A Systematic Review of the Accuracy of Insulin and C-peptide Secretion Ratios During the Oral Glucose Tolerance Test to Diagnose Insulinoma

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Abstract

Background. Insulinoma is one of the causes of recurrent hypoglycemia, one of the chief complaints for emergency department admission. The gold standard in diagnosing insulinoma is a 72-hour fasting test which is inconvenient and inefficient as it requires hospitalization. Research has found that measurement of insulin and C-peptide during OGTT may help diagnose insulinoma. We aimed to assess the diagnostic value of OGTT in diagnosing insulinoma.

Methodology. The literature search was conducted on 19 August 2022 using several databases (MEDLINE, Scopus, Embase, and ScienceDirect). All studies that measured OGTT as diagnostic tools in diagnosing insulinoma and 72-hour fasting test as reference standard were included. The quality assessment of the selected studies was based on the Centre of Evidence-Based Medicine University of Oxford and the Quality Assessment of Diagnostic Accuracy-2 tool (QUADAS-2). Analysis of the included studies was performed qualitatively. This study was registered on PROSPERO (CRD42022360205).

Results. A total of two case-control studies (106 patients) were included, which were at risk of bias and low concern of applicability. Both studies demonstrated that the combination of insulin and C-peptide levels measured during OGTT had high specificity, sensitivity, positive predictive value, and negative predictive value in diagnosing insulinoma compared to the reference standard. A logistic regression model of 8.305 – (0.441 × insulin 2-h/0-h) – (1.679 × C-peptide 1-h/0-h) >0.351 has the highest diagnostic value in one study (AUC 0.97, Sensitivity 86.5%, Specificity 95.2%, PPV 94.1, NPV 88.9).

Conclusion. The measurement of 0-h and 2-h insulin and C-peptide levels during 2-h OGTT was found in two small case-control studies with a total of 106 patients to have good sensitivity and specificity. However, due to these limitations, future research is still needed to validate the potential use of OGTT for the diagnosis of insulinoma.

Key words: hypoglycemia, insulinoma, 72-h fasting test, oral glucose tolerance test

INTRODUCTION

Hypoglycemia is one of the major reasons for Emergency Department admissions.[1] Hypoglycemia is characterized by: (1) low blood glucose level (<50 mg/dL), (2) signs or symptoms of hypoglycemia, and (3) alleviation of signs or symptoms following treatment, known as the Whipple's triad.[2] The most frequent etiology of the admission is the usage of hypoglycemic agents in diabetes mellitus patients. Endocrine disorders, malignancies, malnutrition, and renal insufficiency are among the other causes of hypoglycemia in non-diabetic patients.[1] In one study of 1196 episodes of hypoglycemia, most of the episodes (69.3%) happened in diabetic patients. While the other episodes (30.7%) happened in non-diabetic patients, 9.28% were due to malignancies.[1] The most common functioning pancreatic neuroendocrine tumor is an insulinoma.[3]

Insulinomas account for 1-2% of all pancreatic tumors. It occurs in 1 to 4 people per million people annually.[3,4] More frequently, insulinomas present as a single benign tumor. However, an insulinoma may be malignant in 5.8% of cases and 6% to 7.6% of cases linked with MEN1 syndrome.[4]

To this date, the gold standard in diagnosing insulinoma is the induction of a symptomatic hypoglycemia state

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by a 72-hour fasting test.[5] The presence of consistent symptoms or signs of hypoglycemia accompanied with plasma glucose less than 55 mg/dL (3 mmol/L), insulin at the minimum of 3.0 μIU/mL (18 pmol/L), c-peptide at the minimum of 0.6 ng/ml (0,2 nmol/L), and proinsulin at the minimum of 5.0 pmol/L indicate hyperinsulinemia due to endogenous insulin. β-hydroxybutyrate at most 2.7 mmol/L and elevation in plasma glucose of at least 25 mg/dL after administration of IV glucagon indicate that insulin mediated the hypoglycemia. The coexistence of hypoglycemia and endogenous hyperinsulinemia characterizes insulinoma. Nonetheless, screening for circulating oral hypoglycemic medications and insulin antibodies is crucial in individuals with hypoglycemia and endogenous hyperinsulinemia before diagnosing insulinoma.[6]

