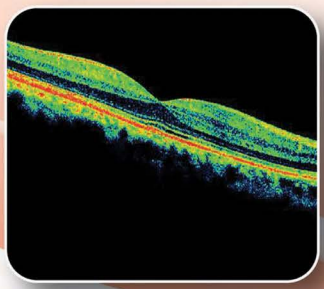
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Clinical Case Series-II


Editors
Viswanathan Mohan
Ranjit Unnikrishnan

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4
Chapter

Improvement in Pancreatic β Cell Function after Early and Aggressive Treatment with Insulin at Diagnosis of Type 2 Diabetes: A Case Report

Varalakshmi Muthukrishnan, Ranjit Unnikrishnan, Viswanathan Mohan

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INTRODUCTION

Diabetes is a chronic progressive disease associated with serious long-term complications, which can be largely prevented by achieving and maintaining target glycemic control. It has been shown that attaining these targets as early as possible in the natural history of diabetes has salutary effects on the long-term risk of complications. Indeed, recent evidence suggests that one can even favorably alter the natural history of type 2 diabetes mellitus (T2DM) by aggressive treatment with insulin right at the time of diagnosis. Here the authors present a case of a young patient with short duration of diabetes in whom aggressive treatment with insulin had helped to achieve not only target glycemic control, but also improvement in β cell function within a period of 3 months.

CASE PRESENTATION

A 42-year-old male patient came to the authors' center for glycemic evaluation. He had been diagnosed to have diabetes 4 years ago at the age of 38 years. He had been treated with oral hypoglycemic agents but glycemic control remained poor. At the initial visit, his glycosylated hemoglobin (HbA1c) was 10.5%. His fasting and postprandial plasma glucose levels were 213 mg/dL and 409 mg/dL, respectively. His initial C-peptide values were fasting 1.3 pmol/L and stimulated 1.7 pmol/L, indicating decreased pancreatic insulin reserve.

Systemic examination was normal. Body mass index was 23.8 kg/m^2. Lipid profile showed triglycerides 125 mg/dL, low density lipoprotein cholesterol 105 mg/dL, and high density lipoprotein cholesterol 41 mg/dL. Microalbuminuria was positive (53 μg/mg) and mild proteinuria was

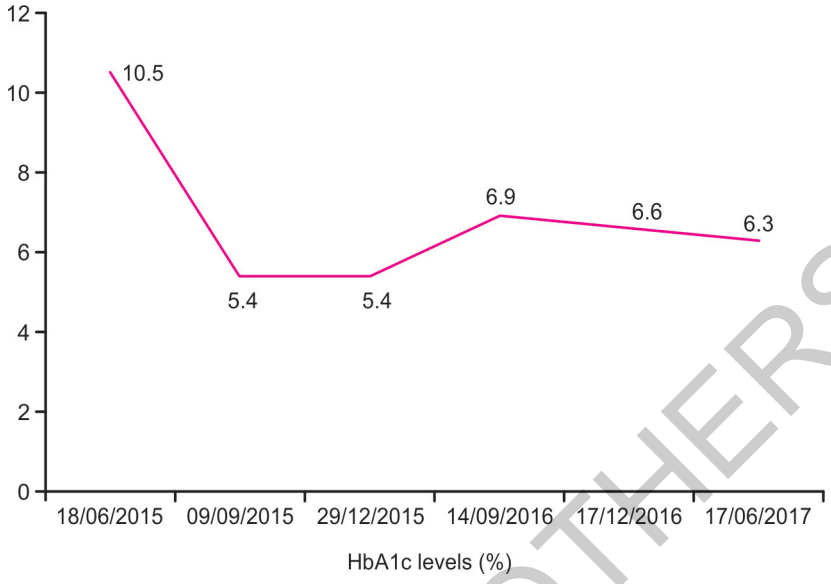


Fig. 1: Change in glycosylated hemoglobin (HbA1c) levels

present (243 mg/day). Hemoglobin was 14.4 g/dL. Liver function test showed bilirubin 1.5 mg/dL, serum glutamic oxaloacetic transaminase 35 U/L, serum glutamic-pyruvic transaminase 57 U/L, alkaline phosphatase 298 U/L, and gamma glutamyltransferase 79 U/L. Serum electrolytes and thyroid function tests were within normal limits. Eye test revealed no evidence of diabetic retinopathy. Biothesiometry revealed evidence of early sensory neuropathy.

