Comparison of the diagnostic accuracy of the current guidelines for detecting insulinoma

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Abstract

Objective: Insulinomas are rare pancreatic endocrine tumors characterized by hypoglycemia. Guidelines by the Endocrine Society (ES), the European (ENETS) and the North American (NANETS) Neuroendocrine Tumor Societies provide divergent diagnostic criteria. This study compared the diagnostic accuracy of these different criteria during the 72-h fasting test.

Design: Retrospective cohort study.

Methods: From 2000 to 2014, 64 patients with a suspected insulinoma underwent a 72-h fasting test and were included in the analysis. This study assessed the diagnostic sensitivity, specificity and accuracy based on venous blood glucose and corresponding insulin levels measured by electrochemiluminescence immunoassay (ECLIA).

Results: Based on 64 individuals (18 with, 46 without insulinoma), the ES criteria provided a diagnostic sensitivity of 0.94 (0.73–1.00), specificity of 0.89 (0.76–0.96) and accuracy of 0.91 (0.81–0.96). ENETS/NANETS criteria reached a diagnostic sensitivity of 0.78 (0.52–0.94), specificity of 1.00 (0.92–1.00) and accuracy of 0.94 (0.85–0.98).

Conclusions: These results point to a higher diagnostic sensitivity with less specificity for diagnosing insulinoma using ES criteria and a higher specificity at lower sensitivity by using ENETS/NANETS criteria. Before considering these results when applying the different criteria in clinical practice, the results should be confirmed in further studies comprising larger cohorts.

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Introduction

Insulinomas are rare functional endocrine tumors located in the pancreas (1, 2, 3). Symptoms of hypoglycemia in the presence of documented low blood glucose and the relief of symptoms by intake of carbohydrates (Whipple's triad) indicate an insulinoma (4). However, a supervised 72-h fasting test, which is considered the gold standard, is needed to confirm the diagnosis of insulinoma (1, 4, 5).

The Endocrine Society (ES) as well as the European (ENETS) and the North American (NANETS) Neuroendocrine Tumor Societies published clinical

practice guidelines with diagnostic criteria for insulinomas. Both current ENETS (2012) and NANETS (2010) consensus guidelines determined the same six criteria for the diagnosis of insulinoma, including the assessment of blood glucose levels with the concomitant insulin, C-peptide, proinsulin and β -hydroxybutyrate levels as well as the absence of sulfonylurea in plasma and/or urine (2, 3). The ES (2009) clinical practice guideline also covers these characteristics, but defines divergent thresholds for the blood glucose and insulin levels in the fasted

state. Furthermore, the ES guideline adds two additional criteria for diagnosing insulinoma, that is, the absence of circulating insulin antibodies in the blood and plasma glucose concentration of ≥ 1.4 mmol/L 30 min after an intravenous injection of 1 mg glucagon (Supplementary Table 1, see section on [supplementary data](#) given at the end of this article) (6). Additionally, previous studies have shown that the use of insulin-glucose ratio could be a diagnostic tool in order to diagnose insulinoma (7, 8, 9).

The purpose of this study was to test the diagnostic accuracy of the criteria of the ES, ENETS and NANETS guidelines and to determine the impact of the different thresholds on the sensitivity and specificity for diagnosing insulinoma. Given that the guidelines differ in glucose and insulin thresholds, the analysis focused on these criteria during the 72-h fasting test. Furthermore, we studied the diagnostic value of diverse insulin-glucose ratios.

Subjects and methods

Study design and participants

Baseline and follow-up clinical data of patients who were admitted to the Division of Endocrinology and Diabetology at the University Hospital of Düsseldorf due to clinical signs and symptoms of a suspected insulinoma, for example, headache, sweating, tremor, fatigue and dizziness, from April 2000 to May 2014 were analyzed retrospectively (Supplementary Table 2). The Ethics Committee of the Heinrich Heine University Düsseldorf had no concerns about the study. The follow-up data of these individuals were collected until January 2015 in order to exclude a false-negative diagnosis of an insulinoma.

Diagnostic procedures

All patients ($n=64$) with a suspected insulinoma underwent a 72-h fasting test. The 72-h fasting test began after the last meal of the day ($n=17$) or with a prolonged oral glucose tolerance test (OGTT) ($n=47$). The fasting test was conducted in an in-patient ward according to the modified standardized protocol from Service (1995), without the injection of glucagon at the end of the test (4).

