



BMH Med. J. 2026;13(2):47-51. **Case Report**

Alpha Lipoic Acid Related Insulin Autoimmune Syndrome

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Abstract

Background: Insulin Autoimmune Syndrome, also known as Hirata disease, is a rare cause of spontaneous late postprandial hypoglycemia characterised by elevated insulin levels and insulin autoantibodies in the absence of prior exposure to exogenous insulin. Drug-induced Insulin Autoimmune Syndrome, particularly with alpha-lipoic acid, is emerging as a significant etiology.

Case Report: A middle aged patient presented with recurrent symptomatic late postprandial hypoglycaemia (plasma glucose: 62 mg/dL) relieved on taking fruit juice. Her oral hypoglycaemic medications were recently titrated in view of poor glycaemic control. There was no history of insulin or sulfonylurea use, organ failure, critical illness or skipping of meals. She was on vitamin supplements containing alpha lipoic acid in the last 2 months for diabetic peripheral neuropathy. Investigations showed no features of pituitary or adrenal insufficiency. For further evaluation of probable endogenous hyperinsulinism, she was subjected to an extended oral glucose tolerance test. Inappropriately elevated insulin and C-peptide levels were detected at a plasma glucose nadir of 55 mg/dL at 240 minutes. The molar ratio of insulin/C-peptide was more than 1 and insulin autoantibodies were grossly elevated. She was managed conservatively with dietary measures including low-carbohydrate frequent small meals and withdrawal of the vitamin supplement with alpha lipoic acid. There was a good response in 3 months.

Conclusion: Insulin Autoimmune Syndrome should be considered in patients with hyper insulinemic hypoglycaemia without insulin therapy, particularly when there is an exposure to alpha-lipoic acid. This awareness prevents unnecessary invasive interventions.

Keywords: Insulin autoimmune syndrome, Hirata disease, hypoglycaemia, alpha-lipoic acid, insulin autoantibody

Introduction

Insulin autoimmune syndrome was first described by Yukuhamu Hirata in 1970 in a Japanese patient with spontaneous hypoglycemia and insulin autoantibodies [1]. As of 2023, 795 cases have been documented from East Asia (Japan, China) with sporadic cases reported from Europe, USA, Italy, Argentina and 29 cases from India. Both sexes in the mean age of 40-70 years were affected [2-5].

A strong genetic predisposition (HLA-DRB1*0406 allele in East Asians and HLA-DRB1*0403 in Caucasians) and drug triggers, particularly those containing sulfhydryl groups such as methimazole, carbimazole, and alpha-lipoic acid, are well documented. Disruptions appear within 4-6 weeks of starting alpha lipoic acid and clinical symptoms remit after its discontinuation. Other drugs included hydralazine, procainamide, diltiazem, isoniazid, clopidogrel, insulin and its analogues, omeprazole, loxoprofen, imipenem, alpha-lipoic acid, captopril, d penicillamine and propranolol. Insulin Autoimmune Syndrome is commonly associated with other autoimmune conditions, such as Grave's disease, latent autoimmune diabetes in adults, systemic lupus erythematosus, Hashimoto thyroiditis, Sjogren's syndrome, scleroderma, rheumatoid arthritis, multiple myeloma, ankylosing spondylitis, autoimmune polyglandular syndrome Type 3, and ANCA associated nephritis [6].

Viral infections, as superantigens implicated to trigger formation of autoantibodies include measles virus, mumps virus, rubella virus, varicella zoster virus, coxsackie B virus and hepatitis C.2

Here we describe a case of alpha-lipoic acid associated Insulin Autoimmune Syndrome in a middle-aged Indian woman with unstable blood sugar levels managed conservatively.

Case Report

A middle aged patient presented with episodes of sweating, dizziness, and near-syncope occurring both in the fasting state and 3-4 hours after meals for 1 month. The symptoms were relieved on having high carbohydrate foods. Blood sugar level during such episodes was 62 mg/dl. There was no history of altered sensorium or seizures. She was on sitagliptin and metformin for control of blood sugar. She had no history of insulin or sulfonylurea use. 2 months before presenting to our OP she was initiated on vitamin supplements containing alpha-lipoic acid as she was suffering from neuropathic pain and positional vertigo. On examination, BMI was 24, there was no acanthosis nigricans or skin tags. Systemic examination was unremarkable.

