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Case Report

Type A Insulin Resistance Syndrome Due to a Pathogenic Variant in the INSR Gene

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Abstract

Presentation
A woman in her 40s initially diagnosed with type 1 diabetes in 1994 exhibited an atypical 30-year metabolic course, characterised by fluctuating insulin sensitivity, prolonged insulin independence and later insulin resistance despite a non-obese phenotype.

Diagnosis
Owing to the unusual clinical trajectory and a strong family history of young-onset diabetes, genetic testing identified a heterozygous pathogenic INSR mutation (p.M1180K), confirming Type A Insulin Resistance Syndrome (TAIRS).

Treatment
Management evolved from insulin therapy to oral hypoglycaemic agents, including metformin and gliclazide alongside lifestyle modification resulting in partial glycaemic improvement.

Discussion
This case underscores the diagnostic challenge of TAIRS, which is frequently misclassified as type 1 or type 2 diabetes and highlights the importance of early genetic evaluation and multidisciplinary care.

Introduction

Type A insulin resistance syndrome (TAIRS) is a rare autosomal dominant disorder caused by heterozygous mutations in the insulin receptor (INSR) gene, resulting in reduced receptor

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number, impaired insulin binding or defective post-receptor tyrosine kinase signalling, leading to severe insulin resistance in the absence of obesity or lipodystrophy[1,2]. Impaired insulin signalling results in compensatory hyperinsulinemia which drives cutaneous manifestations such as acanthosis nigricans and contributes to ovarian hyperandrogenism in females through insulin-mediated stimulation of androgen production[2]. Clinically, TAIRS typically presents in young, non-obese females with hyperinsulinemia, acanthosis nigricans and variable degrees of glucose intolerance[1]. Misdiagnosis as type 1 or type 2 diabetes is common, delaying appropriate therapy and genetic counselling. We describe a unique case with a 30-year evolving clinical course, culminating in molecular confirmation of TAIRS.

Case Report

A woman in her 40s was diagnosed with diabetes in 1994 at age 13 after presenting with osmotic symptoms, a 9-kg weight loss (65→56 kg) and acanthosis nigricans. Initial HbA1c was 10.3% (89 mmol/mol). She was commenced on insulin with rapid glycaemic improvement. Over the subsequent three years, HbA1c normalised to 4.1-5.4% with minimal insulin requirements, consistent with a prolonged honeymoon phase.

Between 1999 and 2005, glycaemic control progressively deteriorated (HbA1c up to 10% or 86 mmol/mol) despite discontinuation of insulin in 2002, accompanied by weight gain to 79 kg. From 2006 to 2007, she entered a catabolic phase with 16-kg weight loss and fluctuating glycaemic control despite oral hypoglycaemic therapy. Between 2007 and 2012, partial remission was achieved on metformin and gliclazide, with HbA1c ranging from 7-9% (53-75 mmol/mol).

During two pregnancies between 2013 and 2015, she developed marked insulin resistance and required a basal-bolus insulin regimen. In subsequent years, glycaemic control and weight fluctuated, largely related to suboptimal adherence and lifestyle factors.

Given the atypical disease course and a strong family history of early-onset diabetes affecting multiple non-obese and obese siblings, genetic testing was undertaken in august 2022. Testing was performed at the Exeter Genomics Laboratory (UK) using a targeted next-generation sequencing panel for monogenic diabetes genes. This identified a heterozygous pathogenic *INSR* variant [p. (Met1180Lys)], confirming Type A insulin resistance syndrome. C-peptides were normal (1060 pmol/L) and autoimmune antibodies (GAD, ICA, ZnT8) were negative

She was treated with metformin, gliclazide and empagliflozin, titrated to glycaemic targets. HbA1c improved from 9.8% (75 mmol/mol) to 7.3% (56 mmol/mol) with stable weight (65–68 kg) on regular follow-up. A summary of proband's clinical course is presented in Table 1.

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Years	Weight (kg)	HbA1c (%)	Treatment	Remarks
1994-1995	56-58	10	Insulin M3 (46 units/day)	Diagnosed type 1 diabetes
1996-1997	58	5	Insulin M3 (8-10 units/day)	Honey moon phase
1998-1999	62.5	3.85	Insulin M3 (6-8 units/day)	Honey moon phase
2000-2001	70	7.7	Insulin M3 (8-10 units/day)	Poor control
2002-2003	75	9.5	Metformin+ sulfonylurea	Diagnosed type 2 diabetes and transitioned from insulin to oral therapy
2004-2005	NA	9.7	sulfonylurea	
2006-2007	63	6.4	Metformin+ sulfonylurea	Improved glycaemic control
2008-2010	NA	6.7	No medication	
2011-2012	NA	6.8	No medication	
2013-2014	75	6.8	Basal-bolus insulin (Levemir+ NoVo-rapid)	First pregnancy
2015-2016	74	8.4	Basal-bolus insulin	Second pregnancy
2017-2018	NA	8.6		
2019-2020	75	10.2	Metformin+ sulfonylurea	Poor glycaemic control
2021-2022	74	7.4	Metformin+ sulfonylurea + basal insulin	Improved control on combination therapy +diagnosed with INSR mutation
2023-2024	66.5	8.2	Metformin + empagliflozin	Suboptimal glycaemic control
2025	69.3	7.9	Metformin + empagliflozin+ tirzepatide	Persistent dysglycaemia