During the fasting test, blood glucose samples were measured in regular intervals (every 2–6 h) using a manual capillary device. If the glucose level fell below 3.3 mmol/L or symptoms of hypoglycemia appeared during the fasting test, the frequency of the measurements was increased

(up to every 5 min) and venous blood glucose samples (hexokinase method, Roche Diagnostics GmbH) were collected to verify the low values of the capillary samples. These venous blood glucose samples were used for the analysis. The corresponding insulin levels were measured by using the electrochemiluminescence immunoassay (ECLIA) from Roche Diagnostics GmbH.

The fasting test was terminated, if (i) blood glucose value was < 2.2 mmol/L with or without symptoms of hypoglycemia (3) or (ii) the patient refused to continue the test.

Diagnostic criteria

To compare the diagnostic accuracy of the three different guidelines, the 72-h fasting tests were analyzed according to the lowest blood glucose level during the fasting period and its corresponding insulin level. Only if the glucose levels were below and the insulin levels were above the corresponding thresholds, the fasting test was assigned as a positive diagnosis for insulinoma by the respective guideline. These results were compared to the patients' medical outcome within the follow-up period to determine the true-positive and true-negative as well as the false-positive and false-negative identification rate based on the thresholds of each guideline. All patients with an insulinoma underwent surgery and histological confirmation of the tumor after the fasting test.

Simple insulin-glucose ratios were derived by dividing the corresponding insulin values (in pmol/L) from the lowest glucose concentrations (in mmol/L) as previously described, according to the protocols by Wiesli *et al.* (2002), Quinkler *et al.* (2007) and Nauck and Meier (2012) respectively (7, 8, 9). For the amended insulin-glucose ratio, proposed by Turner *et al.* (1971), 1.7 mmol/L were subtracted from the glucose value before deriving the ratios (10). The threshold of amended insulin-glucose ratio was defined by Nauck and Meier (2012). As a result, five of the patients with an insulinoma and complete datasets had to be excluded from the analysis of the insulin-glucose ratios because their lowest glucose concentrations were 1.7 mmol/L or lower during the fasting test.

Statistical analysis

Patients' characteristics are presented as mean $\pm$ standard deviation (s.d.). Diagnostic sensitivity, specificity, accuracy and the positive and negative predictive value as well as the corresponding confidence intervals were calculated based on a 2×2 contingency table and the 95% Clopper

Pearson confidence limits. The diagnostic performance of the simple and amended insulin-glucose ratios was tested using the area under the receiver operating characteristic curve (AROC) and the 95% Wald confidence limits. *P* values <0.05 were considered to indicate statistically significant differences. Statistical analyses were carried out using GraphPad Prism 4 (GraphPad Software) and SAS version 9.4 software (SAS Institute).

Results

Study population

Sixty-four patients (18 with and 46 without an insulinoma) with suspected insulinoma underwent a 72-h fasting test. Patients with insulinoma were older, overweight and had lower blood glucose levels during the 72-h fasting test (all *P*<0.05) than patients without an insulinoma. Furthermore, the corresponding insulin values at the time of the lowest glucose concentration were higher in patients with insulinoma (*P*<0.0001) (Table 1). One patient without insulinoma and one patient with insulinoma were diagnosed with type 2 diabetes. Both of them were treated with lifestyle modification only. Furthermore, one patient without insulinoma had type 1 diabetes treated only with prandial insulin. During the 72-h fasting test, the insulin treatment of this patient was stopped (Supplementary Table 2).

The collection of follow-up data was continued until January 2015. During the mean follow-up of 6 ± 4 years, we did not detect new cases.

Diagnostic accuracy of the current guidelines

With regard to the distribution of the lowest glucose and its corresponding insulin levels, all patients with an

insulinoma had glucose levels smaller than 3.1 mmol/L. Only one of them showed an insulin level smaller than the threshold of the ES criteria (Fig. 1). According to the ES guideline, 94% of the included patients with an insulinoma had a positive fasting test, while 78% of the patients fulfilled the ENETS and NANETS criteria (Table 2). Yet, 11% of the patients without an insulinoma also showed blood glucose and insulin values during the fasting test, suggesting the presence of insulinoma according to the ES guideline. In contrast, none of them reached the thresholds of the ENETS and NANETS criteria. This implies a diagnostic accuracy of 0.91 (0.81–0.96) by the ES guideline and 0.94 (0.85–0.98) by the ENETS and NANETS guidelines.

