Diabetes, Metabolic Syndrome and Obesity

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ORIGINAL RESEARCH

Clinical Characteristics and Risk Factors of Exogenous Insulin Antibody Syndrome in Patients with Diabetes: A Retrospective Cross-Sectional Study

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Background: Insulin autoimmune syndrome (IAS) is a rare hypoglycemic disorder often confused with insulinoma or insulin overdose. Patients with diabetes on insulin therapy increasingly show insulin autoantibodies (IAAs), presenting symptoms similar to classic IAS, termed exogenous insulin antibody syndrome (EIAS). This study examines EIAS clinical features and risk factors.

Methods: Patients with diabetes with IAA test results, admitted to our hospital between June 2023 and March 2024 were retrospectively enrolled. Participants were stratified into control and EIAS groups on the basis of IAA status. Clinical characteristics were compared between groups, independent risk factors for EIAS were identified by multivariate logistic regression, and the diagnostic utility of fasting insulin for predicting EIAS was assessed with receiver-operating-characteristic (ROC) curve analysis.

Results: Of 120 patients with diabetes and available IAAs results, 37 met criteria for EIAS. Compared with controls, EIAS patients were older, had longer diabetes duration, were more often treated with insulin aspart or premixed human insulin, and received higher daily insulin doses. Paradoxically, EIAS patients had markedly lower levels of fasting blood glucose and HbA1c, while higher fasting and 2-h post-prandial insulin concentrations, as well as HOMA-IR. Multivariate logistic regression analysis showed that elevated fasting insulin levels were independently associated with increased risk of EIAS. For every 1 uU/mL increase in fasting insulin, the risk of EIAS increased by 3% (OR = 1.03, 95% CI: 1.00–1.05). The fasting insulin level demonstrated high overall diagnostic and predictive efficacy for EIAS, with an area under the curve (AUC) of 0.782 (95% CI: 0.691–0.872). The optimal diagnostic cutoff value was 6.975 uU/mL, with a sensitivity of 73.0% and a specificity of 81.9%.

Conclusion: EIAS patients were identified with advanced age, prolonged diabetes duration, high insulin dosage, hypoglycemia, and hyperinsulinemia. Fasting insulin level is independently associated with EIAS risk and demonstrates good diagnostic performance.

Keywords: exogenous insulin antibody syndrome, fasting insulin, receiver operating characteristic curve, insulin resistance

Introduction

Insulin autoimmune syndrome (IAS) is a rare autoimmune disorder characterized by the production of autoantibodies against endogenous insulin. Its typical clinical manifestations include recurrent hypoglycemic episodes, accompanied by significantly elevated serum insulin levels and high titers of endogenous insulin autoantibodies (IAAs).[1,2] Current evidence indicates that the pathogenesis of IAS is closely associated with genetic susceptibility (eg, HLA-DRB10406, HLA-DRB10415 alleles) and exogenous triggers (such as exposure to sulfhydryl-containing drugs), leading to abnormal binding and subsequent release of insulin by autoantibodies, thereby disrupting glucose homeostasis.[3,4] This mechanism

https://doi.org/10.2147/DMSO.S571981
Received: 30 November 2025
Accepted: 13 February 2026
Published: 7 March 2026

partly explains the relatively higher epidemiological prevalence of IAS in Asian populations, which is linked to the higher carrier frequency of IAS-related immunogenic determinants—such as HLA-DR4, particularly DRB1*0406—in these groups.[4]