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Table 1. *Temporal trends in weight, glycaemic control (HbA1c) and therapeutic interventions over the disease course. The data demonstrate fluctuations in glycaemic control with transitions between insulin therapy and oral hypoglycaemic agents including intensified insulin regimens during pregnancy. Missing values represent unavailable clinical data.NA=data not available due to inconsistent clinic follow up*

Discussion

TAIRS arises from heterozygous mutations in the INSR gene, resulting in reduced insulin receptor number or signalling efficacy[2,3]. Unlike Type B insulin resistance, there are no autoantibodies against the receptor. The disease is often more pronounced in females, likely due to hormonal modulation of insulin sensitivity[4].

Our case demonstrates a prolonged and evolving metabolic phenotype transitioning from insulin-sensitive to insulin-resistant phases over three decades. Such biphasic evolution reflects dynamic interplay between receptor function, β-cell compensation, and metabolic stress[5]. Moreover, family screening demonstrated that multiple affected first-degree relatives also carry the same variant, confirming co-segregation with the disease phenotype and supporting autosomal dominant inheritance.

Management is largely supportive: metformin enhances insulin sensitivity, thiazolidinediones improve peripheral glucose uptake and IGF-1 analogues or GLP-1 receptor agonists may provide benefit in refractory cases[6,7]. Regular long-term surveillance is advised for glycaemic control, cardiovascular risk, reproductive dysfunction and malignancy risk. Recognition of this condition is crucial, as genetic confirmation allows accurate classification, family screening and avoidance of unnecessary immunosuppressive or excessive insulin therapy.

Declarations of Conflicts of Interest:
None declared.

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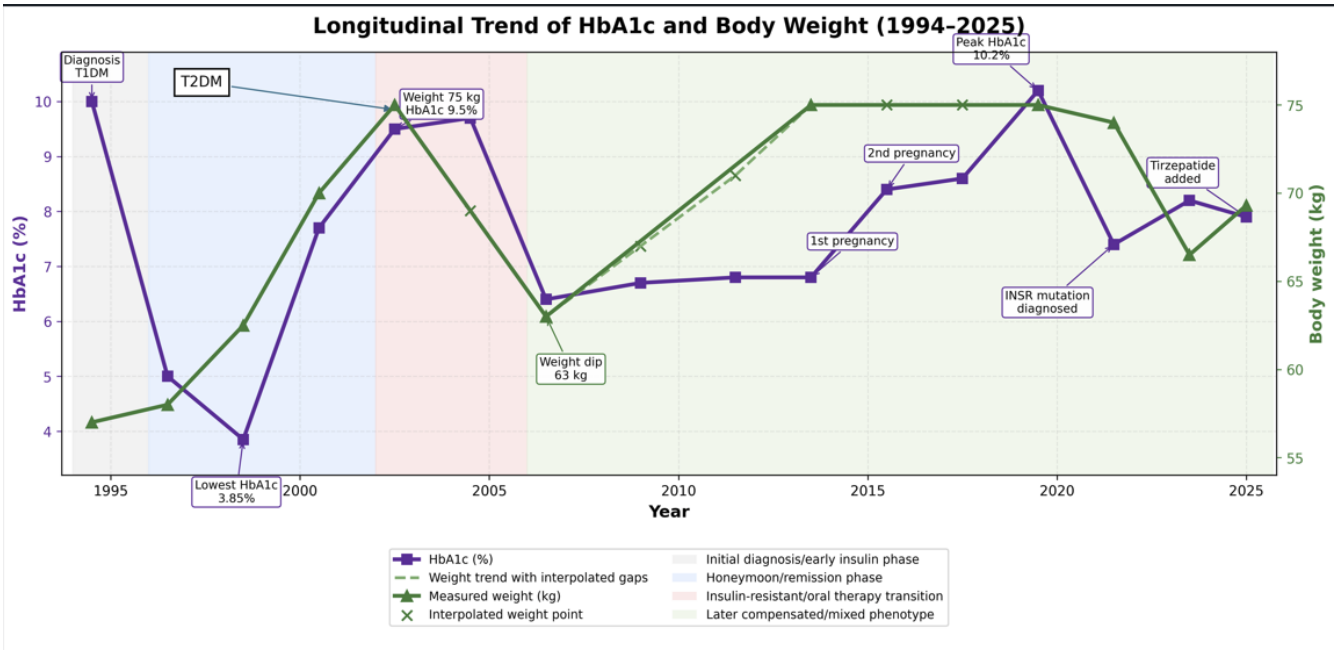

Figure1. Long-term changes in HbA1c and body weight from 1994 to 2025.HbA1c (%) is shown with square markers (left axis) and body weight (kg) with triangle markers (right axis). Solid green points represent measured weight, while dashed lines and "×" markers indicate estimated values where weight data were missing. Background colours represent different clinical phases over time.