Systematic Review

Insulinoma in Patients with Diabetes- A Systematic Review of Previously Reported Cases

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Abstract

Introduction: Paradoxical co-existence of insulinoma and diabetes is extremely rare. Although a few case reports addressed this association, a comprehensive study elucidating this relationship has been lacking. We performed a systematic review of published cases of insulinoma in diabetes. **Methods:** We conducted a literature search using PubMed and Google Scholar, employing various combinations of the following terms: 'insulinoma', 'diabetes', 'nesidioblastosis', 'endogenous hyperinsulinism', 'hypoglycaemia', and 'hyperglycaemia' (from January 1900 to January 30, 2024). Exclusion criteria included non-English publications, duplicate articles, reports lacking sufficient data, cases of endogenous hyperinsulinemic hypoglycaemia other than insulinoma, and inaccessible articles. Statistical analysis was performed using appropriate methods. **Results:** Sixty patients were considered for the final analysis. Mean age was 61 ± 15 years (range: 17–96 years) with a slight female preponderance; 88.3% had type-2 diabetes with a median duration of 8 years. The median delay in diagnosis of insulinoma was 6 months. Median blood glucose varied from 30.5 mg/dL to 235 mg/dL, with a mean HbA1c of 5.6 ± 1.3% (range: 2.9%–8.2%). Critical sampling data were available in 75% of cases. The median size of the insulinoma was 2 cm. Furthermore, 5.2% of insulinomas were extra-pancreatic. Among pancreatic insulinomas, 14.5% were multi-focal. One-third of cases were malignant. Surgical resection was done in 70.9% of cases, while 40% received drug therapy and 12.7% received both, with 20.7% overall mortality. Malignant insulinoma ($P = 0.007$), micro-angiopathic ($P = 0.018$) and macro-angiopathic complications ($P = 0.039$), and other co-morbidities ($P = 0.009$) were associated with unfavourable prognosis, while being overweight and obese ($P = 0.020$) at presentation was associated with favourable prognosis. **Conclusion:** This first systematic review provides insights into the uniqueness of insulinoma in diabetes.

Keywords: Endogenous hyperinsulinemic hypoglycaemia, insulinoma, nesidioblastosis, type-1 diabetes, type-2 diabetes

Introduction

Insulinoma and diabetes mellitus are two contrasting manifestations of pancreatic β-cell pathology and aberrant glucose metabolism. The development of transient hyperglycaemia or permanent diabetes is a common post-operative complication of insulinoma. However, the genesis of insulinoma among patients with known diabetes,[1,2] or the unmasking of hidden diabetes after treatment of insulinoma,[3,4] is a rare phenomenon. After being first reported in 1932 in Germany,[5-8] nearly 75 similar cases have been published in the literature. Studies from the Mayo Clinic among 313 insulinoma patients over 65 years,[9] on a Japanese cohort of 443 insulinoma cases over 15 years,[10] and on a Taiwanese cohort of 23 insulinoma patients over 22 years[11] have found only one diabetic patient each. Other than sporadic case reports, there is no comprehensive study deciphering the natural history of this seemingly paradoxical association to date. As hypoglycaemia is a common complication in diabetes *per se*, it is difficult to diagnose insulinoma in the background of diabetes. Considering the extreme rarity of insulinoma in diabetes, it is unlikely that such a study with a sufficient sample size will ever be conducted. The current study aimed to address this challenging clinical problem by systematically reviewing the published literature.

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Methods

Literature search strategy and data extraction: We systematically searched PubMed and Google Scholar by employing various permutations and combinations of keywords, including 'insulinoma', 'diabetes', 'nesidioblastosis', 'endogenous hyperinsulinism', 'hypoglycaemia', and 'hyperglycaemia', from January 1, 1900, to January 30, 2024. In addition, we comprehensively reviewed the literature by scrutinising the references of relevant articles. We included English-language publications meeting specific criteria: case series, case reports, and letters depicting endogenous hyperinsulinemic hypoglycaemia (EHH) with imaging suggestive of insulinoma in patients with diabetes. We included histopathologically proven insulinoma cases in diabetes, irrespective of biochemical evidence or imaging features. This encompassed cases with concurrent diagnoses of insulinoma and diabetes. Exclusion criteria comprised non-English literature, duplicate publications, reports lacking sufficient data, cases with post-surgical diabetes complications, and instances of EHH unrelated to insulinoma. Cases such as Hirata syndrome, post-gastric bypass hypoglycaemia, nesidioblastosis, or non-insulinoma pancreatogenous hypoglycaemia syndrome, and inaccessible articles were excluded from the analysis.

Parameters studied: Parameters extracted from the selected studies were age, sex, presence of co-morbidities (obesity, hypertension, dyslipidaemia, diabetic micro-angiopathies, and macro-angiopathies or any other), type and duration of diabetes, duration of symptomatic hypoglycaemia, lowest documented blood glucose, highest documented blood glucose, glycated haemoglobin level at presentation, usage of anti-diabetic medications before insulinoma diagnosis and after its treatment, analysis of critical sample (blood glucose, serum insulin, and C-peptide), serum proinsulin, β-hydroxybutyrate, sulfonylurea screening, imaging modalities (both non-invasive and invasive), tumour location, largest diameter of the lesion, presence of metastasis, histopathology including immunohistochemistry, treatment strategies (surgery, drug, radiological intervention), outcome, and weight change before and after insulinoma treatment.

