Routine Glucose Monitoring in Postoperative Pheochromocytoma Patients: Yes or No?

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Abstract

Pheochromocytomas are rare neuroendocrine tumors characterized by the release of catecholamines. In the preoperative setting, the release of these catecholamines can lead to hyperglycemia by promoting liver glycogenolysis and gluconeogenesis, inhibiting pancreatic insulin secretion, and enhancing peripheral insulin resistance. Postoperatively, there is often a period of rebound hypoglycemia that can be dangerously prolonged given the preoperative depletion of glycogen stores secondary to high catecholamine levels. This complication of postoperative hypoglycemia can be extremely detrimental given that it often goes unrecognized secondary to the masking effects of anesthesia. The change in mental status associated with hypoglycemia may be incorrectly attributed to residual anesthesia. Alpha and beta-blockade further blunt the body's natural response to hypoglycemia which is usually tachycardia, palpitations, and sweating. Prolonged, unrecognized hypoglycemia can lead to severe neurologic consequences such as seizures, unconsciousness, or even irreversible brain damage. This complication must therefore be preemptively anticipated and acutely managed. A thorough literature search over the years provides data in favor of routine postoperative glucose monitoring after pheochromocytoma resection. Given the high stakes involved with missing this relatively common diagnosis seen in 4–15% of pheochromocytoma patients undergoing resection, a GRADE 1C

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recommendation for routine monitoring in all postoperative pheochromocytoma patients for the first 5 h has been deemed appropriate.

Keywords

Pheochromocytoma resection · Postoperative hypoglycemia · Unrecognized hypoglycemia · Routine postoperative glucose monitoring in all patients · Elevated preoperative urine metanephrine levels · Alpha and beta blockade · Neurologic complications

Background

Pheochromocytomas are rare neuroendocrine tumors characterized by the release of catecholamines. These neoplasms arise from chromaffin cells of the adrenal medulla and present with signs and symptoms consistent with catecholamine excess. Classical symptoms include palpitations, paroxysmal hypertension, tachycardia, headaches, and diaphoresis [1]. Patients may also have acute attacks of pallor, nausea, and panic attacks lasting several minutes [2]. More elusive symptoms of weight loss and fatigue have also been seen with pheochromoctyomas [3]. In extreme cases patients may have florid heart failure, or takotsubo cardiomyopathy, secondary to a catecholamine surge [3]. More subtle signs may include new onset diabetes as a result of glycogenolysis and insulin inhibition due to catecholamine release [4]. Given the complex nature of this tumor, meticulous perioperative management is extremely important. Table 28.1 summarizes the studies using the Population, Intervention, Comparator, and Outcomes (PICO) format.

Preoperative Hemodynamic Changes and Management

Preoperative management of the patient consists of catecholamine blockade, specifically using alpha-adrenergic blockers for hypertension and beta-blockers for tachycardia. The most commonly used alpha-blocker is phenoxybenzamine secondary to its irreversible and non-selective nature. The drug is titrated as needed and patients usually achieve their goal dose within 10–14 days. Clinical signs of the optimal dose are a stuffy nose and slight dizziness due to postural hypotension [5]. Another alternative to phenoxybenzamine is doxazosin, a selective and reversible alpha-blocker. However, unlike phenoxybenzamine, strong catecholamine bursts can displace doxazosin from its receptor binding site and reduce its efficacy [6]. On

Table 28.1 PICO table

*P*opulation	Postoperative pheochromocytoma patients
*I*ntervention	Routine glucose monitoring
*C*omparator	Selective glucose monitoring
*O*utcomes	Complications, ICU admission

the other hand, some believe that reduced postoperative hypotension may be a benefit of doxazosin [7–9]. During alpha blockade, it is imperative to also replete the intravascular volume as the alpha-mediated vasoconstriction is released. Calcium channel blockers are also occasionally used to control refractory hypertension [10].

Patients with preoperative tachycardia can be managed with a cardioselective beta1-blocker such as metoprolol, bisoprolol, or atenolol [9]. Intraoperative tachycardia is usually controlled using a short acting beta1- blocker such as esmolol [11]. Unlike the other selective beta1-blockers, labetolol, a combined alpha1 and beta-blocker has mixed reviews in terms of its use [12]. Reports of orthostatic hypotension and hypertensive crisis have been observed [13–15].