Of particular note, an increasing number of cases of atypical IAS triggered by exposure to exogenous insulin or its analogs have been reported in recent years, termed exogenous insulin antibody syndrome (EIAS).[5] Both typical IAS and EIAS present with similar clinical manifestations, particularly recurrent hypoglycemic episodes, which closely resemble other hypoglycemic disorders such as insulinoma and reactive hypoglycemia, leading to considerable diagnostic challenges and high rates of misdiagnosis.[6] In recent years, advances in immunological detection techniques have gradually improved the diagnosis rate of EIAS; however, further research is still needed to elucidate its pathophysiology, optimize treatment strategies, and evaluate long-term outcomes. Therefore, clarifying the pathogenesis, clinical characteristics, and key diagnostic criteria of EIAS is of significant clinical value in enhancing physicians' recognition of the disease and reducing misdiagnosis and inappropriate management. This study retrospectively enrolled patients with diabetes and IAA test results who were admitted to the Department of Endocrinology of our hospital from June 2023 to March 2024, aiming to investigate the clinical features and potential risk factors of EIAS patients, thereby providing insights for clinical practice.

Participants and Methods

Participants

This study retrospectively enrolled patients with diabetes with IAA test results who were admitted to the Department of Endocrinology of our hospital between June 2023 and March 2024. The inclusion criteria were: (1) meeting the diagnostic criteria for type 1 or type 2 diabetes mellitus (T1DM or T2DM),[7] including latent autoimmune diabetes in adults (LADA);[8] (2) having undergone IAA testing. Patients with insulinoma or repeated tests were excluded. A total of 120 patients with diabetes were finally included.

The present study was a retrospective observational study that did not include data on patient privacy and was exempt from informed consent by the patients. The study was approved by the Clinical Ethics Committee of the Second Affiliated Hospital of Xi'an Jiaotong University (Approval number: 2023404) and was conducted in accordance with the principles of the Declaration of Helsinki.

Data Collection

Demographic data (including gender, age, and BMI), type of diabetes, duration of disease, types and dosages of insulin administered, history of oral hypoglycemic agent use, as well as laboratory test and oral glucose tolerance test (OGTT) results were collected. The insulin assay was conducted by electrochemiluminescence immunoassay using commercial kits. The HOMA-IR was calculated using the formula: HOMA-IR = fasting blood glucose [FBG] (mmol/L) × fasting insulin (μU/mL) / 22.5.[9] A higher HOMA-IR value indicates a greater degree of systemic insulin resistance (IR).

EIAS Diagnosis

IAA testing was uniformly performed by Xi'an KingMed Medical Laboratory. The diagnosis of EIAS was extracted from the discharge diagnoses recorded in admission summaries and was confirmed by endocrinologists with extensive clinical experience. The diagnostic process was primarily based on clinical manifestations, laboratory investigations, and the detection of insulin autoantibodies, after excluding other causes of hypoglycemia, such as insulinoma or excessive hypoglycemic drug administration.[2] The diagnostic criteria included: (1) documented spontaneous hypoglycemia episodes with hyperinsulinemia and unsuppressed serum C-peptide; (2) positive IAA defined as either insulin antibody binding rate ≥5% by radioimmunoassay or IAA concentration ≥20.00 RU/mL via chemiluminescence immunoassay; (3) history of exogenous insulin injection; (4) radiographic exclusion of insulinoma or pancreatic pathology.[10]

Statistical Analysis

Missing data were addressed via multiple imputation. Normally distributed continuous variables are presented as mean ± standard deviation, while non-normally distributed variables are expressed as median [interquartile range]. Normality was assessed using the Shapiro–Wilk *W*-test. Comparisons between groups for normally distributed continuous variables were performed using the independent samples *t*-test; non-normally distributed variables were compared using the Mann–Whitney *U*-test; and categorical variables were compared using the chi-square test or Fisher's exact test, as appropriate. Univariate and multivariate binary logistic regression analyses were employed to identify risk factors associated with EIAS. Variables showing an association with EIAS in the univariate analysis ($P < 0.1$) were included in the multivariate logistic regression model. Results are presented as odds ratios (OR) with their corresponding 95% confidence intervals (95% CI). ROC curve analysis was used to evaluate the effectiveness of fasting insulin in predicting early EIAS. All analyses were performed using R Statistical Software (Version 4.2.2, http://www.R-project.org, The R Foundation) and Free Statistics analysis platform (Version 1.9, Beijing, China, http://www.clinicalscientists.cn/freestatistics). A two-sided *P* value < 0.05 was considered statistically significant.