Even though the 72-hour fast test yields high efficacy in diagnosing insulinoma qualitatively, this method requires patients to be hospitalized for at least one week. It cannot be performed in an outpatient setting. The induction of hypoglycemia signs and symptoms causes discomfort for the patient. Therefore, further research on more convenient alternative methods of diagnosing insulinoma that could be carried out in an outpatient setting needs to be done. Recent studies have shown measurement of blood components during oral glucose tolerance tests may help diagnose insulinoma.[7,8] Thus, we aimed to evaluate the diagnostic accuracy of oral glucose tolerance test in detecting insulinoma.

METHODOLOGY

This review was reported based on the PRISMA Statement.[9] We published and registered the protocol of this systematic in PROSPERO (CRD42022360205).

Study eligibility

The inclusion criteria that were employed for selecting literature were (1) relevant to the clinical question; (2) a study that includes measurement of any blood component in oral glucose tolerance test as diagnostic tools for diagnosis of insulinoma; (3) a study that includes 72-h fasting test as a reference; and (4) subjects are adult patients with recurrent hypoglycemia episodes.

On the other hand, the exclusion criteria employed for selecting literature were (1) full-text articles are not accessible; (2) study in a language other than English; and (3) studies that include neither sensitivity, specificity, positive predictive value, negative predictive value, nor area under the curve for any blood component measured during oral glucose tolerance test.

Database searches and study selection

The literature search was conducted on 19 August 2022, using several databases such as MEDLINE, Scopus, Embase, and ScienceDirect. The search was done using all relevant

Table 1. Literature search query

Databases	Search query	Results
MEDLINE	Keywords: (("Insulinoma") OR ("Insulinomas") OR ("Insulomas") OR ("Insuloma")) AND (("72 hour fasting") OR ("72 hour fast") OR ("72-hour fasting") OR ("72-hour fast") OR ("72-h fast") OR ("72-h fasting")) AND (("glucose tolerance test") OR ("Glucose Tolerance Tests") OR ("glucose tolerance"))	9
Scopus		30
Embase		15
ScienceDirect	Keywords: (("Insulinoma") OR ("Insulinomas")) AND (("72 hour fast") OR ("72-hour fast") OR ("72-h fast") OR ("72-h fasting")) AND (("glucose tolerance test") OR ("Glucose Tolerance Tests")	76

medical subheading (MeSH) terms based on the clinical question, including "insulinoma", "72-hour fast", "glucose tolerance test," and their synonyms, as depicted in Table 1. Two investigators (FMC and DLT) independently reviewed the title and abstracts. If any potentially eligible study was identified, the two investigators reviewed the full text of any identified study (FMC and DLT).

Data extraction

We collected data from each selected study, including study citations, characteristics of included studies, intervention method, and study outcome. Study citations contain the name of the first author, year of publication, and title of the study. Characteristics of selected studies referred to used study design, location, and the number of study participants. The intervention method covered the oral glucose tolerance test used, including any measurement of blood components during OGTT performed in each study. The study outcome included the value of sensitivity, specificity, positive predictive value, negative predictive value, positive likelihood ratio, negative likelihood ratio, and area under the curve with the respective confidence interval of each model.

Quality assessment and data synthesis

Assessment of included studies was done using the Quality Assessment of Diagnostic Accuracy-2 tool (QUADAS-2) by two independent investigators (FMC and DLT). Qualitative analysis was performed considering the study size, the method of oral glucose tolerance test used, and the value of sensitivity, specificity, positive predictive value, negative predictive value, positive likelihood ratio, negative likelihood ratio, and area under the curve with its confidence interval.