Since the patient was young with a very high HbA1c, he was initiated on short term insulin along with oral hypoglycemic agents in order to correct glucotoxicity. He was reviewed after 3 months, at which time his HbA1c was found to have decreased from 10.5 to 5.4% (Fig. 1). Microalbuminuria decreased from 53 to 9 μg/mg (<30 μg/mg is normal). Liver enzymes became normal.

His C-peptide was repeated, which showed marked improvement in pancreatic insulin reserve from 1.3 to 1.5 (fasting value) and 1.7 to 4.0 (stimulated value). Further, it was repeated after 1 year at which time further improvement was seen (from 1.5 to 2.3 in the fasting state and 4.0 to >4.0 in the stimulated state) (Fig. 2).

His HbA1c remained at 5.4% for 6 months and remained below 6.5% even after 2 years of the initial aggressive therapy with insulin (Fig. 1). Thus, following the early aggressive treatment he was able to maintain good glycemic control with minimal increase in HbA1c even after 2 years of stopping insulin.

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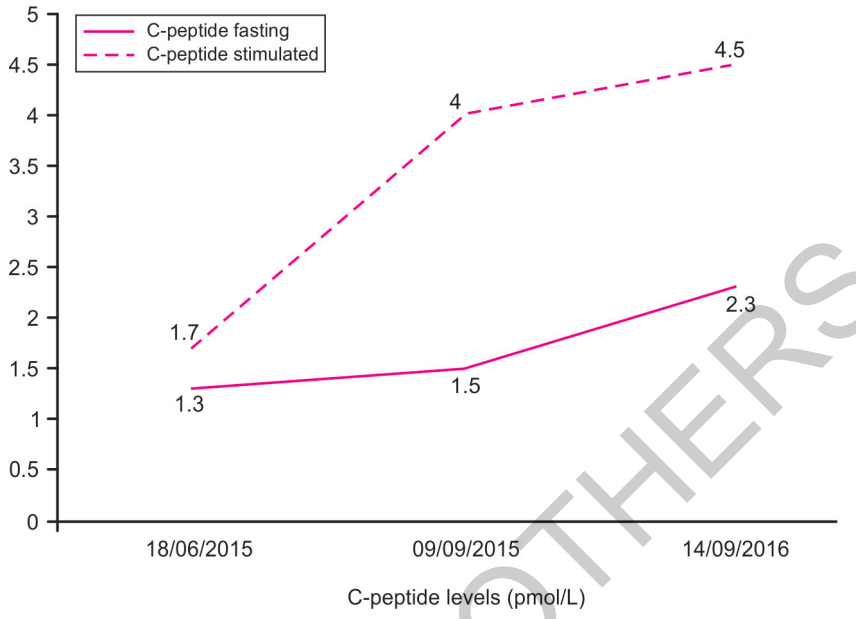


Fig. 2: Change in C-peptide levels

DISCUSSION

Type 2 diabetes mellitus is increasing worldwide and the incidence of diabetes in children and adolescents is increasing as well leading to increased incidence of vascular complications. The fact that good glycemic control will reduce the incidence of microvascular complications is well established through several studies like the United Kingdom Prospective Diabetes Study.[1] However, in spite of clearly understanding the benefits of good glycemic control, only less than 36% of individuals with diabetes are able to attain target glycemic control.[2] There is progressive deterioration in β cell dysfunction over a period of time and hence patients treated with oral hypoglycemic agents may fail to attain or maintain adequate glycemic control. Hence, intensification of therapy is essential in preventing the onset of complications in patients with diabetes. However, clinical inertia, defined as delay in initiation and intensification of diabetic therapy, is very common and this leads to prolonged hyperglycemia, thereby resulting in onset of complications.[3] Hence, we should not hesitate to initiate insulin in the early stage of the disease in order to prevent or reduce the incidence of diabetic complications.