Definitions: Before curating data from the published literature, we established strict pre-specified definitions for the following variables and terms to minimise ambiguity:

1. Duration of diabetes: Considered zero when diabetes was diagnosed concurrently with insulinoma or emerged after insulinoma therapy.
2. Type of diabetes: Categorised as type-2 diabetes (T2D) unless specified otherwise.
3. Co-morbidities: Grouped into overweight/obesity, hypertension, dyslipidaemia, micro-angiopathy, macro-angiopathy, or others.
4. Duration of hypoglycaemia: Defined as the time from the onset of hypoglycaemia symptoms or documented hypoglycaemia (whichever came earlier) to insulinoma diagnosis. This is also considered as diagnostic delay, with zero delay if insulinoma was diagnosed at the first hypoglycaemia presentation.
5. RBSmax and RBSmin: Defined as the highest and lowest blood glucose levels noted during the entire disease course, respectively.
6. Critical sample: Designated as 'critical' when symptomatic hypoglycaemia occurred with concurrent blood glucose <55 mg/dL, and serum insulin and C-peptide data were available.
7. Tumour size: Determined by various imaging techniques, intra-operatively, or biopsy. The longest dimension documented using any of these methods was considered the maximum tumour size.
8. Location of tumour: Classified as pancreatic or extra-pancreatic. Pancreatic insulinomas were further categorised as unifocal or multi-focal, with unifocal tumours sub-divided into the head (and uncinate process), body, body and tail junction, and tail.
9. Immunohistochemistry: Considered only when insulin positivity or negativity was clearly mentioned.
10. Benignity or malignancy: Designated as malignant if insulinomas showed documented vascular invasion, nodal involvement, or metastasis to other organs.
11. Prognosis: Defined as good if there was relief from symptomatic hypoglycaemia (regardless of structural or biochemical cure). Poor prognosis indicated recurrence of symptomatic hypoglycaemia or death directly related to tumour burden or treatment complications.

Statistical analysis

The normality of the distribution of continuous variables was assessed using the Shapiro–Wilk test. The averages of the variables were presented as mean ± standard deviation for normally distributed data and as median ± IQR for non-normally distributed data. Unpaired *t*-test analysis was employed to compare normally distributed continuous variables between the two groups, while the Mann–Whitney test was used for non-normally distributed counterparts. Proportional comparisons were conducted using the chi-square test. The Yates continuity correction was applied when the value in one or more cells was less than 5. Statistical analyses were carried out using JASP version 0.18.1 (the University of Amsterdam, The Netherlands).

Results

Initially, 90 articles were identified based on our search criteria. After excluding 32 articles (13 on EHH other than insulinoma, 12 non-English articles, 5 inaccessible articles, 1 duplicate case, and 1 irrelevant case), the final analysis included 60 patients (56 case reports and 2 case series with 2 cases each) [see Figure 1].

Demographic characteristics revealed a mean presentation age of 61 ± 15 years (range: 17–96 years) with a slight female gender preponderance (male:female = 28:32, 0.9:1).

In terms of diabetes characteristics, the majority (88.3%, 53/60) had T2D, while 11.7% (7/60) had type-1 diabetes (T1D).

There was no statistically significant difference between the two types of diabetes except for the age of onset and serum insulin [Tables 1–3]. Duration of diabetes was mentioned in 90% (54/60) of cases. Of them, 83.3% (45/54) had a prior documented history of diabetes, lasting a median of 8 years [interquartile range (IQR): 14, range: 0.08–35 years]. In 16.7% (9/54) of cases, diabetes (3 T1D and 6 T2D) was diagnosed concurrently with insulinoma or unmasked only after insulinoma treatment. Among those with a history of diabetes, 62.2% (28/45) received oral anti-diabetic drugs (OADs) only (including 1 patient on GLP-1 analogue),[12] 28.9% (13/45) received insulin only, and 8.9% (4/45) received both. The remaining 25% (15/60) did not receive OADs, or there was no mention of them. Co-morbidities and long-term complications were observed in 43.3% of the 60 patients, with the prevalence of obesity, hypertension, dyslipidaemia, micro-angiopathy, and macro-angiopathy being 43.3%, 30%, 8.3%, 25%, and 10%, respectively. In addition, 43.3% (26/60) of patients had other co-morbidities.

Regarding hypoglycaemia characteristics, the duration was mentioned in 88.3% (53/60) of cases. Among them, 9.4% (5/53) were diagnosed with insulinoma at the first presentation of hypoglycaemia. The remaining 90.6% (48/53) were diagnosed with a median diagnostic delay of 6 months (IQR: 23; range: 0.17–312 months). Two patients had no hypoglycaemia symptoms or biochemically documented hypoglycaemia; insulinoma was diagnosed histopathologically after surgical tumour resection.[13,14]

With regards to glycaemic status, RBSmin data was available for 96.7% (58/60) of cases, with a median of 30.5 mg/dL (IQR: 13, range: 7–84). RBSmax was mentioned in 51.7% (31/60) of

Table 1: Comparison between patients with T1D vs T2D harboring insulinoma

Characteristics	T1D	T2D	*P*
Age (Years) (mean±SD)	43±17	66±18	0.003*
Sex			
Male/Female (%)	4/3 (57.1/42.9)	24/29 (45.3/54.7)	0.851
Diabetes duration (months) (median±IQR)	20±24	8±13	0.651
Hypoglyecmia duration (months) (median±IQR)	6 (18)	6 (23)	0.589
Co-morbidities			
Obesity (%)	2 (28.6)	24 (45.3)	0.665
Hypertension (%)	2 (28.6)	16 (30.2)	1
Others (%)	3 (42.9)	23 (43.4)	1
Micro-angiopathic complications (%)	2 (28.6)	13 (24.5)	1
Macro-angiopathic complications (%)	0 (0)	6 (11.3)	0.789
Lowest glucose (mg/dL) (median±IQR)	34±9	30±13	0.413
HbA1c[a] (NGSP %) (mean±SD)	6.1±1.5	5.5±1.3	0.367
Serum insulin (µIU/mL) (median±IQR)	13.1±16.8)	39.1±68	0.044*
Serum C-peptide (ng/mL) (median±IQR)	3.3±3.8	5.9±5.3	0.075