Results

Clinical Features of EIAS Patients

A total of 120 patients with diabetes mellitus were ultimately included in this study, with a mean age of 51.3 ± 17.5 years. The cohort consisted of 68 males (56.7%), 97 patients with T2DM (80.8%), 11 with T1DM (9.2%), and 12 with LADA (10.0%). Compared to the controls, EIAS patients were much older (60.1 ± 17.2 years vs 47.3 ± 16.2 years), had a longer median duration of diabetes (12.0 years vs 6.0 years), required higher daily insulin doses (median 37.0 IU vs 20.0 IU), exhibited lower estimated glomerular filtration rates (eGFR, 88.2 ± 22.3 mL/min/1.73m^2 vs 105.1 ± 24.6 mL/min/1.73m^2), and had higher median urinary albumin-to-creatinine ratios (ACR, 51.8 vs 14.8). Notably, EIAS patients exhibited markedly lower levels of FBG (9.8 ± 3.5 mmol/L vs 12.3 ± 5.9 mmol/L) and glycated hemoglobin (HbA1c, 8.3 ± 1.6% vs 9.9 ± 2.5%), but higher fasting insulin (median 14.2 μIU/mL vs 3.1 μIU/mL), higher 2-hour postprandial insulin (median 19.7 μIU/mL vs 8.4 μIU/mL), and elevated HOMA-IR values, suggesting more severe IR. Furthermore, the use of insulin aspart and human premixed insulin was significantly more frequent in the EIAS group ($P < 0.05$; Table 1).

Table 1 Clinical Features of EIAS Patients

	Total (n = 120)	Controls (n = 83)	EIAS (n = 37)	*P* Value
Age, years	51.3 ± 17.5	47.3 ± 16.2	60.1 ± 17.2	<0.001
Male, n (%)				0.114
Male	68 (56.7)	51 (61.4)	17 (45.9)	
Female	52 (43.3)	32 (38.6)	20 (54.1)	
BMI, kg/m^2	22.8 ± 3.3	22.5 ± 3.2	23.5 ± 3.5	0.146
Type of diabetes mellitus, n (%)				0.167
T1DM	11 (9.2)	8 (9.6)	3 (8.1)	
T2DM	97 (80.8)	64 (77.1)	33 (89.2)	
LADA	12 (10.0)	11 (13.3)	1 (2.7)	
Duration of diabetes, years	9.0 (1.0, 15.2)	6.0 (1.0, 12.5)	12.0 (8.0, 20.0)	0.003
Daily insulin dose, IU	26.0 (9.5, 42.0)	20.0 (0.0, 37.0)	37.0(26.0, 49.0)	<0.001
Smoking history, n (%)	45 (37.5)	35 (42.2)	10 (27)	0.114
History of alcohol use, n (%)	21 (17.5)	18 (21.7)	3 (8.1)	0.071
Platelet count, ×10^{12}/L	222.1 ± 62.6	221.9 ± 62.5	222.7 ± 63.8	0.947
Neutrophil count, ×10^9/L	4.0 ± 1.5	3.9 ± 1.6	4.3 ± 1.4	0.129

(*Continued*)

https://doi.org/10.2147/DMSO.S571981

Table 1 (Continued).

