

A MALE WITH EXTREME SUBCUTANEOUS INSULIN RESISTANCE: A CASE REPORT

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Abstract

Introduction: Though insulin has no upper limit in dosage, we do not encounter very high dose requirements too often. The reported case is the first in Bangladesh to require more than 1000 international units (IU) of subcutaneous insulin per day. **Case presentation:** A 44-year old male diabetic patient from Bangladesh presented with unusually uncontrolled diabetes mellitus due to extreme insulin resistance. Despite dramatic increase in insulin step by step up to 1110 IU of concomitant short and intermediate acting insulin per day by subcutaneous route, his blood glucose remained over 12 mmol/L persistently, in all the fasting, pre-prandial, postprandial and random samples. He was also treated with several oral hypoglycemic agents including metformin, vildagliptin, glimepiride, pioglitazone and miglitol along with insulin but blood glucose levels remained almost unchanged. However, intravenous infusion of insulin over 4 hours caused a plummet in the glucose level. His blood test for insulin autoantibody was negative. **Conclusion:** This paper provides a scope to review literatures on extreme subcutaneous insulin resistance and its management. It also reveals the limitations of management due to lack of facilities in an underdeveloped country, which hinders proper exploration to many medical issues.

key words: Diabetes Mellitus; Insulin Resistance; Subcutaneous Injection.

Introduction

Hyperglycemia is common in hospitalized patients. A lot of factors including underlying medical conditions, stress and some medications can contribute to transient hyperglycemia in diabetic as well as non-diabetic patients. But persistent hyperglycemia for a long period in spite of management following guidelines is usually associated with an underlying pathology. Insulin resistance is a known cause of hyperglycemia. On a clinical basis, severe insulin resistance is defined as a situation in which a patient requires more than 200 units of

insulin daily for more than 2 days [1]. Though physicians are familiar with common diseases that are known to be associated with insulin resistance, the majority of us rarely come across a case of extreme insulin resistance. It is usually seen during the attack of diabetic ketoacidosis, although non-ketoacidotic patients can also develop severe insulin resistance. Here, we report a case of extreme insulin resistance in a stable, diabetic patient without any acute complication related to diabetes mellitus. To our best knowledge, this is the first case of such kind from Bangladesh.

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Case description

A 44-year-old Bangladeshi hypertensive male with a 5 year history of diabetes mellitus was presented with the complaints of weakness in the left side of body for 15 days, occasional numbness with tingling sensation over the whole body for same duration and occasional blurring of vision for same duration. He had a history of physical assault followed by spine surgery about 5 years ago. He denied history of unconsciousness, pain, rash and weight loss. He also denied alcohol, tobacco or any illicit drug abuse. His mother died of stroke and father from coronary heart disease. Family history was negative for diabetes and autoimmune diseases. His medications included metformin 500 mg twice daily and glimepiride 1 mg once daily for 5 years. He received insulin intravenously during surgery and subcutaneously for the following 1 month of surgery, though we could not know the course of treatment as he failed to submit papers of management of that period.

On examination, he looked healthy with BP: 130/85 mmHg, pulse: 92 bpm, temperature: 36.7

°C and respiratory rate: 18/minute. His weight was 76 kg and body mass index (BMI) 28.8 kg/m². His muscle power in both upper and lower limbs of left side was decreased (3/5 in lower limb and 4/5 in upper limb). Ophthalmoscopy revealed non-proliferative diabetic retinopathy. Apart from mild axillary acanthosis nigricans, other examination findings were unremarkable. He did not have lipodystrophy.

His fingerstick blood glucose was 15 mmol/L under fasting condition and 22.8 mmol/L 2 hours after breakfast during admission. His hemoglobin A1c was 11.1%. Ultrasonography of whole abdomen revealed grade II non-alcoholic fatty liver disease. His HDL cholesterol level was <35 mg/dl and serum cortisol was normal. Blood for insulin autoantibody was negative. As the patient was admitted for more than 4 months and blood glucose was measured 3 times daily during this period, his blood glucose level and insulin requirements in some randomly selected days after admission are presented from diabetic chart in Table 1 instead of full data to keep it short.

Table 1. Patient's blood glucose level and dose of insulin in some randomly selected days following hospitalization.

