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Extremely high-dose insulin requirement in a diabetic patient with psychiatric illness: A case report

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Abstract

Severe insulin resistance is defined as the need of insulin requirement of more than two units per kilogram of body weight. It is rarely seen in diabetic patients. Common causes of severe insulin resistance include severe insulin resistance syndromes, drugs, endocrine disorders, factitious causes, lipodystrophy, increased insulin clearance, and impaired insulin absorption. Here, we describe a diabetic patient with major depressive disorder who was prescribed a maximum of 282 units (4.9 units/kg) of insulin a day. However, the cause in this patient was pseudo-resistance to insulin due to the inappropriate use of insulin by the patient. The ability to maintain her glycemia in the target range with lower doses of insulin was confirmed after the patient was admitted to the hospital. It is, therefore, crucial to systematically address any patient who requires an exceptionally high dose of exogenous insulin, starting with technical issues (injection technique, site of administration, or insulin storage), medication adherence, or medication errors.

Keywords

Severe insulin resistance, pseudo-resistance, diabetes

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Introduction

Insulin resistance is a subnormal glucose response to endogenous and/or exogenous insulin.[1] Patients who require an insulin dose of greater than 1 unit/kg/day are considered to have insulin resistance. Patients with severe insulin resistance require greater than 2 units/kg of body weight or 200 units/day of insulin.[2] It is considered an extremely high insulin dose if the patient needs greater than 3 units/kg/day.[3]

Although insulin resistance is a common pathogenesis of type 2 diabetes, cases of severe exogenous insulin resistance are uncommon. Five-year follow-up in a UK national specialist referral center found that 283 patients have confirmed severe insulin resistance and/or lipodystrophy.[4]

Common clinical features include obesity, acanthosis nigricans, increased waist-to-height ratio, hypertension, lipodystrophy, hirsutism, oligomenorrhea, and infertility, and during the early course of illness, they may have symptomatic postprandial hypoglycemia.[5]

The causes of severe insulin resistance are shown in Table 1.[3] Unfortunately, many of the physicians who treat these patients limit themselves to prescribing ever higher doses of insulin, without questioning why.[1] Here is a report of a patient who was missing or taking an inappropriate dose of insulin, which leads to the prescription of an extremely high dose of insulin (4.9 iu/kg/day) in addition to her oral medications. To the best of our knowledge, this case is one of the rarely reported causes of extremely high insulin resistance.

Case summary

The patient is a 50-year-old female type 2 diabetes mellitus patient for the past 7 years and is currently on neutral protamine Hagedorn (NPH—intermediate acting human insulin)

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70/60 units and regular insulin (RI-short acting human insulin) 14 units four times a day (QID) and metformin 1 g PO (oral) two times a day (BID), which is poorly controlled (fasting blood sugar 350–500). She was initially on PO medications, and insulin was added in the past 4 years. Poor glycemic control started a month back and was referred to a tertiary hospital for better treatment. She was advised for lifestyle modification and diabetic education, and microvascular complication screening was normal. The patient was also given education on how to inject or store insulin, and she responded accurately to the questions we asked her about insulin injection techniques and storage. Her diabetic treatment and glycemic measurement history at the outpatient follow-up clinic are shown in Table 2.

She was a known hypertensive patient on enalapril (10 mg PO daily) for the past 6 years. She was also a known post-ischemic stroke patient (left-sided weakness) and has had epilepsy for the past 6 years. Her seizures were controlled, and she takes phenytoin 100 mg PO BID and phenobarbital 130 mg daily, aspirin 81 mg PO daily, and atorvastatin 20 mg PO daily. She had a right frontal lobe, subcortical old lacunar infarct on brain computerized tomography (CT), and epileptogenic activity were observed throughout the recording on her electroencephalogram assessment. She had a controlled toxic multinodular goiter for the past 6 months on propylthiouracil (PTU) 100 mg PO daily.