[Keys: T1D- type-1 diabetes, T2D- type-2 diabetes, SD- standard deviation, IQR- interquartile range, HbA1c- glycated hemoglobin, NGSP- National Glycohemoglobin Standardisation Programme, *P<0.05 has been considered as statistically significant)]

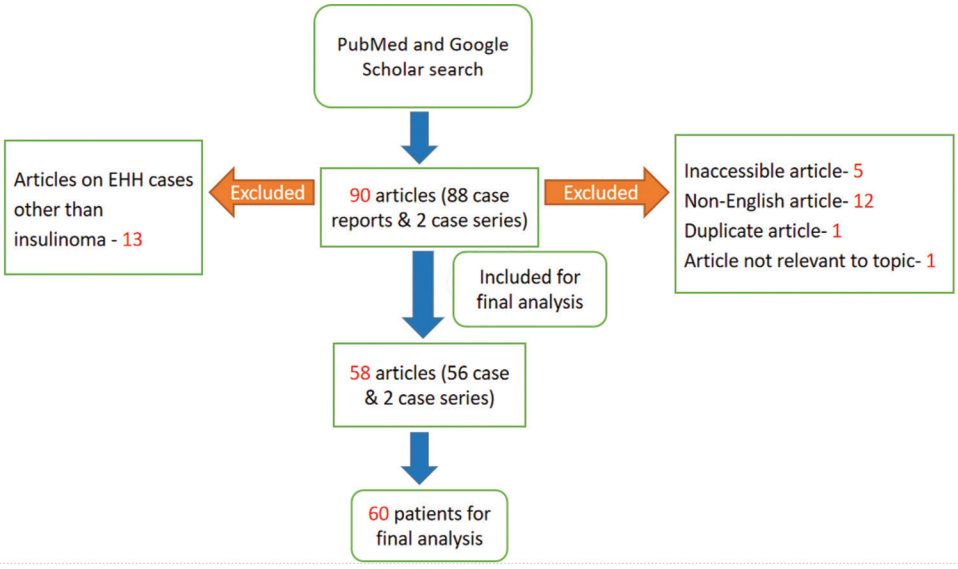

Figure 1: Flow-chart depicting the selection of articles for the present study

cases, with a median of 235 mg/dL (IQR: 150, range: 54–538). The gap between RBSmax and RBSmin was calculable in 50% (30/60) of cases, with a median of 200.5 mg/dL (IQR: 138, range: 14–498). HbA1c data (National Glycohemoglobin Standardisation Programme - NGSP) at presentation was available for 58.3% (35/60) of patients, with a mean of 5.6 ± 1.3% (range: 2.9%–8.2%).

Data on all three components of the critical sample were available in 75% (45/60) of cases. Serum insulin was measured in 83.3% (50/60) of cases, with a median level of 36.2 µIU/mL (IQR: 68, range: 2–963). The first reported data on blood insulin levels was in 1978 by Atkinson *et al*.[15] Serum C-peptide data was available in 76.7% (46/60) of cases, with a median level of 5.7 ng/mL (IQR: 5.7, range: 0.8–37.2). Serum C-peptide level was initially reported in 1993 by Kane *et al*.[9] and Grunberger *et al*.[16] Proinsulin was measured in only 11.7% (7/60) of patients, with a median of 99.9 pmol/L (IQR: 315, range: 7.7–2500 pmol/L). Serum β-hydroxybutyrate was measured in 13.3% (8/60) of cases. Data about sulfonylurea screening (from blood or urine samples) was present in only 38.3% (23/60) of cases.

With regards to imaging, at least one imaging method (abdominal ultrasonography - AUS, endoscopic ultrasonography - EUS,

Table 2: Comparison between patients with diabetes harboring benign vs malignant insulinoma

Characteristics	Benign insulinoma	Malignant insulinoma	*P*
Age (Years) (mean±SD)	64±16	68±32	0.437
Sex			
Male/Female (%)	17/23 (42.5/57.5)	11/9 (55/45)	0.360
Diabetes type			
T1D/T2D (%)	4/36 (10/90)	3/17 (15/85)	0.887
Diabetes duration (months) (median±IQR)	6±15	12±14	0.084
Hypoglycemia duration (months) (median±IQR)	8±26	4.5±19.8	0.332
Serum insulin (µIU/mL) (median±IQR)	32±40	61±73	0.214
Serum C-peptide (ng/mL) (median±IQR)	5.1±5.8	7.9±4.5	0.345
Maximum tumor dimension (cm) (median±IQR)	2±0.8	5±4.3	<0.001*
Multi-focality of pancreatic insulinoma (%)	3 (7.5)	5 (25)	0.140
Unfavorable prognosis (%)	5 (13.2)	9 (45)	0.007*

[Keys: T1D- type-1 diabetes, T2D- type-2 diabetes, SD- standard deviation, IQR- interquartile range, *P<0.05 has been considered as statistically significant)]

Table 3: Patients with diabetes and insulinoma stratified according to their prognosis