	Total (n = 120)	Controls (n = 83)	EIAS (n = 37)	*P* Value
Lymphocyte count, $\times 10^9$/L	0.4 ± 0.1	0.4 ± 0.1	0.4 ± 0.1	0.886
Monocyte count, $\times 10^9$/L	1.7 ± 0.7	1.7 ± 0.7	1.7 ± 0.7	0.619
Aspartate aminotransferase, IU/L	19.0 (13.5, 28.0)	17.0 (13.0, 28.0)	20.5 (15.0, 27.2)	0.489
Alanine aminotransferase, IU/L	22.0 ± 12.2	22.0 ± 13.7	22.0 ± 8.2	0.999
Albumin, g/L	44.5 ± 3.8	44.6 ± 3.4	44.3 ± 4.5	0.755
Serum uric acid, umol/L	294.1 ± 99.2	288.9 ± 107.4	305.6 ± 77.9	0.416
Blood urea nitrogen, mmol/L	5.5 ± 2.1	5.5 ± 2.1	5.6 ± 2.0	0.761
Serum creatinine, umol/L	65.7 ± 27.1	62.9 ± 28.1	72.1 ± 23.8	0.090
eGFR, mL/min ·1.73m^2	100.0 ± 25.1	105.1 ± 24.6	88.2 ± 22.3	<0.001
TC, mmol/L	4.6 ± 1.5	4.8 ± 1.6	4.3 ± 1.3	0.145
TG, mmol/L	1.4 (1.0, 2.1)	1.4 (1.0, 2.3)	1.4 (0.9, 1.7)	0.358
HDL-C, mmol/L	1.3 ± 0.3	1.3 ± 0.3	1.3 ± 0.4	0.914
LDL-C, mmol/L	2.7 ± 1.0	2.8 ± 1.0	2.5 ± 1.0	0.187
FBG, mmol/L	11.5 ± 5.4	12.3 ± 5.9	9.8 ± 3.5	0.021
Fasting insulin, uU/mL	4.4 (2.1, 14.5)	3.1 (1.3, 6.2)	14.2 (5.7, 37.3)	<0.001
Fasting C-peptide, ng/mL	0.9 (0.6, 1.6)	0.9 (0.6, 1.5)	1.2 (0.7, 1.9)	0.071
2h postprandial blood glucose, mmol/L	14.9 ± 4.7	14.9 ± 4.3	15.0 ± 5.5	0.902
2h postprandial insulin, uU/mL	11.1 (4.5, 23.1)	8.4 (3.6, 15.3)	19.7(11.2, 43.8)	<0.001
2h postprandial C-peptide, ng/mL	1.8 (1.2, 3.1)	1.8 (1.0, 3.0)	2.0 (1.4, 3.5)	0.267
HbA1c, %	9.4 ± 2.4	9.9 ± 2.5	8.3 ± 1.6	0.001
HOMA-IR	2.3 (0.9, 6.1)	1.8 (0.7, 3.4)	6.2 (2.4, 14.4)	<0.001
ACR, g/ug	17.1 (7.1, 83.5)	14.8 (6.6, 53.9)	51.8(8.1, 114.6)	0.045
Medication, n (%)				
Insulin aspart	57 (47.5)	34 (41)	23 (62.2)	0.032
Insulin glargine	46 (38.3)	28 (33.7)	18 (48.6)	0.121
Insulin lispro	8 (6.7)	6 (7.2)	2 (5.4)	1.000
Insulin detemir	13 (10.8)	7 (8.4)	6 (16.2)	0.217
Insulin degludec	40 (33.3)	31 (37.3)	9 (24.3)	0.162
Premixed human insulin	20 (16.7)	9 (10.8)	11 (29.7)	0.010
Metformin	61 (50.8)	44 (53)	17 (45.9)	0.475
Alpha-glucosidase inhibitors	31 (25.8)	21 (25.3)	10 (27)	0.842
SGLT2 inhibitors	16 (13.3)	10 (12)	6 (16.2)	0.567
DPP-4 inhibitors	13 (10.8)	9 (10.8)	4 (10.8)	1.000
Sulfonylureas	5 (4.2)	3 (3.6)	2 (5.4)	0.643
Thiazolidinediones	5 (4.2)	5 (6)	0 (0)	0.322
GLP-1 receptor agonists	8 (6.7)	5 (6)	3 (8.1)	0.701

Notes: Data are shown as mean ± standard deviation (SD) or median (IQR) for continuous variables and proportions (%) for categorical variables.