For a diagnosis of major depressive disorder secondary to a general medical condition, she was started on fluoxetine 80 mg PO/day. There is no family history of substance use, psychiatric illness, or other chronic illness. On physical examination, her vital signs are all within normal limits. She weighs 57 kg and is 162 cm tall, giving her a body mass index of 21 kg/m^2. She has a small anterior neck mass measuring 3 cm × 2 cm, which is firm and moves with deglutition, with no substernal extension. The injection sites were clear, and the foot examination was normal. She had a normal waist circumference of 74 cm, no acanthosis nigricans, no lipodystrophy, and no evidence of hyperandrogenism. The central nervous system examination was normal, and there was no motor weakness.

Basic laboratory tests, including complete blood count, liver enzymes, renal function test, serum electrolytes (Na, K, Ca, and Cl), and thyroid function tests, were normal. She was nonreactive to retroviral infection, there is no ketonuria in the urine, and the retinal examination was normal. She had dyslipidemia (triglyceride = 170 mg/dl, total cholesterol = 215 mg/dl, high-density lipoprotein(HDL) cholesterol = 35 mg/dl and low-density lipoprotein(LDL) cholesterol = 133 mg/dl). The patient was admitted to the general ward and given half the previous doses for two days, and a pseudo-resistance was diagnosed (Table 3). The blood sugar level is greatly reduced and ranges from 64 to 123 mg/dl when nurses administer NPH 47/40 BID and R/I of 18/18/18 at each meal. She denies adherence problem despite correction of her glycemia during in hospital treatment. The patient is currently supported by her family, endocrinologist, and psychiatrist. Based on self-monitored blood glucose, the dose was further adjusted at the outpatient follow-up clinic on two visits. Her fasting blood sugar levels

Table 1. Common causes of severe insulin resistance.

Causes of high insulin requirements in diabetic patients	
A	Severe insulin resistance syndrome type A
B	Severe insulin resistance syndrome type B
C	Severe insulin resistance syndrome type C
D	Drugs
E	Endocrine
F	Factitious
G	Genetics
H	Hypersensitivity
I	Increased insulin clearance, Impaired insulin absorption

Table 2. Diabetic treatment and glycemic measurement history at outpatient follow-up clinic.

Date	NPH IU SC (AM, PM)	RI IU SC (AM, PM, or each meal)	Oral medications	SMBG (mg/dl)/FBS (mg/dl)/HBA1C
27/8/2021	70/60	14Iu each meal (4 times)	Metformin 1 g BID	FBS 350–500, HbA1c-9.1
15/9/2021	70/60	14/14	‘’	
1/10/2021	74/64	16/16	‘’	FBS = 500
26/11/2021	78/66	16/16	‘’	FBS = 300–400
10/12/2021		18/18/18	‘’	HbA1c = 14.6%
18/2/2022	80/74	22/22/22	‘’	FBS = 270–400, 2-h post meal = 270–440, insulin dose (3.85 U/kg/day). HbA1c = > 15%
1/4/2022	86/74	26/26/26	‘’	FBS 350–400, 2-h post meal 370–400, HbA1c = 12%, could not afford 2nd PO drug
26/8/2022	88/76	26/26/26	‘’	HbA1c = 15.6, FBS 773, 661
25/11/2022	94/80	36/36/36	Glimepiride 2 mg PO/day added on metformin	FBS = 200–300

NPH: neutral protamine Hagedorn; RI: regular insulin; IU: international unit; SC: subcutaneous; SMBG: self-monitoring of blood glucose; FBS: fasting blood sugar; HbA1c: hemoglobin A1C.

Table 3. Diabetic treatment and glycemic measurements at admission.

Date	NPH (IU) SC (AM, PM)	RI (IU) SC (each meal)	Blood glucose measurement in mg/dl (FBS, 2-h post breakfast, 2 h post lunch, predinner and 2 h post dinner respectively)
Day 1	47/40	18/18/18	267, 110, 84, 96,104
Day 2	47/40	18/18/18	64, 78, 87,116, 123

NPH: neutral protamine Hagedorn; RI: regular insulin; IU: international unit; SC: subcutaneous; FBS: fasting blood sugar.

were 134 and 125 during her out patient follow ups. She could not continue her further follow-up at our hospital due to financial issue for transportation and investigations and referred back to nearby health institution.