No. of Day	Fasting blood glucose (mmol/L)	Blood glucose before lunch (mmol/L)	Blood glucose before dinner (mmol/L)	Total insulin required (units/24 hours)
Day 1	20.1	–	15.8	68
Day 2	15.8	–	14.7	68
Day 5	16.2	–	14.4	78
Day 15	15.7	19.3	17.5	174
Day 50	13.0	14.0	13.5	444
Day 100	15.1	21.0	23.0	950

For the control of diabetes, initially, he was prescribed 28 units of short acting insulin and 16 units of intermediate acting insulin subcutaneously per day, when he was attended on referral from physical medicine department. Later, as his diabetic chart revealed persistently uncontrolled blood glucose level, he was

transferred in the Department of Endocrinology for better care of diabetes. 500 mg Metformin was added with previous dose insulin and increased up to 3400 mg per day step by step for achieving glycemic target. Later, Vildagliptin 50 mg was added with Metformin and continued for a week and as no change occurred with that,

Glimeperide 4 mg was added and continued for another week. Pioglitazone 45 mg per day was then added and continued for about a month. As his blood glucose level was not controlled with those drugs combined, Pioglitazone and Glimepiride were removed and Miglitol 37.5 mg was added along with increasing doses of subcutaneous insulin and 3400 mg of Metformin. Each of these drugs was continued for at least 1 week but the lowest blood glucose level recorded was 12 mmol/L after adding Pioglitazone. Insulin was given by using 100U/ml plastic insulin syringes throughout the period. We also infused 100 units of regular insulin diluted in 1000 ml normal saline intravenously for about 4 hours, resulting in a plummet in blood glucose level to 8.5 mmol/L that was sustained for about 6 hours. This was withdrawn in order to establish an insulin regimen that the patient can continue at home. But after switching to subcutaneous insulin, continuous glucose monitoring for 3 days showed almost unchanged blood glucose level with an average of 14 mmol/L. So, the dose of insulin was increased step by step up to 510 units of short acting and 600 units of intermediate acting insulin (total 1110 units) per day after 4 months of inpatient management and discharged from hospital. So, at the time of discharge, he was advised to take 510 units of short acting and 600 units of intermediate acting insulin per day along with Metformin 2000 mg daily. Implantable pump for insulin delivery as well as U-500 insulin could not be used due to unavailability of these in Bangladesh.

Discussion

Insulin resistance has been defined as “a state (of a cell, tissue or organism) in which a greater than normal amount of insulin is required to elicit a quantitatively normal response” [2]. Severe insulin resistance should be suspected

when an individual requires more than 2 units/kg/day of insulin [3]. A condition where an individual insulin requirement is more than 3 units/kg/day is known as extreme insulin resistance [4]. Extreme subcutaneous insulin resistance is characterized by severe resistance to subcutaneous insulin with normal or near normal intravenous insulin sensitivity [5]. Though mechanism unknown, insulin degradation in subcutaneous adipose tissue and muscle has been reported [6,7]. Established mechanisms of insulin resistance include genetic defects in insulin receptors, insulin receptor antibodies and interference with intracellular insulin action due to the excess of counter-regulatory hormones of inflammatory cytokines and increased insulin clearance [3].

It is sometimes difficult to classify the state of insulin resistance clearly [8]. We assigned two doctors to monitor the patient while administering insulin to ensure that appropriate technique was followed to inject in proper site and also to exclude non-compliance of the patient.

In two case reports, insulin antibodies developed after switching human insulin to analogue insulin in elderly patients [9]. Our patient also received human insulin for a brief period 5 years ago. This is why, after finding out, this time we gave both human and analogue insulin only to find both ineffective in the subcutaneous route.

Management of such cases is more challenging. Intraperitoneal insulin delivery has been reported to be successful to overcome subcutaneous resistance, though the reported patient had associated pancreatitis [5]. Protease inhibitors, including Nafamostat ointment has been shown to be beneficial [10]. This drug is not available in our country.

For choosing drugs, we were traditional with locally manufactured drugs due to their lower

cost, as studies from Bangladesh suggest [11]. However, later we replaced these drugs with those produced by multinational companies. We could not measure insulin level of the patient while infusing insulin intravenously due to lack of facility. It would indicate the clearance rate as studies suggest that increased insulin clearance may play a role behind high insulin requirement [3], though mechanism also unknown.

Conclusion

Resistance due to non-compliance or technical error is a common cause of apparently high insulin needs. Our patient showed an unusually prolonged course of insulin resistance even after we thoroughly examined and ruled out the factors related to non-compliance such as fear of injection and self-testing, expectations regarding positive insulin-related outcomes, stigmatization by injections and fear of hypoglycemia. Initially, patient was allowed to inject himself insulin, but later all shots were subjected to monitoring. So, subcutaneous insulin resistance was the diagnosis we can conclude. However, we could not measure

insulin receptor antibodies and we do not believe they played a role because of the absence of clinical features of an autoimmune disease or malignancy in this case. Insulin, plasma leptin and serum adiponectin levels could not be measured due to unavailability of these tests in our country. Although C-peptide level was available, the cost was out of reach for the patient party. With these limitations, we could not explore the exact mechanism for the extreme insulin resistance in this case. This report is a message that non-obese individuals can have extreme insulin resistance and they are not uncommon in this part of the world. Reports of such cases warrant the issue of large scale studies with adequate fund to understand the exact pathophysiology of subcutaneous insulin resistance at cellular level for developing a proper guideline to manage such cases.

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