Characteristics	Favorable prognosis	Unfavorable prognosis	*P*
Age (Years) (mean±SD)	63.5±18.3	69.5±19.3	0.131
Sex			
Male/Female (%)	19/25 (43.2/56.8)	9/5 (64.3/35.7)	0.169
Diabetes type			
T1D/T2D (%)	5/39 (11.4/88.6)	2/12 (14.3/85.7)	1
Diabetes duration (months) (median±IQR)	8±15	11±12	0.4
Hypoglycemia duration (months) (median±IQR)	8±21	2±31	0.079
Co-morbidity			
Obesity and overweight (%)	24 (54.5)	2 (14.3)	0.020*
Hypertension (%)	14 (31.8)	4 (14)	0.332
Others (%)	15 (34.1)	11 (78.6)	0.009*
Micro-angiopathic complications (%)	8 (18.2)	7 (50)	0.018*
Macro-angiopathic complications (%)	2 (4.6)	4 (28.6)	0.039*
Lowest glucose (mg/dL) (median±IQR)	30±13	31±13	0.738
Highest glucose (mg/dL) (median±IQR)	157±114	240±151	0.582
Difference glucose (mg/dL) (median±IQR)	134±121	212±119	0.468
HbA1c (NGSP %) (mean±SD)	5.3±1.8	5.8±1.8	0.392
Serum insulin (µIU/mL) (median±IQR)	34±73.1	66.2±40.2	0.718
Serum C-peptide (ng/mL) (median±IQR)	5.7±5.6	7.9±4.4	0.719
Maximum tumor dimension (cm) (median±IQR)	2±2.2	2.8±3.6	0.488
Multi-focality of pancreatic insulinoma (%)	3 (7.5)	5 (25)	0.140
Malignant insulinoma (%)	11 (25)	9 (64.29)	0.007*

[Keys: T1D- type-1 diabetes, T2D- type-2 diabetes, SD- standard deviation, IQR- interquartile range, HbA1c- glycated hemoglobin, NGSP- National Glycohemoglobin Standardisation Programme, *P<0.05 has been considered as statistically significant)]

computed tomography - CT, magnetic resonance imaging - MRI) was used in 88.3% (53/60) of cases. Imaging data was scarce in cases reported before 1993,[9,16] when the diagnosis of insulinoma used to be primarily made by autopsy or biopsy from surgical specimens. Before 1993, imaging data were available in only one case published in 1970.[17] AUS, EUS, CT, MRI, and nuclear scan were performed in 22.6% (12/53), 15.1% (8/53), 26.4% (14/53), 24.5% (13/53), and 24.5% (13/53) of cases, respectively. Invasive imaging to localise pancreatic insulinoma, such as the selective arterial calcium stimulation test (SACST), was performed in only 11.3% (6/53) of cases.

Insulinoma characteristics revealed a median size of 2 cm (IQR: 0.77), ranging from 0.011 to 13 cm. Among the 60 cases, the tumour location was mentioned in 58 cases. Of these, 94.8% (55/58) were in the pancreas, while 5.2% (3/58) were extra-pancreatic (1 in the liver,[18] 1 at the splenic hilum,[19] and another in the vermiform appendix[20]). Among pancreatic insulinomas, 14.5% (8/55) were multi-focal. Among unifocal pancreatic insulinomas, the majority (23/47, 48.9%) were located at the tail, followed by the head and uncinate process (15/47, 31.9%), the body (5/47, 10.6%), and the junction of the body and tail (4/47, 8.5%). Only 50% of all cases (30/60) mentioned data regarding immunohistochemistry to identify insulin antigens in the histopathological specimen. Of these, 80% (24/30) tested positive. One-third (20/60) of insulinomas were malignant, with the liver being the most common site of metastasis (85%, 17/20). Among the different variables, greater tumour dimension was statistically significantly associated with more risk for malignancy ($P < 0.001$) [Table 2].

The management of insulinoma in the reviewed cases revealed that 8.3% (5/60) of patients received no definitive therapy. Among them, insulinoma was detected only through autopsy studies in three patients.[13,21] One patient died before receiving any treatment,[22] and another patient was discharged after refusing surgery.[23] Surgical resection was the primary intervention in the majority (70.9%, 39/55), while 40% (22/55) of patients received drug therapy. Among these cases, 58.2% (32/55) received only surgical intervention, 25.5% (14/55) received only drug therapy, and 12.7% (7/55) received both surgical and medical therapies. Diazoxide was the most frequently used drug (72.7%, 16/22), followed by somatostatin analogues (59.1%, 13/22), glucocorticoids (22.7%, 5/22), chemotherapy (18.2%, 4/22), and streptozocin (13.6%, 3/22). Nuclear therapy,[24] glucagon,[17] corn starch, and acarbose[25] were each utilised in one patient (4.5%, 1/22). More than one drug was administered in 63.6% (14 cases). Interventional radiological procedures were employed in two cases (3.6%, 2/55) – one with radiofrequency ablation,[1] and another with hepatic artery chemoembolization.[26]

Post-insulinoma treatment anti-diabetic regimen information revealed that 25 patients either did not require OADs (including those with an unfavourable prognosis) or information about their regimen was not mentioned. Among the remaining 35 patients, 31.4% (11/35) required only oral OADs, 62.9% (22/35) needed only insulin, and 5.7% (2/35) required both.

Regarding weight changes, there was no mention of weight change (gain, loss, or unchanged) before and after treatment in 55% (33/60) and 76.7% (46/60) of cases, respectively. Among the patients with available data on weight, 66.7% (18/27) had a history of weight gain before presentation, while 11.11% (3/27) experienced weight loss and 22.22% (6/27) reported no change in weight. Of the 14 patients with available data on post-treatment weight change, 21.4% (3/14) gained weight, while 78.6% (11/14) experienced weight loss.