Preoperative Hyperglycemia

In addition to the aforementioned hemodynamic changes caused by pheochromocytomas, endocrine changes are also well documented. La Batide-Alanore et al. reports the rate of diabetes of 68 of 191 (35.6%) patients with pheochromocytoma. Pheochromocytoma patients with or without diabetes did not differ in body mass index, plasma noradrenaline concentration, metanephrine excretion, or tumor characteristics. Age, duration of hypertension, and plasma epinephrine concentration were significantly and independently associated with diabetes in patients with pheochromocytoma. Specifically, pheochromocytoma patients with diabetes were younger, more likely female, and had a lower body mass index than those with essential hypertension ($P < 0.01$). After adjustment for these three variables, the odds ratio for pheochromocytoma in hypertensive patients with diabetes was 5.5 (95% confidence interval, 3.5–8.7). For patients younger than 51 years old with a body mass index <25 kg/m^2, the odds ratio was 18.9 (95% confidence interval, 5.9–58.8) [4]. The use of preoperative alpha or beta blockade has not proven very effective in controlling preoperative glucose levels [16]. In fact, alpha and beta blockade may inhibit the symptoms of hypoglycemia such as palpitations, diaphoresis, and tremors, leading to a precarious situation.

Overall, diabetes is present in one of three patients with pheochromocytoma. In young patients with hypertension and normal body weight, the presence of diabetes should be used to further investigate the presence of a pheochromocytoma. In severe cases, patients may initially present with diabetic ketoacidosis [4].

The hyperglycemia seen with pheochromocytomas can be attributed to an imbalance in glucose homeostasis. Normal glucose levels are maintained by a system of checks and balances involving the liver, the pancreas, and the adrenal gland, all of which are under control of the autonomic nervous system [17]. Over the years, much research has been conducted on the effect of catecholamines and glucose control.

Both the liver and pancreas are innervated by the autonomic nervous system. Catecholamine release secondary to the pheochromocytoma promotes liver glycogenolysis and gluconeogenesis. Epinephrine is the predominant driver of this phenomenon in the liver through beta-adrenergic stimulation [17, 18]. Additionally, hepatic

glucoreceptors have been hypothesized to be coupled with capsaicin-sensitive afferent nerves to convey blood glucose levels to the central nervous system [17].

The autonomic nervous system controls pancreatic islet cell insulin secretion, and in turn has a major effect in glucose homeostasis. Catecholamines inhibit pancreatic insulin secretion through agonist effects on alpha2-adrenergic receptors [19]. This has been replicated in human study patients where the administration of norepinephrine inhibits insulin release from pancreatic beta cells [20]. Furthermore, the administration of phentolamine, an alpha-receptor blocker, counteracts the inhibitive effect of catecholamines on insulin secretion [19]. Ostenson et al. also reported that alpha2-receptor agonists inhibit insulin release. Besides the well documented adrenergic and cholinergic effects on pancreatic islet cells, the role of neuropeptides is also being researched [21]. Vasoactive intestinal polypeptide, pituitary adenlyate cyclase activating polypeptide, and gastrin releasing peptide are neuropeptides regulated by the parasympathetic nervous system, whereas galanin and neuropeptide Y are part of the sympathetic nervous system [22]. Insulin secretion is stimulated by neuropeptides that are part of the parasympathetic nerves and is inhibited by those which are part of the sympathetic nervous system.

Unlike the liver and the pancreatic islet cells, the adrenal medulla receives its main nerve supply from the greater and lesser splanchnic nerves. Catecholamine secretion by the adrenal medulla is regulated by adrenoceptors, dihydropyridine-sensitive Ca2+ channels, and capsaicin-sensitive sensory nerves. In response to stress, the sympathoadrenal system is activated and releases adrenal catecholamines and pancreatic glucagon, both leading to hyperglycemia [17].

Catecholamines also play an important role in enhancing peripheral insulin resistance. Administration of epinephrine increases peripheral insulin resistance through beta-adrenergic receptors [23]. This has been demonstrated in the pheochromocytoma population by Wiesner et al. who were able to show a reversal of insulin resistance after tumor resection [24]. In extreme situations, this reversal may actually contribute to acute postoperative hypoglycemia.