When not considering the time point of the lowest blood glucose, but the time point of the discontinuation of the fast, diagnostic sensitivity, specificity and accuracy were lower (Supplementary Table 3). Reasons for the discontinuation of the fast were due to progressive hypoglycemia and its accompanying symptoms, upon completing the 72-h fasting test or when the patient refused to continue the test.

Performance of insulin-glucose ratios

Comparing the insulin-glucose ratios at the time of the lowest glucose concentration during the fasting test of the given thresholds, diagnostic sensitivity ranged from 46% according to the criteria by Quinkler *et al.* to 92% according to Nauck and Meier. All insulin-glucose ratios reached a diagnostic specificity of 100%. This implies a diagnostic accuracy of 0.88 (0.77–0.95) according to Quinkler *et al.*, 0.90 (0.79–0.96) according to Wiesli *et al.* and Nauck and Meier and an accuracy of 0.98 (0.91–1.00) when using the threshold of the amended insulin-glucose ratio by Nauck and Meier (Table 3).

Table 1 Patients' characteristics. Data are presented as *n* (%) and mean $\pm$ s.d. (min–max).

	Patients with an insulinoma	Patients without an insulinoma	<i>P</i> value
<i>n</i> (% male)	18 (28%)	46 (15%)	
Age (years)	52.4 $\pm$ 15.2 (30.0–81.0)	41.7 $\pm$ 13.6 (19.0–78.0)	0.03
Body weight (kg)	75.7 $\pm$ 11.9 (50.0–97.0)	68.0 $\pm$ 16.4 (41.0–115.0) [§]	0.03
BMI (kg/m ²)	26.3 $\pm$ 2.5 (20.5–30.2)	24.1 $\pm$ 5.3 (16.4–40.7) ^{§§}	0.02
72-h fasting test			
LGC (mmol/L)	1.9 $\pm$ 0.4 (0.9–2.5)	3.4 $\pm$ 0.8 (2.2–6.7)	<0.0001
Corresp insulin conc (μIU/mL)	17.1 $\pm$ 12.8 (1.4–45.2)	3.4 $\pm$ 3.6 (0.2–18.8)	<0.0001
Time point of LGC after last meal (h)	17 $\pm$ 13 (4–39)	55 $\pm$ 18 (8–84)	<0.0001

Data only available for [§]*n* = 45 and ^{§§}*n* = 44 patients without an insulinoma.

BMI, body mass index; conc, concentration; corresp, corresponding; LGC, lowest glucose concentration.

Figure 1

Minimal venous blood glucose measurements of the patients with (black square) and without (black open circles) an insulinoma during the fasting test plotted versus the corresponding ln-transformed insulin values. Insulin was ln-transformed prior to analysis to achieve a normal distribution. X-axis shown with natural logarithm scale. Lines illustrate the glucose and insulin thresholds of the ES guideline (black line) and of the ENETS and NANETS guidelines (dotted line).

By considering the entire study group, the diagnostic accuracy of the different insulin-glucose ratios was similar to the results when excluding patients with a plasma glucose of 1.7 mmol/L or lower (Supplementary Table 4). The AROC's of the insulin-glucose ratios were 0.95 (0.87–1.00) for the simple ratios and 0.98 (0.95–1.00) for the amended ratio and there was no significant difference between the two curves (Fig. 2).

Table 2 Diagnostic accuracy of the guidelines' criteria with the lowest glucose levels and corresponding insulin levels of the 72-h fasting test. Data are *n* and sensitivity/specificity/accuracy/positive and negative predictive value (95% Clopper Pearson confidence limits).