Prognostic information for 58 patients indicated that 24.1% (14/58) had a poor outcome, while 75.9% (44/58) had a favourable prognosis. Interestingly, 20.7% (12/58) of patients died due to complications of insulinoma or its management. A malignant insulinoma ($P = 0.007$), micro-angiopathic ($P = 0.018$), and macro-angiopathic complications ($P = 0.039$), and other co-morbidities ($P = 0.009$) were significantly associated with unfavourable prognosis, while being overweight and obese ($P = 0.020$) at presentation was significantly associated with favourable prognosis. On the contrary, there was a trend that greater age, male sex, longer duration of diabetes, shorter duration of hypoglycaemic symptoms, greater HbA1c, and multi-focality of the pancreatic tumour were associated with a poorer prognosis, but it did not achieve statistical significance. In addition, greater tumour dimension, serum insulin, and C-peptide levels were unable to predict prognosis [Table 3].

Discussion

In English medical literature, the first documented case of a functioning insulinoma in a patient with diabetes was reported by Van der Sar *et al*. in 1956.[27] Diagnosing insulinoma in the context of diabetes poses a challenging clinical task. Although the case described by Sandler *et al*.[8] in 1975 was more suggestive of adult-onset nesidioblastosis, the criteria proposed by him remain relevant for diagnosing EHH in patients with diabetes. These criteria include (1) occurrence of fasting hypoglycaemia in a patient with documented diabetes mellitus, (2) ruling out exogenous insulin administration, (3) biochemical evidence of endogenous hyperinsulinemia, (4) exclusion of other causes of fasting hypoglycaemia, and (5) reversal of hypoglycaemia by resecting an islet cell tumour or performing partial pancreatectomy.

Until the late 1970s, most cases used to be diagnosed during autopsy studies due to the lack of insulin and C-peptide assays in clinical settings and the absence of sensitive imaging modalities to localise the tumour.[13,15,17,21,27-29] Improvement in glycaemic control despite progressive weight gain, even after discontinuation of insulin or insulin secretagogues, might serve as a clinical clue that a patient with diabetes is harbouring an insulinoma.[4,30] However, malignant insulinomas may be associated with weight loss.[26] The diagnosis of EHH is further complicated by the frequent occurrence of

common co-morbidities capable of causing hypoglycaemia, such as nephropathy.[31] In addition, it may be challenging to detect spontaneous hypoglycaemia early among patients with diabetes due to co-existing autonomic neuropathy, leading to a delayed diagnosis.[32] Furthermore, the diagnosis of EHH in diabetes becomes difficult as fasting hypoglycaemia can often be accompanied by post-prandial glycaemic excursions.[25,33,34] Sapountzi *et al*.[35] first used a continuous glucose monitoring system (CGMS) in this context. CGMS could be a reliable, safe, and non-invasive method to investigate unusual causes of hypoglycaemia in diabetes. Tumour localisation by imaging sometimes becomes challenging as patients with pre-existing, long-standing diabetes usually have an atrophic pancreas resulting from the progressive decline of β-cell mass.[36]

The first report of insulinoma in association with T1D was presented by Svartberg *et al*.[6] Bertheau *et al*.[37] reported the initial case of proinsulinoma developing in a patient with pre-existing T1D. There are documented instances of the revelation of pre-existing T1D only after insulinoma resection.[3,4] Establishing that a patient with insulinoma already had underlying T2D is more challenging. Authors cited the following reasons in support of the claim that their patients already had T2D, which was masked due to the concurrent presence of insulinoma: (1) selective removal of insulinoma by wedge resection of the tumour was unlikely to cause permanent diabetes; (2) post-operative serum insulin and C-peptide levels were well within a range that should have maintained euglycemia in the absence of insulin resistance; (3) these patients were already clinically insulin-resistant (evidenced by obesity and the presence of acanthosis) and biochemically insulin-resistant; and (4) glycaemic control was achieved with insulin sensitisers only.[38-40] However, in the current analysis of all the reported cases most patients (68.6%) required insulin therapy after their insulinoma surgery. This does not necessarily indicate damage to the β-cell during surgery but is indicative of an already exhausted β-cell reserve in T1D or long-standing T2D. Moreover, after successful insulinoma resection, patients typically experience considerable weight loss, which reduces insulin resistance, making diabetes management easier.

There are significant differences and similarities between insulinomas in individuals with diabetes and those in the non-diabetic population. In alignment with the findings from the current systematic review, the incidence of insulinoma generally peaks around the 5th–6th decade, with a slight female predominance.[41] Extra-pancreatic or ectopic insulinomas appear to be more common in patients with diabetes (5.2% as revealed in the current analysis) compared to the general population (1%–2%) reported elsewhere.[42,43] Typically, insulinomas are almost equally distributed in various parts of the pancreas,[43,44] but among patients with diabetes, around half of the tumours were localised in the tail. Multi-focality is more frequent in diabetes than in the general population (14.3% vs 10%).[42,45] In contrast to sporadic insulinoma cases, which are usually smaller in diameter (<2 cm),[43] insulinomas associated with diabetes tend to be larger. Similarly, 33.3% of cases of diabetes-associated insulinomas are malignant, a figure more than three times greater than multiple endocrine neoplasia-1-associated insulinomas.[46,47] Diagnostic delay is the most plausible explanation for larger tumour size and high incidence of malignancy or aggressiveness.[2] Not surprisingly, in this systematic review, larger tumour size is significantly associated with a higher risk of malignancy, and the latter, in turn, carries a poorer prognosis in diabetes-associated insulinomas, findings similar to previous large insulinoma registries.[48,49] Although diabetes is an established risk factor for poor surgical outcomes, there is a limited study evaluating the impact of diabetic angiopathies on the same. Birch *et al*.[50] have shown that patients with diabetic angiopathic complications experience a significantly poorer outcome than those without it. Findings from the current review also resonate with this fact.