Abbreviations: TC, Total cholesterol; TG, Triglyceride; HDL-C, High-density lipoprotein cholesterol; LDL-C, Lows-density lipoprotein cholesterol; HOMA-IR, Homeostasis Model Assessment of Insulin Resistance; ACR, albumin-to-creatinine ratios; SGLT2, Sodium-glucose cotransporter 2; DDP4, Dipeptidyl-peptidase 4; TZD, Thiazolidinedione; GLP-1RA, Glucagon like peptide-1 receptor agonists.

Factors Associated with EIAS

Univariable logistic regression analysis revealed that age (OR = 1.05, 95% CI: 1.02–1.08), duration of diabetes (OR = 1.07, 95% CI: 1.02–1.12), insulin dose (OR = 1.03, 95% CI: 1.01–1.05), decreased GFR (OR = 0.97, 95% CI: 0.96–0.99), use of insulin aspart (OR = 2.37, 95% CI: 1.07–5.25), use of human premixed insulin (OR = 3.48, 95% CI: 1.30–9.34), FBG (OR = 0.90, 95% CI: 0.82–0.99), and fasting insulin (OR = 1.01, 95% CI: 1.00–1.03) were significantly associated with EIAS. In the multivariable logistic regression model, only elevated fasting insulin level remained independently and significantly associated with an increased risk of EIAS (OR = 1.03, 95% CI: 1.00–1.05, $P = 0.048$) (Table 2).

Table 2 Univariable and Multivariable Logistic Regression Analyses

	Univariable		Multivariable	
	OR (95% CI)	***P* Value**	**OR (95% CI)**	***P* Value**
Age, years	1.05 (1.02~1.08)	<0.001	1.04 (0.99~1.09)	0.107
Duration of diabetes, years	1.07 (1.02~1.12)	0.007	0.95 (0.87~1.04)	0.265
Daily Insulin dose, IU	1.03 (1.01~1.05)	0.001	1.03 (0.99~1.06)	0.087
History of alcohol use	0.32 (0.09~1.16)	0.082	0.22 (0.03~1.46)	0.116
eGFR, mL/min ·1.73m^2	0.97 (0.96~0.99)	0.002	0.99 (0.96~1.02)	0.354
FBG, mmol/L	0.9 (0.82~0.99)	0.024	0.91 (0.80~1.04)	0.179
Fasting insulin, uU/mL	1.01 (1.00~1.03)	0.029	1.03 (1.00~1.05)	0.048
Use of insulin aspart	2.37 (1.07~5.25)	0.034	2.49 (0.67~9.27)	0.173
Use of premixed human insulin	3.48 (1.30~9.34)	0.013	1.24 (0.26~5.93)	0.785

Diagnostic Performance of Fasting Insulin

ROC curve analysis demonstrated that fasting insulin exhibited good overall predictive efficacy for EIAS, with an AUC of 0.782 (95% CI: 0.691–0.872). The optimal diagnostic cut-off value was determined to be 6.975 μIU/mL, yielding a sensitivity of 73.0% and a specificity of 81.9% (Figure 1).

Discussion

Currently, clinical research on the risk factors for EIAS remains limited. Many studies were published in the last century, and the insulin used at that time was primarily animal-derived rather than the human insulin or insulin analogs that are widely used today. Consequently, the extrapolation of their findings to contemporary clinical practice has significant limitations.[1,11,12] The relevant studies in recent years are mainly retrospective studies and case reports, which have limited level of evidence.[13–15] A recent case-control study revealed that EIAS is also associated with unique HLA-DR-DQ risk haplotypes and enhanced immunoinflammatory response, with remarkably elevated molar ratio of insulin to C-peptide and prone to glycemic variability.[16] Based on this, we analyzed the clinical data of 120 patients with diabetes