She was subjected to a 75-g oral glucose tolerance test (OGTT) which produced a glucose nadir of 55 mg/dL [Figure 1] at 240 minutes. Inappropriately elevated insulin (888), C peptide (10.6) levels were detected. As the molar ratio of insulin/C-peptide was more than 1, insulin autoantibodies tested were grossly elevated (>300). The constellation of recurrent hypoglycaemia, hyperinsulinemia, positive insulin autoantibodies, and absence of exogenous insulin use established the diagnosis of Insulin Autoimmune Syndrome.

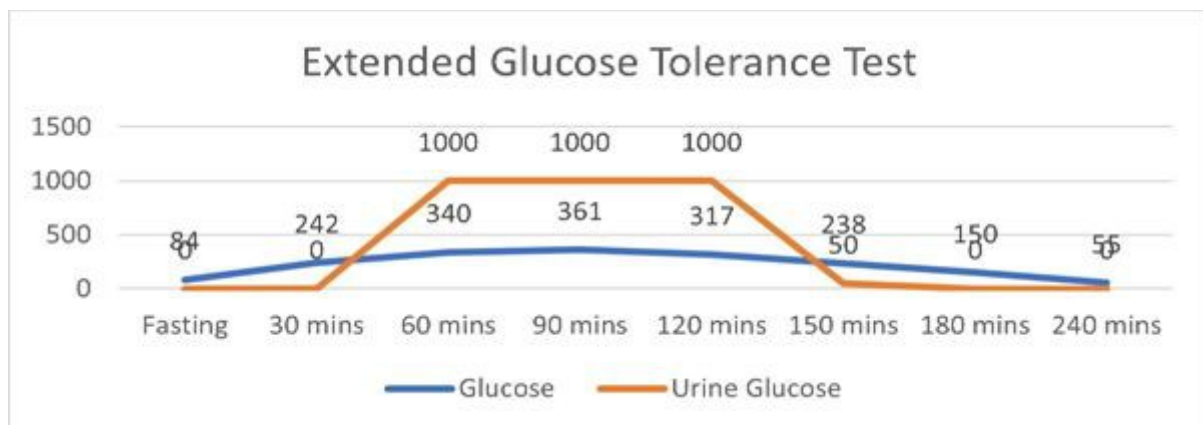
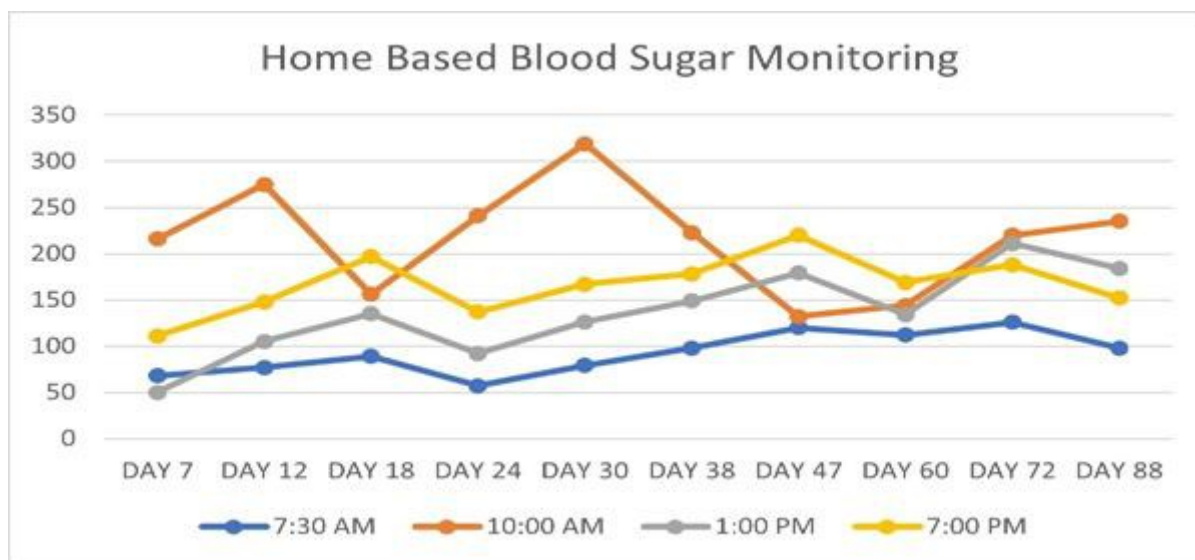