RESULTS

The flow of the study selection is presented in Figure 1. A total of 130 results were gathered based on a literature search in four scientific databases, in which 23 articles were identified as duplicated. One hundred seven articles were screened through titles and abstracts. Of these, 56 articles were irrelevant to the clinical question, and 45 had the wrong study design. Six articles were left to be

Table 2. Summary of included study characteristics

Author (Year)	Location	Study Design	Population	Method of intervention	Main outcome
Liao et al.[7] (2020)	West China Hospital, China	Case-control	79 patients with recurrent hypoglycemia of which 37 patients had insulinoma and 42 others insulinoma absent from January 2009 to January 2019.	Level of plasma glucose, serum insulin, c-peptide, and HbA1c during 3-h oral glucose tolerance test	2-h/0-h insulin ratio combined with 1-h/0-h c-peptide ratio had high diagnostic accuracy for insulinoma. (Sensitivity 86.5%, Specificity 95.2%, PPV 94.1%, NPV 88.9%, AUC 0.97)
Li et al.[8] (2017)	Sixth People's Hospital Shanghai, China	Case-control	15 patients were diagnosed with insulinoma and 12 patients were diagnosed with reactive hypoglycemia as a control group between December 2009 and December 2014.	Level of plasma glucose, insulin, and c-peptide during 5-h oral glucose tolerance test	5-h Insulin to glucose ratio combined with 0-h c-peptide to glucose ratio had high specificity (83.3%) and sensitivity (100%) for predicting insulinoma. (AUC 0.94)
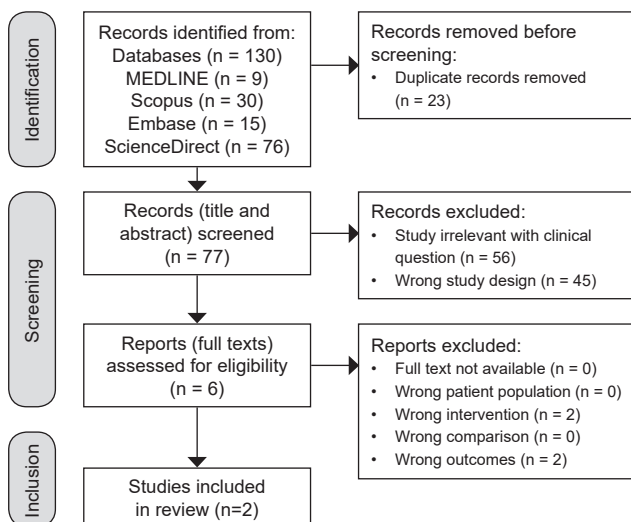
Figure 1. The PRISMA flowchart of search strategy and article selection.

assessed through full text for their eligibility. Two studies were excluded from these articles due to inappropriate intervention and two other studies were excluded due to the inappropriate outcome. Hence, only two studies were left to be further assessed in this systematic review.

The characteristics of the two included studies are shown in Table 2. Both studies were case-control studies with level 4 of evidence based on Oxford Centre for Evidence-Based Medicine: Levels of Evidence 2011. The results of critical appraisal can be found in Table 3 below. Overall judgment was at risk of bias due to unclear risk in both patient selection domains, with low concern regarding applicability.

When compared to the other models, Liao et al.,[7] discovered that the 2-h/0-h insulin ratio and 1-h/0-h C-peptide ratio

Table 3. Quality assessment of included studies using QUADAS-2

Study	Risk of bias				Applicability concerns		
	P	I	R	FT	P	I	R
Liao,[7] 2020	✗	✓	✓	✓	✓	✓	✓
Li,[8] 2017	✗	✓	✓	✓	✓	✓	✓

P = patient selection; I = index test; R = reference standard; FT = flow and timing.
✓ indicates low risk; ✗ indicates high risk; ? indicates unclear risk.

had the highest diagnostic value while Li et al., found that the combination of insulin-to-glucose ratio at 5-h and C-peptide-to-glucose ratio at 0-h had the highest diagnostic value in their research. Table 4 and Table 5 encompass the main outcome of the study by Liao et al.,[7] and Li et al.,[8] respectively.