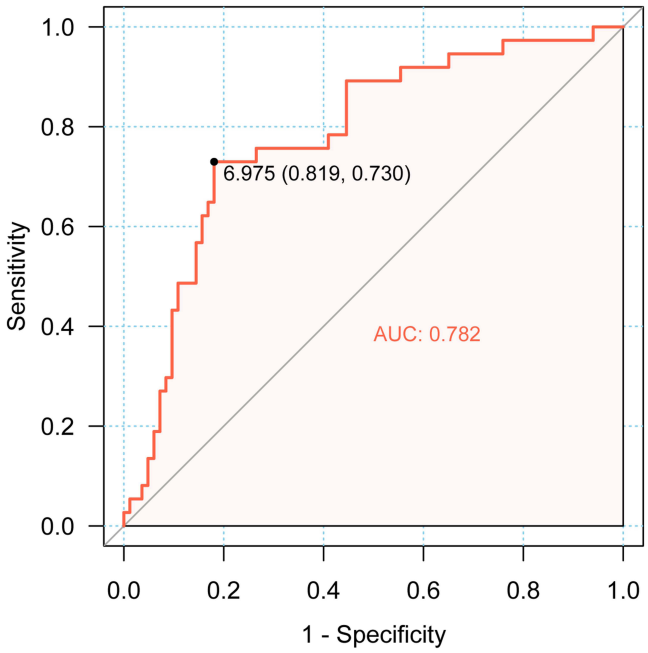

Figure 1 ROC curve analysis the efficacy of fasting insulin in EIAS diagnosis. The numbers in the brackets (0.819, 0.730) represent a sensitivity of 0.730 and a specificity of 0.819.

https://doi.org/10.2147/DMSO.S571981

who underwent IAA testing at our institution. Comparisons between groups found that patients with EIAS were characterized by an older age, a longer duration of DM, and a higher daily insulin dose. Meantime, patients with EIAS typically exhibit lower mean FBG and HbA1c levels, yet demonstrate markedly elevated fasting and postprandial 2-hour insulin levels. This distinctive metabolic profile predisposes them to an increased susceptibility to hypoglycemic episodes. Additionally, the EIAS group exhibited a higher prevalence of insulin aspart and premixed human insulin use compared to the controls. Multivariable logistic regression analysis demonstrates that only increased fasting insulin level is independently associated with the risk of EIAS, for every 1 uU/mL increase in fasting insulin levels, the risk of developing EIAS increased by 3%. These findings suggest that endocrinologists should maintain a high index of suspicion for EIAS in patients with diabetes, particularly in those who exhibit significant glycemic variability and recurrent hypoglycemic episodes despite receiving high doses of insulin therapy. In addition, fasting insulin monitoring contributes to the early detection and diagnosis of EIAS. The optimal cut-off of 6.975 μU/mL derived from ROC analysis represented a balance between sensitivity (73.0%) and specificity (81.9%). This value may aid in screening high-risk patients before confirmatory IAA testing.

Our study further conformed that patients with EIAS have lager insulin dose, suggesting a close association between EIAS and high insulin exposure. This is consistent with the retrospective findings by Li et al[6] which reported that hypoglycemia resolved within several days to three months after discontinuing insulin alone, combining with oral hypoglycemic agents, or switching insulin formulations. Moreover, a single-center study also reported that EIAS occurs more frequently in patients with diabetes with a history of autoimmunity or allergies.[17] Of note, although patients with EIAS exhibited lower mean FBG and HbA1c levels, they demonstrated a lower eGFR and a higher urinary ACR, suggesting more advanced diabetic kidney disease. This phenomenon may be related to the following two mechanisms: On the one hand, recurrent severe hypoglycemic episodes induced by IAA may cause acute kidney injury or exacerbate pre-existing renal disease.[18] This finding further underscores the clinical importance of recognizing and managing EIAS to minimize potential target organ damage. On the other hand, it reveals the prevalent state of hyperinsulinemia and severe IR in EIAS patients evidenced by significantly elevated fasting and 2-hour postprandial insulin levels as well as HOMA-IR indices, highlighting that glycemic management in diabetes should not only focus on absolute glucose levels but also emphasize glycemic variability and time in range.[19,20] Substantial evidence indicates that IR per se is an independent risk factor for the development and progression of diabetic kidney disease. Hyperinsulinemia may accelerate renal pathology through mechanisms such as promoting inflammatory responses and endothelial dysfunction.[21–23] Therefore, the management of EIAS should not merely focus on the correction of hypoglycemia, but should also aim at comprehensive control of underlying hyperinsulinemia and IR, so as to minimize the risk of target organ damage and improve long-term patient outcomes.

