2004).

CONCLUSIONS

Thalassaemia is a disease which can be prevented by creating awareness among people about the disorder and its lifelong complications and management. Lack of awareness is increasing the global burden of this rare disorder. Improved measures should be taken up to promote Thalassemic trait determination, prenatal diagnosis Pre-implantation diagnosis, and genetic counselling in the general population. Prevention and management of diabetes in thalassaemia is a major challenge to combat. Improved chelation therapy drugs with minimum side effects should be designed for reducing iron overload in the thalassaemics; and should also be cost effective. Patients should be aggressively and regularly monitored for the assessment of iron overload and diabetes. Transfusions and its frequency should be judiciously planned.

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