Endocrinología, Diabetes y Nutrición 70 (2023) 634–639

Endocrinología, Diabetes y Nutrición

www.elsevier.es/endo

ORIGINAL ARTICLE

Evaluation of plasma cortisol during fasting test in patients with endogenous hyperinsulinemic hypoglycemia. Fifteen years experience

María Eugenia Gullace[a,*], María Victoria Ortuño[b], Teresa Mabel Canteros[c], Belén Bosco[c], Cintia Rodriguez[c], Javier Giunta[c], Lucas Costa[d], Andrea Kozak[c], Valeria de Miguel[c], Luis Grosembacher[c]

[a] *Unidad de Endocrinología, Hospital Municipal de Agudos «Dr. Leónidas Lucero», Bahía Blanca, Argentina*
[b] *Servicio de Endocrinología, Hospital Alemán, Ciudad de Buenos Aires, Argentina*
[c] *Servicio de Endocrinología, Hospital Italiano de Buenos Aires, Ciudad de Buenos Aires, Argentina*
[d] *Unidad de Bioestadística, Facultad de Ciencias Médicas, Universidad Nacional del Litoral, Santa Fe, Argentina*

Received 25 June 2023; accepted 24 September 2023
Available online 27 November 2023

KEYWORDS
Cortisol in hypoglycemia;
Fasting test;
Insulinoma;
Recurrent hypoglycemia

Abstract
Background: Endogenous hyperinsulinemic hypoglycemia (EHH) is a rare clinical condition. The aim of this study was to evaluate baseline plasma cortisol concentration and its concentration during hypoglycemic crisis in fasting tests (FT) performed in our center. Secondarily, the aim was to establish the relationship between baseline cortisol and the time of evolution of EHH.
Material and methods: A retrospective, observational, descriptive study was carried out which included patients with hypoglycemic disorder with positive FT.
Results: Of a total of 21 patients, 16 presented insulinoma, 1 nesidioblastosis, 2 malignant insulinoma and 2 EHH without pathological diagnosis. The time from the onset of symptoms to diagnosis was 2 years (Q1 = 1.5–Q2 = 5.5). The comparison between median baseline cortisol (BC) = 11.8 mcg/dl (nmol/L 340.68) (Q1 = 9–Q3 = 14.1) and median cortisol during hypoglycemic episode (HC) = 11.6 mcg/dl (nmol/L: 303.44) (Q1 = 7.8–Q3 = 16.1) showed no differences ($Z = -0.08$; $P > .05$). When correlating BC with HC, no significant relationship was observed ($r = 0.16$; $P > .05$). When correlating the glycemic value in the crisis and the HC, a slight negative trend was found ($r = -0.53$; $P = .01$). In addition, we found that recurrent hypoglycemic disorder is associated with lower baseline cortisol values the longer the time of its evolution.

* Corresponding author.
E-mail address: meugeniagullace@gmail.com (M.E. Gullace).

Conclusion: We confirmed that cortisol values remain low during hypoglycemic episodes, reinforcing the hypothesis of lack of response of this counterregulatory hormone in cases of recurrent hypoglycemia.

PALABRAS CLAVE
Cortisol en hipoglucemia;
Test de ayuno;
Insulinoma;
Hipoglucemia recurrente

Evaluación del cortisol plasmático durante el test de ayuno en pacientes con síndrome hipoglucémico por hiperinsulinismo endógeno. Experiencia de 15 años

Resumen
Introducción: El síndrome hipoglucémico por hiperinsulinismo endógeno (SHHE) es una condición clínica poco frecuente.
Objetivos: El objetivo primario fue evaluar el cortisol plasmático basal y en la crisis hipoglucémica durante los tests de ayuno y el objetivo secundario, establecer la relación entre cortisol basal y el tiempo de evolución del SHHE.
Materiales y métodos: Estudio retrospectivo, observacional y descriptivo que incluyó pacientes adultos con síndrome hipoglucémico con test de ayuno positivo.
Resultados: De un total de 21 pacientes, 16 presentaron insulinoma, 1 nesidioblastosis, 2 insulinoma maligno y 2 SHHE sin diagnóstico anatomopatológico. El tiempo de síntomas del inicio del cuadro hasta el diagnóstico fue 2 años (Q1 = 1.5–Q2 = 5.5). La comparación entre la mediana de cortisol basal = 11.8 mcg/dl (Q1 = 9–Q3 = 14.1) y la mediana de cortisol durante la crisis hipoglucémica = 11.6 mcg/dl (Q1 = 7.8–Q3 = 16.1) no mostró diferencias (Z = —0.08; *P* > .05). No se observó relación significativa entre cortisol basal y cortisol en la crisis hipoglucémica (r = 0.16; *P* > .05). Se halló correlación con tendencia negativa entre la glucemia de la crisis y el cortisol basal (r = —0.53; *P* = ,01). Además, cuanto mayor fue el tiempo de evolución del síndrome hipoglucémico, menores fueron los valores de cortisol basal.
Conclusiones: Los valores de cortisol se mantienen bajos durante la crisis hipoglucémica reforzando la hipótesis de la falta de respuesta de esta hormona contrarreguladora en casos de hipoglucemia recurrente.