Postoperative Hypoglycemia

Hypoglycemia following pheochromocytoma resection is an insidious complication that contradicts the hyperglycemia usually seen in postoperative patients secondary to the body's normal response to the stress of surgery. The hypoglycemia following tumor resection can be attributed to the preoperative suppression of endogenous insulin secretion and a reactive postoperative rebound hyperinsulinemia. This reactive rise in insulin results from the sudden decrease in catecholamines and reduction of alpha-receptor stimulation, which preoperatively had inhibitive effects on the pancreatic insulin secreting islet cells [16]. Additionally, once the tumor is resected, the beta cells of the pancreas become rapidly sensitive to the preoperative hyperglycemia and respond with a reactive hyperinsulinemia. Improved peripheral insulin sensitivity with increased glucose use by skeletal muscle further contributes to hypoglycemia [24].

The body's normal compensatory response to hypoglycemia is the release of glucagon, epinephrine, and cortisol to stimulate the sympathetic nervous system to increase blood glucose levels via gluconeogenesis, glycogenolysis, and inhibition of insulin secretion. However, hypoglycemia usually persists in the acute postoperative period since liver glycogen stores are depleted preoperatively by the pheochromocytoma. The use of beta blockers also diminishes sympathetic tone secondary to the stress of surgery and impairs gluconeogenesis and glycogenolysis, further inhibiting recovery from postoperative hypoglycemia [25]. The effect of beta blockers combined with alpha blockers, which increase insulin secretion, exacerbates postoperative hypoglycemia.

Postoperative hypoglycemia can be extremely detrimental given that it often goes unrecognized secondary to the masking effects of anesthesia. The change in mental status associated with hypoglycemia may be attributed to residual anesthesia [26]. Alpha and beta-blockade further blunt the body's natural response to hypoglycemia which is usually tachycardia, palpitations, and sweating. Prolonged, unrecognized hypoglycemia can lead to severe neurologic consequences such as seizures, unconsciousness, or even irreversible brain damage.

Meeke et al. describe a case of a 45 year old female whose symptoms of postoperative drowsiness and mild hypotension were initially thought to be due to the effects of 3.5 h of general anesthesia using enflurane, nitrous oxide, droperidol, and fentanyl. It turned out that hypoglycemia was the cause of this patient's drowsiness. This case report urges physicians to consider hypoglycemia when confronted with a postoperative pheochromocytoma resection patient who fails to fully awaken from anesthesia or in severe cases develops a postoperative coma up to 2 h after surgery [26].

Another case report by Kato et al. describes a 39 year old male with severe hypoglycemia following resection of a right 7.5 × 5 × 7 cm pheochromocytoma. This patient received doxazosin and propranolol for 43 days prior to the adrenalectomy. After 2 h in the intensive care unit, the patient became drowsy and diaphoretic. The patient was found to be hypoglycemic (38 mg/dl) and hyperinsulinemic (63.67 μU/ml, normal being 8.4–8.8 μU/ml). The study concluded with a recommendation for close monitoring of blood glucose for at least 6 h after pheochromocytoma resection [27].

Preoperative Factors Associated with or Predictive of Postoperative Hypoglycemia

Given that hypoglycemia after pheochromocytoma resection can have serious consequences, it behooves one to identify preoperative risk factors that are associated or predictive of postoperative hypoglycemia. A literature review reveals multiple possible factors associated with an increased risk of postoperative hypoglycemia such as greater preoperative urine catecholamine excretion, larger tumor size, longer operative time, and pre-existing diabetes mellitus [16, 28, 29]. Plouin et al. reported a postoperative hypoglycemia rate requiring hypertonic glucose at 15%. This number is supported by Akiba et al. who reported a rate of 13.3% (6 of 45) for severe postoperative hypoglycemia defined as less blood glucose levels less than

50 mg/dL [16]. This group looked at an 8-year-period from 1981 to 1989 where 6 out of 45 pheochromocytoma patients developed severe hypoglycemia (12–50 mg/dl) 2–4.5 h after tumor resection, with an average of 3 h. In order to study the pathophysiology behind postoperative hypoglycemia, levels of plasma immunoreactive insulin (IRI) and glucose were measured at surgery in ten patients with pheochromocytoma, from the beginning of the operation to 5 h after tumor resection. Two of these ten patients developed postoperative hypoglycemia. The highest plasma IRI levels were observed in the two patients with post-resection hypoglycemia and the levels were 174 and 2081 μU/ml. IRI levels in the eight patients without hypoglycemia ranged from 13–222 μU/ml (mean, 77) and were only 14–33 μU/ml (mean, 22) in the five control patients made up of patients with primary aldosteronism and Cushing's syndrome [16].