	ENETS/NANETS	ES
<i>n</i>	64	64
Sensitivity	0.78 (0.52–0.94)	0.94 (0.73–1.00)
Specificity	1.00 (0.92–1.00)	0.89 (0.76–0.96)
Accuracy	0.94 (0.85–0.98)	0.91 (0.81–0.96)
PPV	1.00 (0.77–1.00)	0.77 (0.55–0.92)
NPV	0.92 (0.81–0.98)	0.98 (0.87–1.00)

Comparison of the glucose and insulin criteria suggested by the European (ENETS) and North American (NANETS) Neuroendocrine Tumor Societies Consensus guidelines (criteria are identical for diagnosing insulinoma) (2, 3) with the criteria published by the Endocrine Society (ES) clinical practice guideline (6). PPV, positive predictive value; NPV, negative predictive value.

Figure 2

Area under the receiver operating characteristic curve (AROC) of the simple (black line) and the amended insulin-glucose ratios (black dotted line).

Discussion

The criteria of the ES guideline showed high sensitivity with a rather poor specificity, whereas the criteria of the ENETS and NANETS guidelines showed higher specificity with lower sensitivity for diagnosing insulinoma. Consequently, the diagnostic accuracy of the thresholds of the ENETS and the NANETS guidelines was similar to the diagnostic accuracy of the ES guideline (94 and 91%, respectively).

Previous studies evaluated only the diagnostic performance of the ES guideline criteria and the use of insulin-glucose or C-peptide-glucose ratios for diagnosing insulinomas (9, 11, 12, 13). All these studies showed a consistently high sensitivity of 70–100% by analyzing the diagnostic criteria individually. The corresponding specificity varied between the studies and its parameters. These previous results from the consistently high sensitivity by using the ES criteria are comparable to the current findings of the present study. The glucose and insulin thresholds of the ES guideline included all patients with insulinoma except one female patient presenting with the lowest glucose concentration of 2.2 mmol/L at a corresponding insulin value of 1.4 mIU/L during the fasting test. However, these thresholds also included some patients without an insulinoma. Most of the patients without an insulinoma, whose glucose and/or insulin levels were close to the thresholds (*n*=6), were females aged between 25 and 42 years with a normal or overweight body mass index (BMI). A further female patient with an insulinoma, whose insulin levels were also close to the

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Table 3 Diagnostic accuracy of insulin-glucose ratios ($n = 59$). Values are presented as (pmol/L)/(mmol/L). Comparison of the existing thresholds of simple and amended insulin-glucose ratios from Wiesli *et al.*, Quinkler *et al.* and Nauck and Meier (7, 8, 9). Values were used from the time point of the lowest glucose level during the 72-h fasting test. Five patients with an insulinoma were excluded from this analysis because their lowest glucose concentrations were 1.7 mmol/L or lower.

	Wiesli <i>et al.</i> (2002)	Quinkler <i>et al.</i> (2007)	Nauck and Meier (2012)	
			Simple	Amended*
Thresholds	≥ 30.0	≥ 60.0	> 32.2	> 53.6
Sensitivity	0.54 (0.25–0.81)	0.46 (0.19–0.75)	0.54 (0.25–0.81)	0.92 (0.64–1.00)
Specificity	1.00 (0.92–1.00)	1.00 (0.92–1.00)	1.00 (0.92–1.00)	1.00 (0.92–1.00)
Accuracy	0.90 (0.79–0.96)	0.88 (0.77–0.95)	0.90 (0.79–0.96)	0.98 (0.91–1.00)

*Turner *et al.* derived amended insulin-glucose ratios by subtracting 1.7 mmol/L from the glucose concentration (10).

ES threshold, was a 64-year-old with a BMI of 25 kg/m². This is in line with a previous case study, which indicates that insulin levels at or around the threshold of 3 μ IU/mL should be considered in the entire clinical context instead of only using absolute levels of diagnostic criteria of insulinoma (14).

The use of simple or amended insulin-glucose ratios showed high diagnostic accuracy for determining insulinoma in previous literature (7, 8, 9). The results in this study only partly confirm these findings. In particular, the simple insulin-glucose ratios had lower diagnostic sensitivities. However, the amended insulin-glucose ratio showed a high diagnostic accuracy of 98% for confirming insulinoma. Of note, the current international guidelines of ENETS and ES neither include the simple nor the amended insulin-glucose ratios for the diagnosis of insulinoma (2, 3, 6). However, the results from the present study and from Nauck and Meier (2012) suggest the use of the amended insulin-glucose ratio as a potential advantageous diagnostic tool for insulinoma.