Introduction

Endogenous hyperinsulinaemic hypoglycaemia (EHH) is a clinical condition caused by excess insulin secretion. Insulinoma is the most common cause of EHH, with an incidence of 1–4 persons per million in the general population.[1] Other causes of EHH include pancreatic islet cell hyperplasia, nesidioblastosis[2] and the presence of anti-insulin or anti-insulin receptor antibodies.

The manifestation of symptoms, signs or both, associated with blood glucose values below 55 mg/dl, insulin greater than or equal to 3 μU/mL, C-peptide greater than or equal to 0.6 ng/mL, proinsulin of at least 5.0 pmol/l and beta hydroxybutyrate less than or equal to 2.7 mmol/l, makes it possible to document EHH and subsequently perform localisation diagnostic studies and finally confirm the aetiology.[3]

In hypoglycaemia episodes, counterregulatory hormones such as cortisol, growth hormone (GH), glucagon, adrenaline and noradrenaline play an essential role in elevating blood glucose to the normal range. However, the physiological response of these hormones to acute and chronic hypoglycaemia is not the same. In experimental models in which intravenous insulin is administered to induce acute hypoglycaemia, recovery from hypoglycaemia coincides with the counterregulatory hormones' response and increased endogenous glucose production. Reduced glucose utilisation does not seem to play an essential role. The main hormone involved in this case is glucagon, and catecholamines do not appear to be initially important, although they take on a critical role when the glucagon response is deficient.[4] Erturk et al. assessed the response of ACTH and cortisol in an insulin hypoglycaemia test in 193 patients and observed that cortisol values above 18 μg/dl was indicative of an adequate response of the hypothalamic-pituitary-adrenal axis.[5]

In contrast, a decrease in the response of the counterregulatory hormones is observed in recurrent hypoglycaemia episodes. As published by Davis et al.,[6] Widam[7] and Moheet,[8] by provoking two or more episodes of hypoglycaemia on different days in healthy patients, they observed a reduction in the blood glucose threshold value required to trigger a counterregulatory hormone response. This phenomenon has also been observed in clinical studies in patients with hypogly-

caemia in other contexts.[9] In a study involving 112 patients with type 2 diabetes with hypoglycaemia, 23 of them (20.5%) had an inadequate cortisol response (<18 μg/dl).[10] Another experimental study in patients with type 1 diabetes, in which the hypoglycaemic clamp procedure was performed, found a similar defective response of cortisol concentration with a decrease in the latter (20 ± 3 μg/dl in euglycaemia and 10 ± 2 μg/dl in hypoglycaemia; $P < .01$).[11] In neonates with hyperinsulinaemic hypoglycaemia in whom cortisol values were tested against hypoglycaemia, there was also an inadequate cortisol response to hypoglycaemia.[12] For adult patients with EHH (insulinoma, nesidioblastosis), studies are limited and the results are mixed. Some publications have compared pre- and post-surgery counterregulatory hormone values in patients with insulinoma by performing a hypoglycaemic clamp procedure, finding that there is an inadequate initial response that normalises after surgical treatment.[13,14]

When the hypoglycaemic episode does not occur spontaneously, the fasting test can be used to recreate the circumstances in which symptomatic hypoglycaemia is likely to occur. At the Hospital Italiano de Buenos Aires, a national reference centre for the study and treatment of hypoglycaemic syndromes for 30 years, an average of 5 fasting tests a year are performed. In these years of experience, variability in cortisol response in hypoglycaemic seizure during the fasting test has been observed in EHH patients. Considering that there are no data related to this observation available in Latin America, the primary objective of this study is to evaluate the behaviour of baseline plasma cortisol values and in hypoglycaemic seizures during the fasting tests performed at our centre over the last 15 years, whereas the secondary objective is to establish the relationship between the baseline cortisol value and duration of EHH.