Figure 1: Extended Glucose Tolerance Test

Table 1: Laboratory Data

		Unit	Normal range
HbA1c	7.1	%	4.6 – 6.2
Cortisol	14.2	µg/dl	4 - 20
TSH	2.33	µIU/ml	0.5 - 5
Insulin	888	µU/ml	1-23
C peptide	10.6	ng/ml	0.8-3.1
Insulin/ C peptide molar ratio	1.52		<1
Insulin Autoantibody	>300		

She was managed by discontinuation of alpha-lipoic acid containing drug along with frequent, small low-carbohydrate meals. Over the following 3 months, her hypoglycaemic episodes decreased significantly. There was no need for pharmacological immunosuppression.

**Figure 2:** Home Based Blood Sugar Monitoring

Discussion

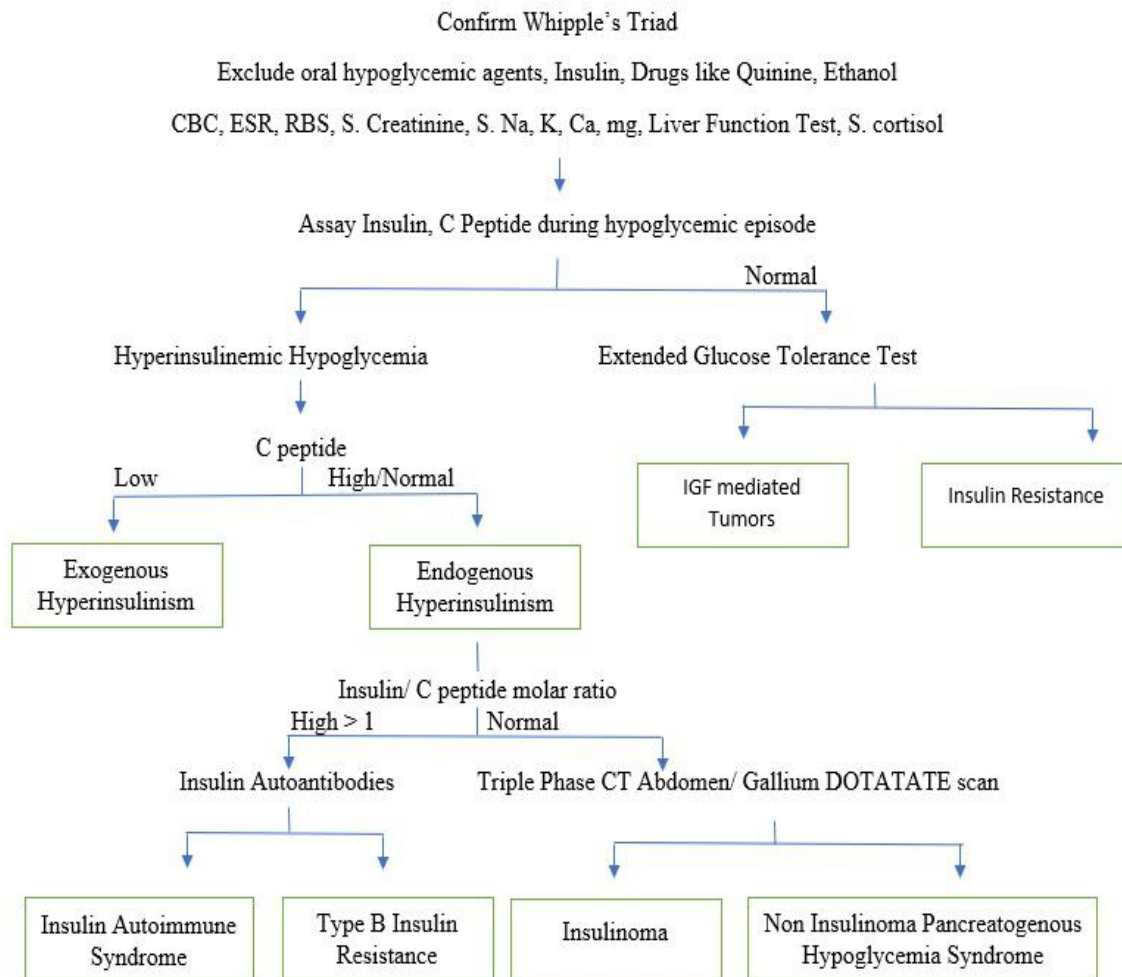
Insulin Autoimmune Syndrome is postulated to occur due to the formation of insulin autoantibodies with low affinity but high binding capacity. Recent studies highlight increasing reports of Insulin Autoimmune Syndrome globally, with emerging associations to viral infections and medications in genetically predisposed individuals. Drugs containing sulfhydryl group act as haptens and augment immunogenicity.