DISCUSSION

Liao et al.,[7] enrolled a total of 79 patients with recurrent hypoglycemia from January 2009 to January 2019 in West China Hospital. They found 37 patients with insulinoma, of those three patients were diagnosed clinically, while the 34 others were diagnosed pathologically. On the other hand, 42 patients with hypoglycemia due to other causes such as liver damage, endosecretory diseases, and paraneoplastic syndrome, were categorized into the control group. Both groups were significantly distinct in terms of duration of hospitalization, HbA1c, fasting glucose, insulin, and C-peptide level (p <0.05). In contrast, the age and sex of the patients between them were not significantly different (p >0.05).

The main outcome of this study was the 2-h/0-h insulin ratio combined with the 1-h/0-h C-peptide ratio taken during 3-h OGTT had the highest diagnostic value in the diagnosis of insulinoma, which had the largest AUC (0.97; 95% CI 0.90–0.99) in this study. The sensitivity and specificity were 86.5% (95% CI 71.2–95.5%) and 95.2% (95% CI 83.8–99.4%), respectively. 2-h/0-h insulin ratio combined with 1-h/0-h C-peptide ratio was calculated from the logistic regression model as 8.305 – (0.441 × insulin 2-h/0-h) – (1.679 × C-peptide 1-h/0-h), with the cut-off value of >0.351. A score greater than 0.351 indicates the diagnosis of insulinoma and vice versa. The positive predictive value of 2-h/0-h insulin ratio + 1-h/0-h C-peptide ratio was 94.1% (95% CI 80.4-98.4%). This value means that of 100 people diagnosed with insulinoma using this method, only 5.9 were falsely accused of insulinoma. The negative predictive value of 2-h/0-h insulin ratio + 1-h/0-h C-peptide ratio was 88.9 (95% CI 77.9–94.8%), which explains that in 100 people tested for negative results using this method, 11.1 of them were had an insulinoma.[7]

One of the advantages of their study was the comparison of the diagnostic value between their model and the 72-h fast test as the reference standard. The sensitivity and

Table 4. Main outcome of the study by Liao et al.[7]

Results	Insulin 2-h/0-h + C-peptide 1-h/0-h* >0.351 (95% CI)	C-peptide 1-h/0-h + HbA1c > −0.142 (95% CI)	C-peptide 1-h/0-h + Glucose 1-h >0.554 (95% CI)	C-peptide 1-h/0-h + Glucose 0-h > −0.333 (95% CI)	C-peptide 1-h/0-h ≤3.582 (95% CI)	Insulin 2-h/0-h + Glucose 0-h >0.258 (95% CI)
Sensitivity	86.5 (71.2–95.5)	94.6 (81.8–99.3)	83.8 (68.0–93.8)	89.2 (74.6–97.0)	89.2 (74.6–97.0)	78.4 (61.8–90.2)
Specificity	95.2 (83.8–99.4)	90.5 (77.4–97.3)	92.9 (80.5–98.5)	88.1 (74.4–96.0)	85.7 (71.5–94.6)	90.5 (77.4–97.3)
Positive predictive value	94.1(80.4–98.4)	89.7 (77.4–95.7)	91.2 (77.5–96.9)	86.8 (74.2–93.8)	84.6 (72.2–92.1)	87.9 (73.8–94.9)
Negative predictive value	88.9 (77.9–94.8)	95.0 (83.1–98.7)	86.7 (75.7–93.1)	90.2 (78.5–95.9)	90.0 (78.0–95.8)	82.6 (71.8–89.8)
Positive likelihood ratio	18.2 (4.7–70.7)	9.9 (3.9–25.3)	11.7 (3.9–35.2)	7.5 (3.3–17.2)	6.2 (3.0–13.2)	8.2 (3.2–21.2)
Negative likelihood ratio	0.1 (0.1–0.3)	0.1 (0.0–0.2)	0.2 (0.1–0.4)	0.1 (0.1–0.3)	0.1 (0.1–0.3)	0.2 (0.1–0.4)
Area under the curve	0.97 (0.90–0.99)	0.95 (0.87–0.98)	0.94 (0.86–0.98)	0.92 (0.84–0.97)	0.91 (0.82–0.96)	0.89 (0.80–0.95)