From a handful of sporadic case reports, it remains challenging to discern whether the association between insulinoma and diabetes is causal or coincidental. Despite the rarity of insulinoma among patients with diabetes, a notable portion of insulinoma cases exhibit a family history of diabetes. For instance, in the Mayo Clinic series, approximately 30% of insulinoma patients had a familial history of diabetes.[9] This observation has led to the proposition of inherent insulin resistance and subsequent hyperinsulinism as a shared underlying pathogenic mechanism for both diabetes and insulinoma.[51] The emergence of hyperinsulinism, whether due to insulin resistance, sulfonylurea therapy, or exogenous insulin administration, has been speculated to stimulate β-cell proliferation.[52-54] Supporting this hypothesis, studies such as that by Beith *et al*.[55] have demonstrated that insulin can induce β-cell proliferation via the Raf-1 kinase pathway in rodent models. However, it remains uncertain whether a similar mechanism applies to insulinoma formation in humans, given the substantial difference between rodent and human islets. Research efforts, including the work by Iacovazzo *et al*.,[56] have explored the genetic underpinnings linking these seemingly disparate conditions. Mutations such as the p.Ser64Phe mutation in MAFA, recurrent somatic T372R mutation in Yin and Yang 1 protein, and insulin-like growth factor-2 overexpression, along with factors such as aging and obesity, have been identified as common risk factors for both insulinoma and diabetes.[56,57]

The mechanism underlying insulinoma formation in T1D patients may involve pluripotency.[54,58,59] Siraj *et al*.[54] proposed that surviving non-β islet cells containing the proinsulin gene could undergo neoplastic transformation, leading to insulin or proinsulin secretion. Histopathological examination typically reveals insulinoma lesions infiltrated by inflammatory cells alongside insulitis in non-tumorous pancreatic tissue in these patients.[3] However, the mechanism by which insulinoma cells evade autoimmune attacks in T1D remains unclear.[59]

There were several limitations in this current study. In many cases, there was a lack of complete data, and critical sample analysis and exclusion of other causes of endogenous hyperinsulinism were not possible, especially in cases before the 1990s. In addition, imaging data were scarce in older reports, and sulfonylurea screening was not performed in many cases. Despite these apparent limitations, this is the first systematic review conducted on this rare topic, providing valuable insights into the natural history of this rare and complex clinical scenario.

Conclusion

In the pursuit of a comprehensive systematic analysis of the previously reported cases of insulinoma in diabetes in English literature, the current study analysed the demography, presenting clinical, biochemical, and radiological features, treatment received, and prognosis. The possible pathogenesis of this seemingly contrasting manifestation of glucose metabolism has also been discussed. The results demonstrated that insulinoma in diabetes was frequently associated with larger tumour size, multi-focality, extra-pancreatic tumours, and malignancy. The overall prognosis of insulinoma in patients with diabetes seemed to be poorer than reported in the general population. Malignant insulinoma, diabetic micro- and macro-angiopathic complications, and other co-morbidities were significantly associated with unfavourable prognosis.

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Author's contribution

SC, RB and RG conceptualized the idea. SC and RG did the literature search and extracted data. RB did the statistical analysis. SC wrote the initial draft of the manuscript which was revised by RB. RG, PPC, AS and AM further critically reviewed the manuscript. All authors agreed upon the final form the article before submission.

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Conflicts of interest

There are no conflicts of interest.