Patients with EIAS exhibited a characteristic triad of hypoglycemia, hyperinsulinemia, and severe IR, which highly consistent with the underlying pathophysiology of EIAS. Due to its high binding capacity and low affinity, IAA non-specifically binds to insulin, forming immune complexes that dissociate during glycemic fluctuations, releasing large amounts of free insulin.[1] This process not only precipitates hypoglycemic episodes but also leads to overactivation of insulin signaling pathways, thereby exacerbating IR and perpetuating a "hyperinsulinemia–IR" vicious cycle.[1] In contrast, insulin antibodies generated in response to exogenous insulin therapy typically exhibit higher affinity and lower binding capacity than IAAs, and are thus less likely to cause significant glycemic variability.[24] This mechanism also explains why, despite lower average FBG levels in the EIAS group compared to controls, the severity of hypoglycemia was not pronounced.

This study also has several limitations. First, its single-center design and relatively small sample size may limit the generalizability of the findings. Furthermore, the study population consisted exclusively of individuals who underwent IAA testing—a decision influenced by both clinician discretion and patient preference, as the test was performed externally and often self-paid. This inclusion criterion may have introduced selection bias. Second, data on the use of thiol-containing medications, such as alpha-lipoic acid and methimazole, which are established triggers of EIAS,[25] were not collected. This omission may have resulted in unmeasured confounding. Besides, inclusion patients with T1D or LADA may constitute a potential confounder, since these patients can also generate IAA against endogenous insulin. Finally, the lack of universally standardized diagnostic criteria for EIAS, particularly regarding hypoglycemia frequency

or glycemic variability, represents a major limitation. Since hypoglycemia is common in insulin-treated patients, our study might overestimate the true prevalence of EIAS.

Conclusions

In summary, this study confirms that EIAS patients were featured with advanced age, longer duration of diabetes, high insulin dosage, low FBG, hyperinsulinemia, and diabetic kidney injury. Elevated fasting insulin is associated with EIAS risk and may serve as a practical screening marker at a cut-off of 6.975 μU/mL. Clinicians should emphasize screening for EIAS in patients with diabetes, particularly those with high insulin exposure and recurrent hypoglycemia. Monitoring fasting insulin and IAAs may facilitate early diagnosis and improve patient prognosis.

Data Sharing Statement

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Ethics Approval and Consent to Participate

Our study complies with the Declaration of Helsinki, and the study was approved by the Clinical Ethics Committee of the Second Affiliated Hospital of Xi'an Jiaotong University (Approval number: 2023404). The informed consent requirement was exempted because of the retrospective study.

Author Contributions

Tuo Han: investigation, conceptualization, resources, supervision, and writing–review & editing. Jing Zhou and Jiajun Li: data curation, formal analysis, writing–original draft. Ziyue Wang, Xulei Dai: software, visualization, and writing–review & editing. Nenghan Zhang, Lingqi Kong, Siyuan Wu, Jiangyan Liu: methodology, validation, and writing–review & editing. Yan Zhang: investigation, conceptualization, supervision, funding acquisition, and writing–review & editing. All authors gave final approval of the version to be published. All authors have agreed on the journal to which the article has been submitted and agreed to be accountable for all aspects of the work.

Funding

This work was supported by National Natural Science Foundation of China (82100359), Xi'an Science and Technology Plan Project (24YXYJ0148), and Scientific Research Fund Youth Project of the Second Affiliated Hospital of Xi'an Jiaotong University (YJ(QN)202325).

Disclosure

The authors declare that they have no competing interests.

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