The necessity of a supervised 72-h fasting test for diagnosing insulinoma has been discussed repeatedly over the last few decades. In our study, the lowest glucose concentrations during the 72-h fasting test were measured after 17 ± 13 h in patients with an insulinoma and after 55 ± 18 h in patients without an insulinoma. In previous studies, it has been considered that a 48-h fast is sufficient to identify patients with an insulinoma (8, 15). In 2014, Felício *et al.* concluded that in most cases, the measurement of blood glucose, insulin and C-peptide levels after a 12-h overnight fast over three consecutive days might replace the prolonged 72-h fasting test for diagnosing insulinoma (16). The Mayo Clinic examined the 72-h fasting test in 170 patients with regard to the length of the fasting test. They concluded that after 48 h, only 93% of patients with insulinoma were diagnosed, whereas after 72 h, 99% of the patients with insulinoma were diagnosed (5). By comparing the results of the fasting

test to other diagnostic methods, the present study would not have detected six patients with an insulinoma within the 72-h fasting test by the criteria of ES for the simple insulin-glucose ratio (8). However, the application of the amended insulin-glucose ratio at the end of the fasting test provided a higher diagnostic accuracy (0.98) than using the glucose and insulin ES criteria (0.91) (9).

The present study has several limitations, that is, the small number of insulinoma patients, which is mainly given by the low incidence of these endocrine tumors. Additionally, we only included the plasma blood glucose and concomitant insulin values during the fasting period and solely determined the diagnostic accuracy of these two criteria of the guidelines without including the other characteristics or thresholds. Of note, only the plasma glucose and insulin levels vary between the ES guideline and the guidelines of the ENETS and NANETS, therefore, the comparison of the diagnostic accuracies of the three different guidelines appears to be reasonably based on these two variables. Further analyses that include all thresholds, such as an 'insulinoma score', are required. In the present study, the other criteria of the guidelines for diagnosis of insulinoma such as proinsulin, C-peptide and β -hydroxybutyrate were not available for all patients. Furthermore, the use of the OGTT as a starting point of the 72-h fasting test could have influenced the results of this study.

The strength of the study is the average follow-up of 6 years of all patients with initially suspected but later not confirmed insulinoma, which allows the exclusion of false-positive and false-negative results in our cohort.

In conclusion, the ES guideline criteria show high sensitivity with lower specificity for diagnosing insulinoma, whereas the thresholds of the ENETS and NANETS criteria result in improved specificity at lower sensitivity. Furthermore, the amended insulin-glucose ratio could potentially be a suitable additional tool to the current diagnostic method of insulinoma.

Supplementary data

This is linked to the online version of the paper at <https://doi.org/10.1530/EJE-18-0879>.

Declaration of interest

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of this study.

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Author contribution statement

L D researched data, wrote/drafted the manuscript and contributed to the statistical analysis; M C S conceived the project and formulated the research questions; K S contributed to the statistical analysis; M C S and K S W critically reviewed the manuscript and contributed to the statistical analysis; S S researched data; V B and M R critically reviewed/edited the manuscript; M C S, K S W and K M contributed to results and discussion and reviewed/edited the manuscript. K M is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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References