*Insulin 2-h/0-h + C-peptide 1-h/0-h was calculated as: 8.305 – (0.441 × insulin 2 h/0 h) – (1.679 × C-peptide 1 h/0 h)

Table 5. Main outcome of the study by Li et al.[8]

Results	Insulin-to-glucose ratio* 5-h >20.45 pmol/mmol + C-peptide-to-glucose ratio† 0-h <0.19 nmol/mmol (95% CI)	Insulin-to-glucose ratio* 5-h >20.45 pmol/mmol + Insulin-to-glucose ratio* 0-h >13.54 pmol/mmol (95% CI)	Insulin-to-glucose ratio* 5-h >20.45 pmol/mmol (95% CI)	Insulin-to-glucose ratio* 0-h >13.54 pmol/mmol (95% CI)	C-peptide-to-glucose ratio† 5-h (95% CI)	C-peptide-to-glucose ratio† 0-h <0.19 nmol/mmol (95% CI)
Sensitivity	100 (78.0–100)	93.33 (68.0–98.9)	80.0 (51.9–95.4)	93.33 (68.0–98.9)	86.67 (59.5–98.0)	73.33 (44.9–92.0)
Specificity	83.3 (51.6–97.4)	83.33 (51.6–97.4)	91.67 (61.5–98.6)	75.0 (42.8–94.2)	75.0 (42.8–94.2)	83.33 (51.6–97.4)
Positive predictive value	88.2 (63.5–98.2)	87.5 (61.6–98.1)	92.3 (63.9–8.7)	82.4 (56.6–96.0)	81.2 (54.3–95.7)	84.6 (54.5–97.6)
Negative predictive value	100 (69-100)	90.9 (58.7–98.5)	78.6 (49.2–95.1)	90.0 (55.5–98.3)	81.8 (48.2–97.2)	71.4 (41.9–91.4)
Positive likelihood ratio	6.0 (4.7–7.7)	5.6 (4.2–7.5)	9.6 (7.1–13.0)	3.73 (2.6–5.3)	3.47 (2.4– 5.1)	4.4 (3.0–6.5)
Negative likelihood ratio	0.00 (N/A)	0.08 (0.01–0.8)	0.22 (0.03– 1.8)	0.09 (0.01–0.7)	0.18 (0.04–0.9)	0.32 (0.07–1.5)
Area under the curve	0.94 (0.78–1.00)	0.94 (0.78–1.00)	0.91 (0.74–0.99)	0.87 (0.68–0.97)	0.82 (0.62–0.94)	0.84 (0.65–0.95)

N/A = not applicable
*Insulin-to-glucose ratio = insulin (pmol/L)/glucose (mmol/L)
†C-peptide-to-glucose ratio = C-peptide (nmol/L)/glucose (mmol/L)

specificity of the 72-h fast test, described as blood glucose <3 mmol/L, insulin >3 μIU/ml, and C-peptide >0.2 nmol/l measured after 10-h overnight prolonged fasting had high specificity but low sensitivity in diagnosing insulinoma. The sensitivity and specificity were 88.1% (95% CI 75.0–94.8%) and 43.2% (95% CI 28.7–59.1%), respectively. A total of 16 (43.2%) subjects from the insulinoma group and 5 (11.9%) subjects from the control group had positive results using the 72-hour fast test. While using Liao et al., model, they yielded a total of 32 (86.5%) subjects with positive results in the insulinoma group, and only two (4.8%) subjects in the control group had positive results. Hence, compared to the reference standard, the 2-h/0-h insulin ratio + 1-h/0-h C-peptide ratio had higher diagnostic accuracy in diagnosing insulinoma.[7]

In the study conducted by Li et al.,[8] a total of 15 patients with the diagnosis of insulinoma and 12 patients with diagnosis of reactive hypoglycemia as control group were enrolled. This study covered all patients with insulinoma and reactive hypoglycemia in Sixth People's Hospital between December 2009 and December 2014. Patients in the insulinoma group had significantly higher BMI but lower total bilirubin, high-density lipoprotein cholesterol (HDL), glycated albumin, and HbA1c than patients in the reactive hypoglycemia group.