Akiba et al. also concluded that patients with higher levels of preoperative urine epinephrine and those with either diabetes mellitus or impaired glucose tolerance, identified preoperatively by the World Health Organization criteria, were at a higher risk for postoperative hypoglycemia. These observations suggest that excessive rebound secretion of insulin after removal of a pheochromocytoma occurs because preoperative endogenous insulin secretion is suppressed by the elevated plasma catecholamine level. They also found that intraoperative infusion of glucose and/or postoperative infusion of epinephrine and norepinephrine did not necessarily prevent hypoglycemia. They conclude by recommending glucose monitoring for at least 5 h after tumor resection, however they do not comment on the frequency of glucose checks. They also concluded that patients with high preoperative urine catecholamime levels or impaired glucose intolerance are at high risk. Additionally, based on the findings of a single patient with elevated intraoperative plasma catecholamine levels, they suggest that patients with an extreme increase in intraoperative plasma catecholamines can also be at high risk of postoperative hypoglycemia [16].

Chen et al. conducted a retrospective chart review of patients who underwent pheochromocytoma resection between 1993 and 2013 at two large academic medical centers to elucidate the incidence of postoperative hypoglycemia and to identify predisposing risk factors. The primary endpoint was postoperative hypoglycemia defined as blood glucose less than 55 mg/dl. A total of 213 patients were identified. Nine patients (4.2%) experienced postoperative hypoglycemia, and eight of these patients presented within the first 24 h. The average lowest postoperative glucose in these patients was 41 mg/dl (range 20–53), which occurred between 0.4 and 142 h postoperatively. In the majority of patients (5 of 9), the first episode of hypoglycemia occurred in the first four postoperative hours. In three patients, the first episode was within 24 h. Two of these patients also experienced a second episode of hypoglycemia up to 42 h postoperatively. One patient even had hypoglycemia after 162 h. This patient, however, had undergone a bilateral adrenalectomy complicated by critical illness and the need for total parenteral nutrition [29].

In comparing the patients with and without postoperative hypoglycemia, Chen et al. found no difference in patient demographics, history of diabetes mellitus, preoperative baseline glucose levels, type of preoperative adrenergic receptor blockade received, or operative approach. However, patients with postoperative

hypoglycemia had higher preoperative 24-h urinary metanephrine levels (4726 vs. 2461 μg/24 h, $P = 0.05$), longer operative times (270 vs. 142 min, $P < 0.01$), and larger tumors (7.6 vs. 4.6 cm, $P = 0.02$). These patients required frequent intensive care level monitoring (88.9% vs. 34.5%, $P < 0.01$) but there was no statistically significant difference in length of hospital stay (5 vs. 3 days, $P = 0.10$) [29].

Multivariate analysis revealed that the only independent predictors of postoperative hypoglycemia are increased preoperative 24-h urine epinephrine levels ($P = 0.03$) and longer operating time ($P < 0.01$) [29]. This finding of a longer operative time associated with postoperative hypoglycemia is supported by Chernow et al. who concluded that the magnitude of the stress response is proportional to the extent of operation and that postoperatively there may be a component of relative hypoadrenalism contributing to hypoglycemia [30]. Chen et al., much like other studies, does not comment on a recommended frequency or duration for glucose monitoring.

Along with elevated preoperative urine metanephrines and longer operative times, epinephrine-predominant pheochromocytomas may also predispose patients to developing postoperative hypoglycemia. In animal studies prolonged stimulation of adrenergic receptors by epinephrine results in tachyphylaxis and desensitization of these receptors. Additionally, chronic epinephrine exposure and stimulation decreases hepatic glycogen storage levels thereby limiting the body's ability to respond to hypoglycemic episodes [30–32].