Material and methods

This was an observational, descriptive, retrospective and cross-sectional study. All patients over 15 years of age referred for EHH who presented a positive fasting test (see Appendix B Annex 2: Fasting test protocol) between January 2007 and December 2021 were included. Patients with a positive fasting test in whom baseline cortisol and/or cortisol during hypoglycaemic seizure was not measured were excluded, as were those with a diagnosis of adrenal insufficiency previously treated with glucocorticoids, subjects who used corticosteroids during the fasting test and those who did not meet the inclusion criteria. All the data evaluated came from secondary databases of the electronic medical record data repository, which contains all the medical information of each patient in the Hospital Italiano de Buenos Aires health system.

The following variables were considered for analysis: serum cortisol, measured by chemiluminescence (reference range: 5—25 μg/dl), at the beginning of the fasting test and during hypoglycaemic seizure, and EHH duration in years.

The statistical analysis was carried out with the software SPSS v.19.0. The quantitative variables are described with medians with their respective interquartile ranges. The qualitative variables are described with their absolute frequencies. Median comparison tests and linear correlation tests were performed. *P*-values <.05 were considered to be statistically significant.

Ethical considerations

This study was conducted in accordance with ethical principles in line with national and international human health research standards. The protocol was approved by the institutional Research Protocols Ethics Committee.

Results

Of a total of 27 patients, six were excluded for the use of corticosteroids during the fasting test, leaving a final sample of 21 patients. Fourteen were female, median age was 39 years (Q1 = 32−Q3 = 50), 16 had a confirmed diagnosis of insulinoma, one nesidioblastosis, two malignant insulinoma and two with positive fasting test without an aetiological diagnosis. Since neither our centre nor Argentina has the capability to measure sulphonylureas in blood or urine, these data could not be collected.

The median body mass index (BMI) was 27 kg/m^2 (Q1 = 23.5−Q3 = 30.7). The median duration of the fasting test was seven hours (Q1 = 3.5−Q3 = 28) and the time from symptom onset to diagnosis was two years (Q1 = 1.2−Q3 = 5.5). Baseline cortisol was 11.8 μg/dl (340.68 nmol/l) and cortisol during hypoglycaemic seizure was 11.6 μg/dl (303.44 nmol/l); the comparison between the two dependent samples showed no differences ($Z = -0.08$; $P > .05$). No significant correlation was observed between baseline cortisol and cortisol during hypoglycaemic seizure ($r = 0.16$; $P > .05$) (Appendix B, see Annex 1: Fig. 1). A negative correlation was found between the blood glucose value during seizure (median 39 mg/dl; Q1 = 34−Q3 = 42.5) and cortisol during hypoglycaemic seizure ($r = -0.53$; $P = .01$) (see Appendix B, Annex 1: Fig. 2 and Table 1).

A negative correlation was observed between the time since diagnosis and baseline cortisol ($n = 17$; $r = -0.54$; $P = .025$) (see Appendix B, Annex 1: Fig. 3). This correlation was not found with cortisol ($r = -0.19$; $P > .05$) nor with blood glucose during hypoglycaemic seizure ($r = 0.21$; $P > .05$). No relationship was found between patient age and baseline cortisol and cortisol during hypoglycaemic seizure ($r = 0.07$; $P > .05$ and $r = -0.03$; $P > .05$). No correlation was found between baseline cortisol and BMI or between the time since diagnosis and BMI.

Discussion

Defects have been observed in the response threshold of counterregulatory hormones in patients with EHH, although to date it has proved impossible to determine the causal mechanism. Studies evaluating the effect of repeat episodes of hypoglycaemia in healthy individuals have suggested a defect in cortisol secretion, as published by Davis et al.[15] and Widom and Simonson.[7] The latter also ascertained that

the blood glucose values required to stimulate the secretion of counterregulatory hormones were increasingly lower following repeated stimuli.