Discussion

Insulin pseudo-resistance is a need for higher insulin doses due to poor medication-taking behaviors. It may be the result of nonadherence, poor injection technique, improper insulin storage, or malingering for secondary gain. Pseudo-resistance can be ruled out by carefully administering insulin at a hospital.[1] Insulin pseudo-resistance has also been reported from adsorption to burettes, which forced to administer 1200 units of insulin per day. The problem resolved when changing to a syringe.[6] To maximize glucose control and the safety of insulin use, it is crucial to make sure that those patients and/or caregivers understand the proper insulin injection technique. Injections should be made into the proper body locations, the injection sites should be rotated, the injection sites should be properly cared for to prevent infection or other consequences, recognize, and avoid areas of lipohypertrophy, and intramuscular insulin delivery should be avoided.[7]

Severe insulin resistance should be approached to achieve good glycemic control, avoid hypoglycemia, establish the diagnosis, and treat underlying etiology.[8] An insulin receptor defect in the signaling pathway of insulin action can result in insulin resistance.

Severe insulin resistance syndrome type A is caused by a mutation in the insulin receptor gene, which phenotypically manifests as extreme insulin resistance, acanthosis nigricans, hyperandrogenism, onset during adolescence, lean body habitus, oligomenorrhea, infertility, and unusually normal or low fasting triglyceride levels. Severe insulin resistance syndrome type B is due to autoantibodies to the insulin receptor and phenotypically manifested in middle-aged women as extreme insulin resistance, rapid weight loss, acanthosis nigricans on periocular, perioral, and labial regions, hyperandrogenism, nonspecific autoimmune features, and unusually low fasting triglyceride. Severe insulin resistance syndrome type C (HAIRAN—hyperandrogenism, insulin resistance, and acanthosis nigricans syndrome) is like type A insulin resistance syndrome but is in obese patients.[4] Our patient does not have such features.

Drugs like glucocorticoids, statins, beta-blockers, diuretics, antipsychotics, antiretroviral drugs, calcineurin inhibitors, and tyrosine kinase inhibitors are also attributable as a cause of severe insulin resistance.[9] However, our patient's drug lists are PTU,[10] enalapril,[11] aspirin,[12] fluoxetine,[13] phenobarbital, and phenytoin, which are reported to cause hypoglycemia rather than insulin resistance. Only statins are reported to increase the progression of hyperglycemia though not as severe as our patient's case and guidelines recommend not stopping statins.[14]

Endocrine causes of severe insulin resistance include acromegaly, glucagonoma, thyrotoxicosis, Cushing syndrome, and pheochromocytoma.[3] Our patient has only clinically and laboratory controlled thyrotoxicosis and no clinical feature of other diseases.

Lipodystrophy syndromes either of generalized or partial types can be presented with extreme insulin resistance, generalized, selective, or variable loss of adipose tissue, severe hypertriglyceridemia, fatty liver, and organomegaly, which is not present in our patient.[3] Insulin autoimmune syndrome, increased insulin clearance,[15] or impaired insulin absorption[16] can be a cause for severe insulin resistance, but a systematic approach[8] to the case ruled out these possibilities.

Our patient was admitted and administered a subcutaneous lower dose of insulin by nurses, resulting in euglycemia to level 1 hypoglycemia. This clinches our diagnosis pseudo-resistance of poor adherence as a cause of her presentation. The patient was aware of the storage, numbers, and injection technique. The reason she denies her poor adherence is high likely due to her underlying psychiatric illness and a need for secondary gain.

Conclusion

A patient who needs a high dose of insulin every day should have a comprehensive strategy to treat their severe insulin resistance rather than simply increasing their insulin dosage. In order to proceed, it is first necessary to rule out the possibility of various causes of pseudo-resistance. This patient's psychological condition contributes to her poor adherence.

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Presentation at a meeting

None.

Author contributions

All the authors were involved in concept design, preparation, critical analysis, and revision of the manuscript and are involved in the management of the patient.

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Consent to publication

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Availability of data and materials

All data sets on which the conclusions of the case report based, to be available as a medical record document and available from the corresponding author on reasonable request from the editors.

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