

## Hyperinsulinism, Insulin Resistance and Impaired Fasting Glucose Revealing an Insulin Autoimmune Syndrome

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### Abstract:

We report a case of a 55-year-old woman who was evaluated for multiple episodes of late postprandial hypoglycaemia. We diagnosed her condition as insulin autoimmune syndrome (Hirata disease) because of a high insulin autoantibody (IAA) titre in association with high levels of plasmatic insulin and hypoglycaemia in a patient with no history of exogenous insulin administration and the exclusion of other causes of late postprandial hypoglycaemia.

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## Introduction

Insulin autoimmune syndrome (IAS) is defined by the presence of hypoglycaemia and autoantibodies against endogenous insulin in subjects without a history of exogenous insulin administration. This disorder was first described in Japan by Hirata et al. in 1970<sup>1</sup>. The prevalence of the syndrome is still unknown; the majority of the cases were described in Japan, where 244 cases were detected in the period 1970–1997<sup>2</sup>. To date, it represents the third leading cause of hypoglycaemic disorder in that country<sup>2</sup>. This disorder is even more uncommon in non-Asian people, and few cases are described in the European and American literature<sup>3</sup>. In this paper, we report a case of Hirata disease in a middle-aged Italian woman.

## Case report

A 55-year-old woman was referred to our clinic with metabolic syndrome. Routine blood examinations done 3 weeks before showed mild hyperinsulinaemia, impaired glucose tolerance and hypercholesterolaemia, and a glycosylated haemoglobin of 45 mmol/l. She had a family history of diabetes mellitus. She had never smoked or drunk alcohol and had no allergies. She had a history of a thrombophilic syndrome (factor V Leiden heterozygote mutation) and postmenopausal osteoporosis. She had no history of diabetes, gastric surgery or pancreatic disorders. She had been taking aspirin and alendronate. She had never taken insulin or other oral hypoglycaemic agents.

Her weight was 84 kg, body mass index 34.5 kg/m<sup>2</sup> and waist circumference 103 cm, consistent with a diagnosis of metabolic syndrome. Otherwise, her physical examination was normal.

The patient was discharged with nutritional and lifestyle change advice. In the following months, she began suffering from general fatigue, dizziness and palpitations that occurred about three hours after meals. A random measurement of capillary glycaemia during symptoms revealed a glucose level of 40 mg/dl.

Laboratory evaluation revealed normal blood cell counts, blood chemistry and fasting glucose. She also had normal levels of adrenocorticotrophic hormone (ACTH), cortisol, thyroid-stimulating hormone (TSH) and glycosylated haemoglobin, but abnormally high levels of fasting insulin and c-peptide (*Table 1*). No abnormalities were detected in any other autoimmunity markers (*Table 1*). The association of hyperinsulinism, weight gain and hypoglycaemia suggested the presence of an insulinoma.

		Normal range
White blood cells	6980/mmc	4,000–11,000/mmc
Haemoglobin	13.4 g/dl	12–16 g/dl
Platelets	260,000/mmc	150,000-400,000 mmc
Fasting insulin	72 $\mu$ UI/ml	3–25 $\mu$ UI/ml
Fasting C-peptide	2.53 ng/ml	0.81–3.85 ng/ml
8:00 a.m. cortisol	549 nmol/l	150–650 nmol/l
ACTH	40 pg/ml	5–49 pg/ml
HbA1c (HPLC)	45 mmol/mol	<48 mmol/mol
Polymerization chain reaction	3.32 mg/l	0–5 mg/l
Antinuclear antibodies	Absent	–
Anti-dsDNA	Absent	–
Extractable nuclear antigen	Absent	–
Anti-SCL-70	Absent	–
Anti-surreal-gland	Absent	–
Anti-GAD	Absent	–
Anti-iInsulin receptor	Absent	–
Anti-insulin	>100 UI/l	–

Table 1: Laboratory findings in our patient

During 48 h of fasting, no hypoglycaemia occurred. However, serum concentration of insulin and c-peptide progressively normalized (Fig. 1).