- de Herder WW, Niederle B, Scoazec JY, Pauwels S, Klöppel G, Falconi M, Kwekkeboom DJ, Öberg K, Eriksson B, Wiedenmann B *et al.* Well-differentiated pancreatic tumor/carcinoma: insulinoma. *Neuroendocrinology* 2006 **84** 183–188. (<https://doi.org/10.1159/000098010>)
- Jensen RT, Cadiot G, Brandi ML, de Herder WW, Kaltsas G, Komminoth P, Scoazec JY, Salazar R, Sauvanet A, Kianmanesh R *et al.* ENETS consensus guidelines for the management of patients with digestive neuroendocrine neoplasms: functional pancreatic endocrine tumor syndromes. *Neuroendocrinology* 2012 **95** 98–119. (<https://doi.org/10.1159/000335591>)
- Vinik AI, Woltering EA, Warner RR, Caplin M, O'Dorisio TM, Wiseman GA, Coppola D, Go VL & North American Neuroendocrine Tumor Society (NANETS). NANETS consensus guidelines for the diagnosis of neuroendocrine tumor. *Pancreas* 2010 **39** 713–734. (<https://doi.org/10.1097/MPA.0b013e3181ebaffd>)
- Service FJ. Hypoglycemic disorders. *New England Journal of Medicine* 1995 **332** 1144–1152. (<https://doi.org/10.1056/NEJM199504273321707>)
- Service FJ & Natt N. The prolonged fast. *Journal of Clinical Endocrinology and Metabolism* 2000 **85** 3973–3974. (<https://doi.org/10.1210/jcem.85.11.6934>)
- Cryer PE, Axelrod L, Grossman AB, Heller SR, Montori VM, Seaquist ER, Service FJ & Endocrine Society. Evaluation and management of adult hypoglycemic disorders: an Endocrine Society clinical practice guideline. *Journal of Clinical Endocrinology and Metabolism* 2009 **94** 709–728. (<https://doi.org/10.1210/jc.2008-1410>)
- Wiesli P, Brändle M, Schwegler B, Lehmann R, Spinass GA & Schmid C. A plasma glucose concentration below 2.5 mmol L⁻¹ is not an appropriate criterion to end the 72-h fast. *Journal of Internal Medicine* 2002 **252** 504–509. (<https://doi.org/10.1046/j.1365-2796.2002.01060.x>)
- Quinkler M, Stelrow F, Pirlik M, Rohde W, Biering H, Lochs H, Gerl H, Strasburger CJ & Ventz M. Assessment of suspected insulinoma by 48-hour fasting test: a retrospective monocentric study of 23 cases. *Hormone and Metabolic Research* 2007 **39** 507–510. (<https://doi.org/10.1055/s-2007-982516>)
- Nauck MA & Meier JJ. Diagnostic accuracy of an 'amended' insulin-glucose ratio for the biochemical diagnosis of insulinomas. *Annals of Internal Medicine* 2012 **157** 767–775. (<https://doi.org/10.7326/0003-4819-157-11-201212040-00004>)
- Turner RC, Oakley NW & Nabarro JDN. Control of basal insulin secretion, with special reference to the diagnosis of insulinomas. *BMJ* 1971 **2** 132–135. (<https://doi.org/10.1136/bmj.2.5754.132>)
- Ahn CH, Kim LK, Lee JE, Jung CH, Min SH, Park KS, Kim SY & Cho YM. Clinical implications of various criteria for the biochemical diagnosis of insulinoma. *Endocrinology and Metabolism* 2014 **29** 498–504. (<https://doi.org/10.3803/EnM.2014.29.4.498>)
- Vezzosi D, Bennet A, Fauvel J & Caron P. Insulin, C-peptide and proinsulin for the biochemical diagnosis of hypoglycaemia related to endogenous hyperinsulinism. *European Journal of Endocrinology* 2007 **157** 75–83. (<https://doi.org/10.1530/EJE-07-0109>)
- Placzkowski KA, Vella A, Thompson GB, Grant CS, Reading CC, Charboneau JW, Andrews JC, Lloyd RV & Service FJ. Secular trends in the presentation and management of functioning insulinoma at the Mayo Clinic, 1987–2007. *Journal of Clinical Endocrinology and Metabolism* 2009 **94** 1069–1073. (<https://doi.org/10.1210/jc.2008-2031>)
- Coelho C, Druce MR & Grossman AB. Diagnosis of insulinoma in a patient with hypoglycemia without obvious hyperinsulinemia. *Nature Reviews: Endocrinology* 2009 **5** 628–631. (<https://doi.org/10.1038/nrendo.2009.198>)
- Hirshberg B, Livi A, Bartlett DL, Libutti SK, Alexander HR, Doppman JL, Skarulis MC & Gorden P. Forty-eight-hour fast: the diagnostic test for insulinoma. *Journal of Clinical Endocrinology and Metabolism* 2000 **85** 3222–3226. (<https://doi.org/10.1210/jcem.85.9.6807>)
- Felício JS, Koury CC, Martins CL, Miléo KB, Neto JF, de Melo FT & de Souza AC. Mini-fasting tests diagnosing endogenous hyperinsulinism: a follow-up of 26 cases. *Experimental and Clinical Endocrinology and Diabetes* 2014 **122** 149–153. (<https://doi.org/10.1055/s-0033-1363260>)

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