References

1. Chang JY, Woo CS, Lui DT, Fung MM, Lee AC, Leung EK, *et al*. Case report: Insulinoma co-existing with Type 2 diabetes - advantages and challenges of treatment with endoscopic ultrasound-guided radiofrequency ablation. Front Endocrinol (Lausanne) 2022;13:957369.
2. Singbo J, Locketz M, Ross IL. Challenge of coexisting type 2 diabetes mellitus and insulinoma: A case report. J Med Case Rep 2021;15:479.
3. Oikawa Y, Katsuki T, Kawasaki M, Hashiguchi A, Mukai K, Handa K, *et al*. Insulinoma may mask the existence of Type 1 diabetes. Diabet Med 2012;29:e138-41.
4. Subramani S, Bellizzi AM, Borcherding N, Kao SC, Dillon J, Howe J, *et al*. Hypoglycemia secondary to insulinoma masking the onset of type 1 diabetes in an adolescent. Clin Case Rep 2021;9:e04868.
5. Bielschowsky F. Zur Klinik und pathologie der spontanhypoglykamie. Klin Wochenschr 1932;11:1492-4.
6. Svartberg J, Stridsberg M, Wilander E, Andersson DE, Eriksson B. Tumour-induced hypoglycaemia in a patient with insulin-dependent diabetes mellitus. J Intern Med 1996;239:181-5.
7. Buchner F. Lnselzellenadenom des Pankreas mit Hypoglykamie bei Diabetes. Klin Wochenschr 1932;11:1494.
8. Sandler R, Horwitz DL, Rubenstein AH, Kuzuya H. Hypoglycemia and endogenous hyperinsulinism complicating diabetes mellitus. Application of the C-peptide assay to diagnosis and therapy. Am J Med 1975;59:730-6.
9. Kane LA, Grant CS, Nippoldt TB, Service FJ. Insulinoma in a patient with NIDDM. Diabetes Care 1993;16:1298-300.
10. Ishii H, Ito T, Moriya S, Horie Y, Tsuchiya M. [Insulinoma--A statistical review of 443 cases in Japan]. Nihon Rinsho 1993;51(Suppl):199-206.
11. Lei WY, Wang TE, Chen TL, Chang WH, Yang TL, Wang CY. Insulinoma causing hypoglycemia in a patient with type 2 diabetes. J Formos Med Assoc 2007;106:392-6.
12. Ruby RJ, Armato JP, Pyke C, Peters AL. GLP-1 provoked severe hypoglycemia in an individual with type 2 diabetes and a benign insulinoma. Diabetes Care 2014;37:e177-8.
13. Rae MV, Lewis RC. Islet cell tumour in diabetes mellitus: Report of two cases. Can Med Assoc J 1957;77:691-4.
14. Kamocki ZK, Wodyńska NA, Pryczynicz A. Co-existence of insulinoma and diabetes: A case report. Oncol Lett 2014;8:1697-700.
15. Atkinson AB, Buchanan KD, Carson DJ, Kennedy T, O'Hare MM, Sloan JM, *et al*. Insulinoma (apud cell carcinoma) in a diabetic. Br Med J 1978;2:1397-8.
16. Grunberger G. Insulin resistance in a case of coexisting insulinoma and type 2 diabetes. Acta Diabetol 1993;30:243-50.
17. Taylor SG 3rd, Schwartz TB, Zannini JJ, Ryan WG. Streptozotocin therapy for metastatic insulinoma. Arch Intern Med 1970;126:654-7.
18. Grycewicz J, Scibór Z, Cwikła JB, Lewiński A, Cypryk K. Recurrent hypoglycaemia in a type 2 diabetes patient - diagnostic difficulties. Arch Med Sci 2010;6:126-9.
19. Mossman AK, Pattison DA, Hicks RJ, Hamblin PS, Yates CJ. Localisation of occult extra-pancreatic insulinoma using glucagon-like peptide-1 receptor molecular imaging. Intern Med J 2018;48:97-8.
20. Lombardi M, Battezzati MA, Grosso F, Muni A, Volante M, Ansaldi E. Appendix insulin secreting neuroendocrine tumor in a diabetic patient: A challenging diagnosis. J Integr Syst Neurosci 2016;2. doi: 10.15761/JSIN.1000128.
21. Haarstad J. Hormone-producing insuloma in diabetes mellitus. Acta Med Scand 1957;159:247-9.
22. Munir A, Toh SL, Arutchelvam V. Insulinoma in a patient with type 2 diabetes. Pract Diab 2011;28:226-226a.
23. Rajagopal G, Amaresh Reddy P, Satish P, Suresh V, Harinarayan CV, Pawan MN. Varied presentation of hyperinsulinaemic hypoglycaemia. J Clin Sci Res 2012;1:43-5.
24. Kumar S, Melek M, Rohl P. Case report: Hypoglycemia due to metastatic insulinoma in insulin-dependent Type 2 diabetes successfully treated with 177 Lu-DOTATATE. Front Endocrinol (Lausanne) 2022;13:906012.
25. Chhatterjee S, Ramiz MR, Mahata R, Chakraborty PP, Maiti A. Recurrent hypoglycemia in a diabetic with Graves' disease and foregut neuroendocrine tumor- diagnostic and therapeutic challenges. IJEM Case Rep 2024;2:39-44.
26. Ferrer-García JC, Tolosa-Torréns M, Hernando-Meliá C, Arribas-Palomar L, Sánchez-Juan C. Everolimus resolving hypoglycemia, producing hyperglycemia, and necessitating insulin use in a patient with diabetes and nonresectable malignant insulinoma. Endocr Pract 2011;17:e17-20.
27. Van Der Sar A, Bosschieter E, Hugenholtz MJ, Van Der Hoeven L. Spontaneous hypoglycaemic attacks due to an insulinoma in a diabetic; Report on a case. Doc Med Geogr Trop 1956;8:85-95.
28. Knight PO. Insulinoma and generalized islet cell hyperplasia in a patient with diabetes mellitus. South Med J 1967;60:119-23.
29. Gittler RD, Zucker G, Eisinger R, Stoller N. Amelioration of diabetes mellitus by an insulinoma. N Engl J Med 1958;258:932-5.