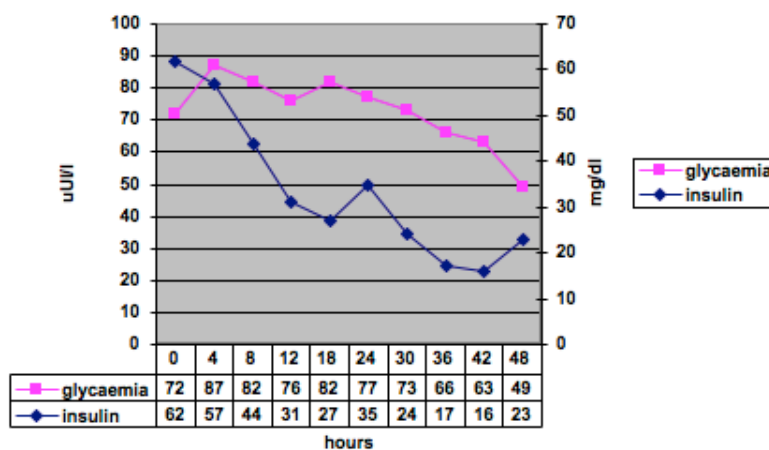


Figure 1: blood glucose and insulin levels during prolonged (48 h) fasting test.

Subsequently, we performed an oral glucose tolerance test, which showed a very high concentration of insulin in the late postprandial period in association with abnormally lower blood glucose levels (Fig. 2).

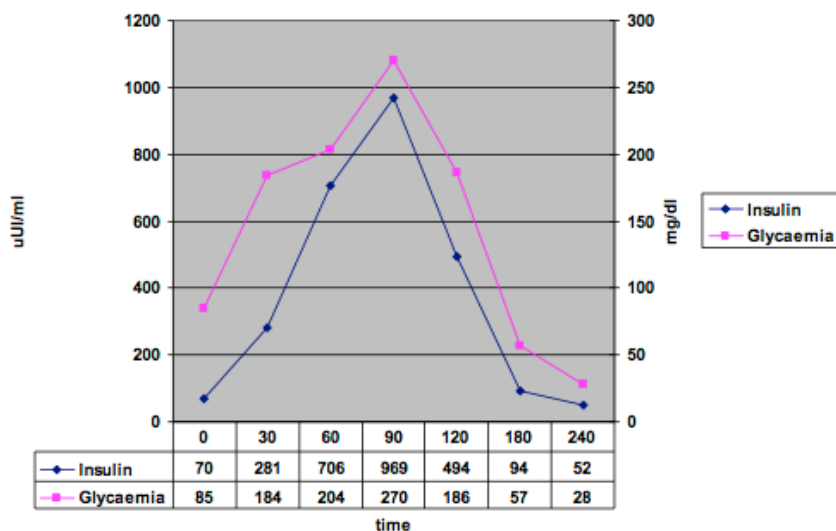


Figure 2: blood glucose and insulin levels during oral glucose tolerance test

Since no pancreatic masses or other suspicious lesions were detected by ultrasound of the abdomen, or by thoracic and abdominal CT scans, we measured anti-insulin antibodies (IAA), which were present in high titres (IAA>100 UI/ml). The presence of a high insulin autoantibody titre in association with high levels of plasmatic insulin and hypoglycaemia without a history of insulin administration confirmed the diagnosis of autoimmune hypoglycaemic syndrome (Hirata disease).

## Discussion

IAS or Hirata disease is very uncommon in Western countries: to date only 60 cases have been reported in the non-Asian population. It is clinically characterized by hyperinsulinaemic hypoglycaemic episodes, often occurring in the late postprandial period. Fasting- and exercise-induced hypoglycaemia has also been described.

IAS has been associated with many comorbidities and exposure to various medications. The diseases most frequently associated with IAS are rheumatologic diseases such as systemic lupus erythematosus (SLE) and systemic sclerosis, and haematological diseases in which there is an improved production of immunoglobulins such as benign monoclonal gammopathy or multiple myeloma<sup>3,4</sup>. Positive antinuclear antibodies, anti-double-stranded DNA and rheumatoid factors in the absence of clinical manifestations are also common findings.

