

Evaluation and management of diabetes in patients with thalassaemia major

Karuppiah D¹

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Introduction

Thalassaemia major is an inherited haemoglobinopathy and the commonest genetic disease in Sri Lanka. Around 3500 patients have been identified up to date and Sri Lanka is considered a country with intermediate prevalence of thalassaemia.¹ This disease is characterised by chronic anaemia and iron overload due to transfusion therapy and gastrointestinal absorption. Excessive iron overload and suboptimal chelation result in deposition of iron in various tissues primarily heart and liver and frequently involves endocrine glands. Chronic hypoxia due to anaemia, viral infections and individual susceptibility are other factors which could potentiate the toxicity of iron deposition and contribute to endocrine dysfunction.^{2,3} Detecting the exact prevalence of endocrinopathies in patients with thalassaemia is challenging due to variability in the study population. This partly relates to ages of patients being studied and the adequacy of chelation therapy. Available data show the leading endocrine complications among patients with thalassaemia are delayed puberty or hypogonadism and growth retardation followed by diabetes mellitus, hypothyroidism, hypoparathyroidism, osteoporosis and adrenal insufficiency.⁴

Diabetes mellitus and impaired glucose tolerance

Although diabetes mellitus and impaired glucose tolerance are not the commonest endocrinopathy, this is an important complication among inadequately chelated patients. As life expectancy in patients with thalassaemia rises, diabetic complications are commonly seen. The prevalence of diabetes mellitus ranges from 6.4 to 14.1%.⁵ Patients with thalassaemia could develop diabetes secondary to their illness and as a complication of recurrent blood transfusion. Glucose intolerance correlates with at least 50% decline in beta cell function which is not entirely reversible even after intensive iron chelation. High transfusion regimes without effective iron chelation can increase the incidence of diabetes mellitus further.⁶ Likewise, with the worldwide epidemic of diabetes, they

could develop type 1 or type 2 diabetes, independently of their thalassaemia.⁷ Although iron overload due to transfusion is the key factor damaging pancreatic beta cells, poor compliance with chelation therapy and delay in starting chelation therapy are other significant contributing factors for developing diabetes.³ It has been shown that reduction in the insulin secretion is present even among normoglycaemic patients with thalassaemia.⁸ Also there may be pancreatic autoimmunity triggered by iron deposition causing selective beta cell damage.⁹ Insulin resistance secondary to liver disease and Hepatitis C infection also affect glucose metabolism.^{6,10}

Diagnosis

Since patients with thalassaemia develop diabetes very gradually, they may not have initial symptoms of hyperglycaemia. Hence it is essential to detect hyperglycaemia early as this allows for prompt treatment of hyperglycaemia and also prevent progression from prediabetes to overt diabetes by intensification of iron chelation therapy. Thalassaemia International Federation and the UK standards of care guidelines recommend oral glucose tolerance test for diagnosis of diabetes in patients with thalassaemia.^{11,12} This should be performed in every patient after 10 years of age or earlier if needed. The diagnostic criteria is similar to non thalassaemic population.

Management

Patients with thalassaemia have complex medical needs. In addition to managing thalassaemia and related complications, the diagnosis of diabetes will burden the patient physically as well as psychologically. Significant psychological issues including anxiety and depression have been noted among these patients.⁷ Thus managing diabetes in patients with thalassaemia is a challenging task unless tackled carefully. Joint clinics where members of both diabetes and thalassaemia teams work together with patients have been shown to be very effective at providing high quality of care in these patients.⁷

The key objectives of managing diabetes are glycaemic control, prevention of micro and macro vascular complications and cardio vascular risk reduction. Intensive chelation therapy with des-

¹ *Consultant Endocrinologist, Teaching Hospital, Batticaloa.*

E-mail: kdharshinik@gmail.com

ferrioxamine and deferiprone are effective to normalize β -cell function and may improve insulin secretion and glucose tolerance and reduce liver iron deposition. Multiple studies have shown deferasirox, a recent oral chelator, to be effective in thalassaemia patients.¹³ In addition, weight loss and exercise are both established ways to reduce insulin resistance and prevent progression to diabetes.¹¹

In established diabetes the medical treatment depends on the severity of β -cell damage and subsequent insulin deficiency. Introducing oral hypoglycemic drugs in the early stage of diabetes before dependence on insulin may be beneficial. Metformin is considered first choice in patients with type 2 diabetes. There is little research on its use in thalassaemia except few case reports.¹⁴ Insulin resistance also plays a part in the pathogenesis of diabetes in thalassaemia. Since metformin reduces insulin resistance, it could be promising and certainly can be considered in early stages. The efficacy of glibenclamide was evaluated in few studies and reported long lasting glycaemic control.¹⁵ There are reports on successful use of acarbose, an alpha glucosidase inhibitor, in these patients.¹⁶ Overall there is limited data on the effect of oral antidiabetic drugs in thalassaemia.

Insulin remains the mainstay of treatment in symptomatic patients or patients with severe hyperglycaemia and who are insulin deficient. There are two common treatment regimens. Twice daily premixed insulin is given before breakfast and evening meal. The basal bolus regimen contain a once a day slow acting basal insulin (isophane, glargine or levemir) and rapid acting prandial insulin given with each meals. The choice depends on many factors including the availability, cost and patient preference.

Monitoring

Compared to general diabetic population, there is no marked difference in monitoring of glycaemic control in thalassaemic patients. The recommendation is daily home capillary glucose monitoring and checking ketones in urine and or blood if blood sugar is above 250mg/dl.¹¹ This may be individualized according to the level of glycaemic control, and other factors in a resource poor setting. HbA1c is not a reliable indicator of glycaemic control because of reduced red cell lifespan, ineffective haemopoiesis and frequent blood transfusions, all of which may potentially affect the validity of the HbA1c result. Fructosamine estimation every month can be considered an alternative test for HbA1c. Because fructosamine is dependent on serum protein glycation, results are unaffected by presence of a haemoglobinopathy.¹⁷ Less than 299 $\mu\text{mol/l}$ is the recommended target level for fructosamine measurement.¹¹

As life expectancy of patients with thalassaemia increases, micro and macro vascular complications related to diabetes are also being seen. In addition to optimizing glycaemic control, routine screening for these complications are an essential part in the management. However, the incidence of retinopathy and nephropathy with diabetes in thalassaemic patients is relatively lower than in patients affected by other forms of diabetes, probably consequent to normal lipids and frequent presence of hypogonadism.¹⁸ The guidelines recommend annual assessment of renal function, urinary microalbumin and protein and evaluation of retinopathy.¹¹ Preventing these complications is a critical aim of diabetes management. This can be done by tight glycaemic control and by controlling other factors such as body weight, blood pressure, lipids and avoiding smoking.

Conclusion

Treatment of diabetes in patients with thalassaemia is an additional burden, and support from family, health care providers and psychologists are needed. Multidisciplinary team with patient centred approach will be the way forward. Training people to self-manage their diabetes and providing support from health care providers are critical for excellent diabetes control. Joint clinics where members of both diabetes and thalassaemia teams work together with patients will be a better option to manage these patients with complex needs. This also allows staff to learn from each other and provide consistent approach.

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