Early initiation of insulin definitely helps to achieve the glycemic target rapidly compared to oral hypoglycemic agents. This is more evident in patients with poor glycemic control with HbA1c greater than 10% prior to

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initiation of insulin. The average reduction in HbA1c with insulin therapy is expected to be between 1.5 and 3.5%, which is greater than that achieved using any oral hypoglycemic agent.[4] In the present case, if oral hypoglycemic agents alone had been used, at best the HbA1c might have come to around 7.0%. However, with the initiation of insulin, the HbA1c had decreased to 5.4%, which is in the nondiabetic range. This is remarkable considering that (i) patient had an HbA1c of 10.5% before insulin and (ii) this improvement occurred after a 4 year duration of diabetes.

Further, early aggressive treatment with insulin not only reduces the glycemic control to a greater extent but also the benefits are found to persist for up to 2 years after stopping the insulin. Patients given insulin early in the natural history of T2DM were able to maintain the good glycemic control that was achieved following insulin therapy for several years compared to others on oral hypoglycemic agents where the glycemic control was found to worsen with progression of the disease. The authors, therefore, suggest that patients with initial HbA1c of more than 10% who are treatment-naïve must be started on insulin therapy as per the American Association of Clinical Endocrinologists recommendations.[5]

The earlier achievement of glycemic control through insulin therapy will further provide additional benefits through metabolic memory, as good glycemic control will definitely help to reduce microvascular complications in the long term. In most instances, insulin therapy is considered as a last option and there is a delay in insulin initiation even in patients who are on multiple oral hypoglycemic agents with poor glycemic control.[6]

In diabetes, even transient hyperglycemic excursions can lead to alterations in the intracellular metabolism and result in glucolipotoxicity, which impairs β cell function through defective insulin biosynthesis.[7] The benefits of early initiation of insulin therapy are multifold. It helps to overcome the glucotoxicity of hyperglycemia, thereby providing rest to the β cells and preserves β cell mass and function as well as increases insulin sensitivity.[8] It also helps to correct lipotoxicity. In diabetes, the basal normoglycemia that is attained as a result of constant basal insulin can benefit β cell function.[9] Whether the β cell function will improve to completely normal is questionable and may be unlikely. However, insulin treatment if given early definitely helps to prevent the irrevocable exhaustion of islets that occurs due to prolonged hyperglycemia.

In the studies done by Turner et al.[9] and Garvey et al.,[10] the clinical benefits of short courses of intensive insulin therapy that was given for a duration of 2–3 weeks was well established. This enhanced the insulin secretion (especially the second phase) and improved the insulin sensitivity as well.[9] In addition, there was beneficial effect on the basal hepatic glucose production, which resulted in near normalization of glucose levels following the short intensive course of insulin.[10]

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In a multicenter randomized parallel group trial done in 382 patients by Weng et al.,[11] it was found that target glycemic control was achieved in the insulin treated group in less time compared to the oral hypoglycemic agents group. Patients with newly diagnosed T2DM treated with insulin were found to have improved outcomes with respect to remission and beta cell recovery. Further the remission was more sustained and β cell function was maintained with the intensive insulin treatment group compared to the oral hypoglycemic agents group.

The oxidative stress or loss of differentiated identity can lead to β cell death or exhaustion and thereby result in β cell failure in T2DM.[12] Hyperglycemia causes inactivation of key transcription factors which activate the gene expression in β cells and repress non-β cell genes.[13] Further, this loss of identity of β cell as well as acquisition of non-β cell identity is reversible when the glucose level is normalized. Such β cells whose identity is compromised will become dysfunctional and insulin secretion response to glucose is lost.[13] While the islet endocrine identity is robust, islet cell type identity is fragile and is dependent on metabolic state. Studies show that there is deep epigenetic similarity between different islet cell types, which can be responsible for the intra-islet cell plasticity.[14,15] The early aggressive treatment that is given temporarily during the onset of diabetes also provides greater benefits with less weight gain and hypoglycemia.[16]

There is increasing evidence to support the use of early insulin initiation in order to obtain multiple metabolic benefits. Hence, as clinicians we should not be hesitant to use insulin at an early stage of the natural history of T2DM as it helps to correct glucotoxicity as well as lipotoxicity and favorably impacts the natural history of the disease.

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Key Features

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