This study concluded that the combination of insulin-to-glucose ratio at 5-h higher than 20.45 pmol/mmol and C-peptide-to-glucose ratio at 0-h lower than 0.19 nmol/mmol had the highest specificity (83.3%; 95% CI 51.6%-97.4%) and sensitivity (100%; 95% CI 78-100%) in

diagnosing insulinoma with highest AUC of 0.94 (95% CI 0.78-1.00). The positive predictive value of this method was 88.2% (95% CI 63.5-98.2%), and the negative predictive value was 100% (95% CI 69-100%). Insulin-to-glucose ratio was calculated as insulin (pmol/L)/glucose (mmol/L), and the C-peptide-to-glucose ratio was calculated as C-peptide (nmol/L)/glucose (mmol/L).[8]

Li et al.,[8] then implemented their new model to screen for insulinoma in 75 patients with a primary complaint of hypoglycemia during the initial visit. All patients underwent 5-h OGTT. The diagnostic value of insulin-to-glucose ratio at 5-h + C-peptide-to-glucose ratio at 0-h in this population were 82.67% for sensitivity, 73.08% for specificity, 57.58% for positive predictive value, and 90.48% for negative predictive value.

In conclusion, the two studies conducted by Liao et al.,[7] and Li et al.,[8] discovered that using OGTT may be a novel approach with good diagnostic value for identifying insulinoma in patients with hypoglycemia. The gold standard 72-hour fasting test requires hospitalization and careful monitoring, which is time-consuming, inconvenient, and unpleasant for the patients. The OGTT provides an easier approach that may be performed in a single outpatient visit. Although Liao et al.,[7] and Li et al.,[8] had different indicators and cut-off values in the diagnosis of insulinoma, both studies had a similar method which measured plasma glucose, serum insulin, and C-peptide level from blood samples taken at 0-h, 1-h, 2-h, and 3-h in Liao et al.[7] study and additional of 4-h and 5-h blood samples in Li et al.[8] study. For the best convenience and

cost-effectiveness, we recommend the 2-h OGTT test after 10 hours of overnight fasting with measurement of insulin and C-peptide during 0-h and 2-h in recurrent hypoglycemia patients suspected of insulinoma. Also, the 2-h OGTT is less expensive than the standard 72-hour fasting test, which requires extensive hospitalization.

Nonetheless, there are several limitations in this systematic review. First, since insulinoma is a rare cause of hypoglycemia, only limited research in OGTT as an alternative to diagnosing insulinoma is available to this date. In this area of research, there were no systematic reviews and meta-analyses available during the literature search. We only included two low-level evidence studies at risk of bias due to patient selection bias. Second, all the studies included in this systematic review were conducted in a small sample size population within the Chinese population. Third, quantitative analysis could not be performed in our systematic review due to a limited number of studies and outcome variety between studies. Additional research with a large sample size is required to validate the established model before implementing OGTT as a diagnostic tool in diagnosing insulinoma.

CONCLUSIONS

The measurement of 0-h and 2-h insulin and C-peptide levels during 2-h OGTT was found in two small case-control studies with a total of 106 patients to have high diagnostic values. However, due to these limitations, future research is still needed to validate the potential use of OGTT for the diagnosis of insulinoma.

Statement of Authorship
All authors certified fulfillment of ICMJE authorship criteria.

CRediT Author Statement
FC: Conceptualization, Methodology, Software, Formal analysis, Investigation Resources, Data curation, Writing – original draft preparation, Visualization, Project administration; **DT:** Conceptualization, Methodology, Validation, Review and editing, Supervision, Funding acquisition.

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