30. Sakurai A, Aizawa T, Katakura M, Sato Y, Kaneko G, Yoshizawa K, *et al*. Insulinoma in a patient with non-insulin-dependent diabetes mellitus. Endocr J 1997;44:473-7.
31. Shimizu M, Suzuki K, Tsuchida K, Kojima M, Hiraishi H, Aso Y. Insulinoma in a patient with chronic renal failure due to type 2 diabetes mellitus treated effectively with diazoxide. Intern Med 2015;54:621-5.
32. Campos-Olivé N, Ferrer-García JC, Safont MJ. Malignant insulinoma in a patient with type 2 diabetes mellitus. Acta Endocrinologica (Buc) 2010;VI:103-9.
33. Assyov Y, Gateva A, Zaharieva E, Tsakova A, Tournev I, Kyoseva D, *et al*. Concomitant insulinoma and type 2 diabetes mellitus diagnoses: A case report. J Diabetes 2016;8:740-2.
34. Nagai T, Imamura M, Takai Y, Mori M. Insulinoma accompanied by diabetes mellitus. Diabetes Res Clin Pract 2003;60:19-23.
35. Sapountzi P, Charnogursky G, Emanuele MA, Murphy D, Nabhan F, Emanuele NV. Case study: Diagnosis of insulinoma using continuous glucose monitoring system in a patient with diabetes. Clin Diabetes 2005;23:140-3.
36. Bhansali A, Walia R, Behra A, Khandelwal N, Vaiphei K. Rare cause of recurrent hypoglycemia in type 2 diabetes- insulinoma. Endocrinologist 2006;16:197-9.
37. Bertheau LA, Herceg RC, Malgor R, Guo A, Schwartz FL. Proinsulinoma causing severe hypoglycemia in a patient with type 1 diabetes mellitus. Case Rep Clin Pathol 2014;1:21-6.
38. Ademoğlu E, Unlütürk U, Ağbaht K, Karabork A, Corapçioğlu D. Type 2 diabetes mellitus in a patient with malignant insulinoma manifesting following surgery. Diabet Med 2012;29:e133-7.
39. Ahn J, Lee SE, Choi YS, Tan AH, Kim J, Chung YJ. Overtly manifested diabetes mellitus after resection of insulinoma. Intern Med 2009;48:2105-7.
40. Levine RA, Sobel BE. Insulinoma, type 2 diabetes and plasminogen activator inhibitor type-I. Coron Artery Dis 2001;12:333-6.
41. Svensson E, Muth A, Hedenström P, Ragnarsson O. The incidence of insulinoma in western Sweden between 2002 and 2019. Ann Gastroenterol 2022;35:434-40.
42. Hofland J, Refardt JC, Feelders RA, Christ E, de Herder WW. Approach to the patient: Insulinoma. J Clin Endocrinol Metab 2024;109:1109-18.
43. Garg R, Memon S, Patil V, Bandgar T. Extrapancreatic insulinoma. World J Nucl Med 2020;19:162-4.
44. Okabayashi T, Shima Y, Sumiyoshi T, Kozuki A, Ito S, Ogawa Y, *et al*. Diagnosis and management of insulinoma. World J Gastroenterol 2013;19:829-37.
45. Shin JJ, Gorden P, Libutti SK. Insulinoma: Pathophysiology, localization and management. Future Oncol 2010;6:229-37.
46. Marini F, Giusti F, Brandi ML. Multiple endocrine neoplasia type 1: Extensive analysis of a large database of florentine patients. Orphanet J Rare Dis 2018;13:205.
47. Zhao Y, Yu J, Liu Y, Lyu L, Ping F, Xu L, *et al*. Analysis of 55 patients with multiple endocrine neoplasia type 1-associated insulinoma from a single center in China. Orphanet J Rare Dis 2022;17:219.
48. Ueda K, Taira T, Hakoda H, Nakata S, Okata S, Nagai T, *et al*. Giant insulinoma: Report of a case and review of published reports. Surg Case Rep 2016;2:136.
49. Service FJ, McMahon MM, O'Brien PC, Ballard DJ. Functioning insulinoma- Incidence, recurrence, and long-term survival of patients: A 60-year study. Mayo Clin Proc 1991;66:711-9.
50. Birch RJ, Downing A, Finan PJ, Howell S, Ajjan RA, Morris EJA. Improving outcome prediction in individuals with colorectal cancer and diabetes by accurate assessment of vascular complications: Implications for clinical practice. Eur J Surg Oncol 2021;47:999-1004.
51. Nastos C, Giannoulopoulos D, Dellaportas D, Mizamtsidi M, Dafnios N, Klonaris N, *et al*. Sudden 'cure' of type two diabetes due to pancreatic insulinoma: A case report. Mol Clin Oncol 2020;12:174-8.
52. Araszkiewicz A, Zozulińska-Ziółkiewicz D, Wierusz-Wysocka B. Insulinoma in a patient with long lasting type 2 diabetes. Arch Med Sci 2009;5:486-8.
53. Ghafoori S, Lankarani M. Insulinoma in a patient with type 2 diabetes mellitus. Acta Med Iran 2015;53:317-9.
54. Siraj ES, Samuel G, Saber S, Samuel S, Hamrahian AH, Reddy SS. Metastatic malignant insulinoma in a patient with type 2 diabetes mellitus: Case presentation and literature review. Endocr Pract 2006;12:411-6.
55. Beith JL, Alejandro EU, Johnson JD. Insulin stimulates primary beta-cell proliferation via Raf-1 kinase. Endocrinology 2008;149:2251-60.
56. Iacovazzo D, Flanagan SE, Walker E, Quezado R, de Sousa Barros FA, Caswell R, *et al*. MAFA missense mutation causes familial insulinomatosis and diabetes mellitus. Proc Natl Acad Sci U S A 2018;115:1027-32.
57. Duvillié B, Kourdoughli R, Druillennec S, Eychène A, Pouponnot C. Interplay between diabetes and pancreatic ductal adenocarcinoma and insulinoma: The role of aging, genetic factors, and obesity. Front Endocrinol (Lausanne) 2020;11:563267.
58. Lablanche S, Chobert-Bakouline M, Risse O, Laverrière MH, Chabre O, Benhamou PY. Malignant insulinoma may arise during the course of type 1 diabetes mellitus: A case report. Diabetes Metab 2015;41:258-61.
59. Gjelberg HK, Hoem D, Verbeke CS, Eide J, Cooper JG, Molven A. Hypoglycemia and decreased insulin requirement caused by malignant insulinoma in a type 1 diabetic patient: When the hoof beats are from a zebra, not a horse. Clin Case Rep 2017;5:761-8.