Following a meal, secreted insulin is bound by antibodies, rendering it temporarily inactive. This leads to transient hyperglycaemia. Later, dissociation of the insulin-antibody complex causes a surge in free insulin, resulting in hypoglycaemia.

Insulin and C-peptide are secreted into the portal circulation in an equimolar ratio by pancreatic beta cells. Insulin is cleared by the liver whereas C-peptide is mainly metabolized by the kidney. The latter process is relatively slower. The half-lives of insulin and C - peptide are 5-10 minutes and 30-35 minutes, respectively. The molar ratio of insulin to C-peptide is generally less than 1. Hence, Insulin Autoimmune Syndrome should be considered in cases of spontaneous hypoglycemia with a

high insulin/ C-peptide molar ratio.

In 82% of cases, IAS is self remitting, treated by the withdrawal of triggers and diet therapy. Pharmacotherapy may include alpha-glucosidase inhibitors (e.g., acarbose) to delay glucose absorption, corticosteroids to suppress antibody production, and agents such as diazoxide or somatostatin analogues to decrease endogenous insulin secretion. Immunosuppressive therapies, including rituximab, azathioprine, cyclophosphamide and plasma exchange, may be reserved for refractory cases.



Conclusion

Diagnosis of Insulin Autoimmune Syndrome relies on demonstrating insulin autoantibodies in patients with hyperinsulinemic hypoglycaemia and no history of prior insulin exposure. Awareness of the condition among physicians is critical to prevent unnecessary invasive procedures such as pancreatic surgery. Most patients can be managed conservatively with drug withdrawal and dietary changes, with immunosuppression reserved for refractory cases.

References

1. Hirata Y. Insulin autoimmunity in a case of spontaneous hypoglycemia. J. Jpn. Diabet. Soc. 1970;13:312-9.
2. Cappellani D, Macchia E, Falorni A, Marchetti P. Insulin autoimmune syndrome (Hirata disease): A comprehensive review fifty years after its first description. Diabetes Metab Syndr Obes. 2020;13:963-78.

3. Lin M, Chen Y, Ning J. Insulin autoimmune syndrome: A systematic review. *Int J Endocrinol* 2023;2023:1225676.
4. Dhaliwal KK, Bector G, Arora S, Singh A, Kalra S. An uncommon case of recurrent hypoglycemic episodes in a healthy non-diabetic male: Insulin autoimmune syndrome. *Cureus* 2023;15:e41183.
5. Patel M, Shah R, Ramteke-Jadhav S, Patil V, Patel SK, Lila A, et al. Management of insulin autoimmune hypoglycaemia: Single-centre experience from Western India with systematic review of world literature. *Clin Endocrinol (Oxf)* 2020;92:409-20
6. Lin M, Chen Y, Ning J. Insulin Autoimmune Syndrome: A Systematic Review. *Int J Endocrinol*. 2023 Feb 15;2023:1225676.