Many drugs have been associated with the development of Hirata disease. Lupsa et al. suggested that in about 47% of the non-Asian patients, IAS seemed to be triggered by exposure to different medications (captopril, penicillamine, pyritinol, imipenem, hydralazine, procainamide, isoniazide, penicillin G)<sup>3</sup>. In the Japanese cases, a clear relation was demonstrated between medications containing the sulphhydryl group and the occurrence of the syndrome<sup>3</sup>.

Our patient did not show any rheumatologic or haematological disorder and had no history of exposure to the drugs mentioned previously.

### **Pathophysiologic considerations**

Hirata disease is a rare cause of postprandial hypoglycaemia whose mechanism is to date not completely understood.

Some authors have suggested a strong association between IAS and human leukocyte antigen (HLA) haplotype. Most HLA-DR4-positive patients with IAS have HLA-DRB1\*0406, DRB1\*0403 or DRB10407. Moreover, it has been suggested that agents such as sulphhydryl compounds (methimazole, carbimazole, penicillamine) may be related to the onset of the syndrome. It has been postulated that the sulphhydryl group interacts with the disulphide bonds in the insulin molecule, making the insulin more immunogenic, either by hapten formation, or by cleavage of the disulphide bonds of the insulin molecule. In most cases, discontinuing the sulphhydryl medications was associated with the remission of the hypoglycaemic episodes<sup>3</sup>.

It has been hypothesized that hypoglycaemia occurs through two main mechanisms:

1. During the early postprandial period, the autoantibody immediately binds to insulin, masking its bioactivity to its receptors in the liver and in peripheral tissues. This results in hyperglycaemia and further insulin secretion.
2. During the late postprandial period, the autoantibody, because of low affinity, dissociates from insulin and the free insulin exerts its intrinsic glucose-lowering effect even in the presence of normal levels of glucose, thus causing hypoglycaemia.

The lower affinity and high binding capacity of IAA were described by Eguchi<sup>5</sup> in 1998. Thus, the autoantibody easily binds to insulin, but the insulin–autoantibody complex becomes unstable and suddenly uncouples once plasma insulin increases above certain threshold levels. In our case, this mechanism appears to have been present. In fact, in the OGTT test we observed that the insulin levels rose rapidly in the early postprandial period, independently of the blood glucose levels, and the glucose levels fell only in the late postprandial period (*Fig. 1*). We also observed that there was a degree of fasting hyperinsulinism that disappeared only after 48 h of fasting (*Fig. 2*).

### Therapeutic Approach

The most widely suggested therapeutic strategies for Hirata disease are educational measures like frequent and small meals, low in simple carbohydrates. The use of alpha-glucosidase inhibitors has also been suggested. Both strategies are intended to decrease glucose-dependent insulin secretion in the first phase of the postprandial period, the former by reducing the glycaemic load and the latter by delaying glucose absorption. Administration of corticosteroids or immunosuppressive drugs in combination with plasmapheresis is another possible therapy, but clinical evidence is lacking for these treatments.

In our patient, acarbose was administered without improvement of postprandial glycaemia. Our choice, therefore, was to educate the patient to eat low-carbohydrate meals, and this was enough to avoid her postprandial symptoms.

In conclusion, Hirata disease is a very uncommon cause of hypoglycaemia, however it should be considered in the differential diagnosis in any patient with hyperinsulinaemic hypoglycaemia because a correct diagnosis may spare a hypoglycaemic patient from an unnecessary pancreatic surgical procedure.

### Learning Points

- Hirata disease is a rare case of hypoglycaemia.
- Frequently, a metabolic syndrome due to chronic hyperinsulinism is associated.
- A correct diagnosis may spare a patient from an unnecessary surgical procedure.
- Therapeutic strategies are focused on decreasing glucose-dependent insulin secretion in the first phase of the postprandial period.

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