This study assessed cortisol levels during a fasting test in people with EHH, finding that cortisol values were not elevated as would be expected in response to a hypoglycaemic seizure. In line with our findings, other reports of cases with insulinomas mention that they might present hypoglycaemia unawareness and a reduction in counterregulatory hormone response, similar to what has been observed in hypoglycaemia in patients with diabetes mellitus on insulin therapy.[13,16,17] Mitrakou et al.[18] also observed that spontaneous and repeat episodes of hypoglycaemia in six patients with insulinoma reduced the counterregulatory hormone response as previously reported, although neurogenic and neuroglycopenic symptoms also diminished.[19]

In contrast, Vella et al.,[20] in a study including 65 patients with insulinoma, eight with NIPHS (*noninsulinoma pancreatogenous hypoglycaemia syndrome*) vs 23 controls during a 72-h fasting test, concluded that patients with insulinoma had significantly higher cortisol values than controls in hypoglycaemia (contrary to our finding). However, the controls never reached hypoglycaemic values that would render it possible to draw an adequate comparison (the lowest blood glucose value was 63 mg/dl).

In this study, no significant differences were found when dependent samples were compared between baseline cortisol and cortisol during hypoglycaemic seizure (see Appendix B, Annex 1: Fig. 1), i.e. no increase in cortisol was observed during the hypoglycaemic event. No significant relationship was found when the correlation was performed. This would reinforce the idea of a lack of a counterregulatory cortisol response to low blood glucose levels in people with recurrent hyperinsulinaemic hypoglycaemia. Similar results may be inferred in patients with insulinoma in previous studies, although the statistical analysis of these results was not reported in all of them,[13,18] except for Simonson et al., who described it in patients with type 1 diabetes mellitus.[11]

When blood glucose values during hypoglycaemic seizure and cortisol values during hypoglycaemia were correlated, a negative trend emerged: the lower the blood glucose values, the higher the cortisol values, which is what would be expected in a normal physiological response (see Appendix B, Annex 1: Fig. 2). Our study found no relationship between patient age and baseline cortisol and cortisol values during hypoglycaemic seizure. This was not reported in previous studies.

Furthermore, a negative correlation was found between symptom progression time and the diagnosis of insulinoma, and baseline cortisol (see Appendix B, Annex 1: Fig. 3), which could translate into a chronic adaptation to a reduced response of the counterregulatory system to recurrent hypoglycaemia. Other studies published to date have not described the correlation between symptom onset and the diagnosis of insulinoma,[13,18] meaning that our study is the first to consider the correlation between these two variables.

Both Vea et al.[21] and Maran et al.,[22] Davis and Shamoon[13] and Mitrakou et al.[18] studied patients before and after insulinoma resection surgery: nine weeks, three, five and six months, respectively, showing an improvement in post-surgical counterregulatory hormone values, achieving values similar to those of healthy subjects. Since this is a retrospective study and we do not have such data, it would be interesting to be able to analyse our post-surgical results for the future. However, it should be borne in mind that to assess the recovery of cortisol response in these cases, it would not be feasible to repeat a fasting test as at diagnosis, but rather this should be studied using a hypoglycaemic clamp, as was reported in the studies mentioned above.[13,18,21,22]

It is hypothesised that the diminished response of counterregulatory hormones to recurrent hypoglycaemia may be due to several reasons. One paper posits that the central nervous system may adapt to recurrent hypoglycaemia, as evaluated *in vivo* in rats with insulinoma implants before and after their excision.[23] In patients with diabetes, it has been proposed that this may be due to paracrine effects at the pancreatic islet level in the case of glucagon,[24] or to subclinical autonomic neuropathy in the case of epinephrine.[19]

Rizza et al.[25] published that patients with insulinoma have hyperinsulinaemia associated with diminished glucose production and utilisation, with a predominance of decreased hepatic gluconeogenesis compared to healthy individuals, possibly due to a direct hepatic effect of insulin. What is not clear is whether these effects are due to hyperinsulinaemia per se, as suggested by Rizza et al.,[25] as well as by Davis and Shamoon,[13] or whether they are also secondary to defects in the release of other counterregulatory hormones (e.g. cortisol).

On the other hand, the decreased counterregulatory response is attributed to a possible adrenal insufficiency (AI). In their case report, Kaffel et al.[17] posit that one patient with insulinoma presented reversible hypopituitarism secondary to insulinoma. Some studies hypothesise that repeat exposure to hyperinsulinaemic hypoglycaemia episodes may lead to secondary AI through the attenuation of the hypothalamic-pituitary-adrenal axis.[26,27] Only one patient in our study underwent a synthetic tetracosactide (Synacthen®) stimulation test prior to surgery, which resulted in cortisol within normal pre- and post-stimulus values. Although the stimulation test is not part of the pre-insulinoma work-up if AI is not suspected, it would be interesting to consider it for future studies evaluating the cortisol response in these cases.

In conclusion, this paper confirms that cortisol values remain inappropriately low during a hypoglycaemic seizure, reinforcing the hypothesis of the lack of response of this counterregulatory hormone in cases of recurrent hypoglycaemia. Furthermore, this same state of recurrent hypoglycaemia was found to have a prolonged association with lower baseline cortisol values the longer the duration of EHH. We believe that given the low prevalence of this condition, having these results in Latin America is extremely valuable.

Main findings

- The time between symptom onset and diagnosis was 2 years.
- No differences were found between baseline cortisol and cortisol during the seizure.
- No significant relationship was observed between baseline cortisol and cortisol during hypoglycaemic seizure.

- A negatively-trending correlation between blood glucose during the seizure and baseline cortisol was found.
- The longer the duration of EHH, the lower the baseline cortisol values.

Funding

This study received no specific funding from public, private or non-profit organisations.

Conflicts of interest

The authors declare that they have no conflicts of interest.

Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.endinu.2023.09.004.

References

1. 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, http://dx.doi.org/10.3748/wjg.v19.i6.829.
2. Jabri AL, Bayard C. Nesidioblastosis associated with hyperinsulinemic hypoglycemia in adults: review of the literature. Eur J Intern Med. 2004;15:407–10, http://dx.doi.org/10.1016/j.ejim.2004.06.012.
3. Cryer PE, Axelrod L, Grossman AB, Heller SR, Montori VM, Seaquist ER, et al. Evaluation and management of adult hypoglycemic disorders: an Endocrine Society Clinical Practice Guideline. J Clin Endocrinol Metab. 2009;94:709–28, http://dx.doi.org/10.1210/jc.2008-1410.
4. Bolli GB, Fanelli CG. Physiology of glucose counterregulation to hypoglycemia. Endocrinol Metab Clin North Am. 1999;28:467–93, http://dx.doi.org/10.1016/s0889-8529(05)70083-9.
5. Erturk E, Jaffe CA, Barkan AL. Evaluation of the integrity of the hypothalamic-pituitary-adrenal axis by insulin hypoglycemia test. J Clin Endocrinol Metab. 1998;83:2350–4, http://dx.doi.org/10.1210/jcem.83.7.4980.
6. Davis SN, Mann S, Galassetti P, Neill RA, Tate D, Ertl AC, et al. Effects of differing durations of antecedent hypoglycemia on counterregulatory responses to subsequent hypoglycemia in normal humans. Diabetes. 2000;49:1897–903, http://dx.doi.org/10.2337/diabetes.49.11.1897.
7. Widom B, Simonson DC. Intermittent hypoglycemia impairs glucose counterregulation. Diabetes. 1992;41:1597–602, http://dx.doi.org/10.2337/diab.41.12.1597.
8. Moheet A, Kumar A, Eberly LE, Kim J, Roberts R, Seaquist ER. Hypoglycemia-associated autonomic failure in healthy humans: comparison of two vs three periods of hypoglycemia on hypoglycemia-induced counterregulatory and symptom response 5 days later. J Clin Endocrinol Metab. 2014;99:664–70, http://dx.doi.org/10.1210/jc.2013-3493.
9. Cryer PE, Davis SN, Shamoon H. Hypoglycemia in diabetes. Diabetes Care. 2003;26:1902–12, http://dx.doi.org/10.2337/diacare.26.6.1902.
10. Rhyu YA, Jang JY, Park S, An JH, Kim DL, Kim SK, et al. Impaired cortisol and growth hormone counterregulatory responses among severe hypoglycemic patients with type 2 diabetes mellitus. Endocrinol Metab (Seoul). 2019;34:187–94, http://dx.doi.org/10.3803/EnM.2019.34.2.187.
11. Simonson DC, Tamborlane WV, DeFronzo RA, Sherwin RS. Intensive insulin therapy reduces counterregulatory hormone responses to hypoglycemia in patients with type I diabetes. Ann Intern Med. 1985;103:184–90, http://dx.doi.org/10.7326/0003-4819-103-2-184.
12. Hussain K, Hindmarsh P, Aynsley-Green A. Neonates with symptomatic hyperinsulinemic hypoglycemia generate inappropriately low serum cortisol counterregulatory hormonal responses. J Clin Endocrinol Metab. 2003;88:4342–7, http://dx.doi.org/10.1210/jc.2003-030135.
13. Davis MR, Shamoon H. Deficient counterregulatory hormone responses during hypoglycemia in a patient with insulinoma. J Clin Endocrinol Metab. 1991;72:788–92, http://dx.doi.org/10.1210/jcem-72-4-788.
14. Mitrakou A, Fanelli C, Veneman T, Perriello G, Calderone S, Platanisiotis D, et al. Reversibility of unawareness of hypoglycemia in patients with insulinomas. N Engl J Med. 1993;329:834–9, http://dx.doi.org/10.1056/NEJM199309163291203.
15. Davis MR, Shamoon H. Counterregulatory adaptation to recurrent hypoglycemia in normal humans. J Clin Endocrinol Metab. 1991;73:995–1001, http://dx.doi.org/10.1210/jcem-73-5-995.
16. Amiel SA, Sherwin RS, Simonson DC, Tamborlane WV. Effect of intensive insulin therapy on glycemic thresholds for counterregulatory hormone release. Diabetes. 1988;37:901–7, http://dx.doi.org/10.2337/diab.37.7.901.
17. Kaffel N, Chakroun E, Dammak M, Mnif M, Smaoui M, Charfi N, et al. Inhibition paradoxale de la réponse somatotrope et corticotrope à l'hypoglycémie par hyperinsulinisme endogène: à propos d'une observation. Ann Endocrinol. 2007;68:204–7. Available from: https://linkinghub.elsevier.com/retrieve/pii/S0003426607000650
18. Mitrakou A, Fanelli C, Veneman T, Perriello G, Calderone S, Platanisiotis D, et al. Reversibility of Unawareness of Hypoglycemia in Patients with Insulinomas. N Eng J Med. 1993;329:834–9, http://dx.doi.org/10.1056/nejm199309163291203.
19. White NH, Gingerich RL, Levandoski LA, Cryer PE, Santiago JV. Plasma pancreatic polypeptide response to insulin-induced hypoglycemia as a marker for defective glucose counterregulation in insulin-dependent diabetes mellitus. Diabetes. 1985;34:870–5, http://dx.doi.org/10.2337/diabetes.34.9.870.
20. Vella A, Service FJ, O'Brien PC. Glucose counterregulatory hormones in the 72-hour fast. Endocr Pract. 2003;9:115–8, http://dx.doi.org/10.4158/EP.9.2.115.
21. Vea H, Jorde R, Sager G, Vaaler S, Sundsfjord J, Revhaug A. Pre- and postoperative glucose levels for eliciting hypoglycaemic responses in a patient with insulinoma. Diabet Med. 1992;9:950–3, http://dx.doi.org/10.1111/j.1464-5491.1992.tb01738.x.
22. Maran A, Taylor J, Macdonald IA, Amiel SA. Evidence for reversibility of defective counterregulation in a patient with insulinoma. Diabet Med. 1992;9:765–8, http://dx.doi.org/10.1111/j.1464-5491.1992.tb01889.x.
23. McCall AL, Fixman LB, Fleming N, Tornheim K, Chick W, Ruderman NB. Chronic hypoglycemia increases brain glucose transport. Am J Physiol. 1986;251 4 Pt 1:E442–447, http://dx.doi.org/10.1152/ajpendo.1986.251.4.E442.
24. Asplin CM, Paquette TL, Palmer JP. In vivo inhibition of glucagon secretion by paracrine beta cell activity in man. J Clin Invest. 1981;68:314–8, http://dx.doi.org/10.1172/jci110251.
25. Rizza RA, Haymond MW, Verdonk CA, Mandarino LJ, Miles JM, Service FJ, et al. Pathogenesis of hypoglycemia in insulinoma patients: suppression of hepatic glucose production by insulin. Diabetes. 1981;30:377–81, http://dx.doi.org/10.2337/diabetes.30.5.377.
26. Mathur S, Boparai J, Mediwala SN, Garcia JM, Cunningham GR, Marcelli M, et al. Reversible adrenal

insufficiency in three patients with Post-Roux-en-Y gastric bypass noninsulinoma pancreatogenous hypoglycemia syndrome. J Investig Med High Impact Case Rep. 2014;2, http://dx.doi.org/10.1177/2324709614526992, 2324709614526992.

27. Chang YH, Hsieh MC, Hsin SC, Shin SJ, Lin KD. Insulinoma-associated transient hypothalamus-pituitary-adrenal axis impairment and amelioration by steroid therapy and surgical intervention: a case report. Kaohsiung J Med Sci. 2007;23:526–30, http://dx.doi.org/10.1016/S1607-551X(08)70011-1.