The role of diabetes in the development of postoperative hypoglycemia remains unclear. It has been hypothesized that patients with pre-existing type 2 diabetes or glucose intolerance may be at decreased risk because the persistent hyperinsulinemia depletes pancreatic stores and prevents the rebound hyperinsulinemia seen after pheochromocytoma resection [33]. Akiba et al. showed that preoperative diabetes or glucose intolerance was a risk factor, however, Chen et al. and Plouin et al. showed differing results [16, 28, 29].

Plouin et al. looked at a total 165 patients, 25 of which had episodes of postoperative hypoglycemia requiring intravenous hypertonic glucose fluids. In their study, there was no significant difference in the proportion of patients with preoperative hyperglycemia [8 of 25 (32.0%) vs. 43 of 131 (32.8%)], malignant pheochromocytoma [3 of 25 (12.0%) vs. 31 of 131 (23.7%)], or in preoperative plasma catecholamine concentrations between cases with and without hypoglycemia [28].

It is also important to keep in mind that if both hypotension and hypoglycemia occur in a patient after bilateral partial or complete adrenalectomy, suspicions about hypocortisolism and Addisonian crisis should be raised [34]. In these situations, plasma and urinary cortisol and plasma adrenocorticotropic hormone (ACTH) levels should be measured [34]. If the diagnosis of hypocortisolism or Addisonian crisis is made, steroids should be administered immediately [35].

Overall, the only factor associated with postoperative hypoglycemia that has been supported by more than one study is elevated preoperative urine metanephrine levels [16, 29]. Chen et al. also found an association with increased operative times and larger tumors. Some studies have found preoperative diabetes or glucose intolerance to lead to postoperative hypoglycemia, however this has been refuted by more contemporary studies [16, 28, 29].

Recommendations

In conclusion, postoperative hypoglycemia is seen in 4–15% of patients undergoing pheochromocytoma resection [16, 28, 29]. If this complication is not anticipated, it can be missed with detrimental neurologic consequences [16, 28, 29]. A thorough literature search over the years provides data in favor of routine postoperative monitoring of glucose levels after pheochromocytoma resection, however the exact duration and frequency of glucose checks remains up for debate. Studies have recommended close postoperative glucose monitoring anywhere from 2 to 24 h [29, 36]. Based on the studies reviewed, most postoperative hypoglycemic events occurred within the first five postoperative hours, thus routine monitoring equivalent to what an intensive care unit would provide at a given institution for hyperglycemia monitoring, usually at 1 h intervals, should be conducted during the postoperative period [16, 29, 37]. Ongoing routine monitoring should continue if any episodes of hypoglycemia are found and should be continued until glucose levels normalize. It is important to remember that the effects of anesthesia can mask postoperative symptoms of hypoglycemia, thus patients who are still emerging from anesthesia should have routine monitoring outside the recommended 5 h period. Similarly, those patients who remain in critical condition postoperatively and require intubation or are unable to manifest signs and symptoms of hypoglycemia due to alpha or beta-blockade should have routine monitoring of their blood glucose levels. Hemodynamically unstable patients should also have prolonged routine glucose monitoring.

It is also important to note that Chen et al. showed postoperative hypoglycemia to be associated with higher preoperative urine metanephrine levels and those who had undergone longer operations for larger tumors [29]. Thus it may be wise to place these patients with known risk factors for postoperative hypoglycemia in the intensive care unit. Chen et al. also showed that patients with complicated postoperative courses or those requiring bilateral adrenalectomy presented with postoperative hypoglycemia up to 162 h after surgery [29]. These patients should also undergo routine monitoring until they are deemed stable to come out of the intensive care unit on an individual to individual basis.

Patients found to be hypoglycemic should be administered intravenous dextrose solutions immediately. Some studies even recommend routine administration of dextrose containing intravenous fluids with the assumption that by the time hypoglycemia is detected it may be severe and refractory to large amounts of glucose administration. For example, Yanaru et al. describes a case of a 54 year old female who presented with a glucose level of 30 mg/dl 4 h after tumor resection. Despite intravenous administration of glucose at a rate of 15 g/h. with intermittent boluses of 5 g of glucose, it took about 2 h to obtain glucose levels above 100 mg/dl. They recommend that all patients who undergo pheochromocytoma resection have regular postoperative glucose monitoring and receive dextrose-containing fluids routinely. They also had a low threshold for checking serum glucose levels in patients who had excessive drowsiness or hyperadrenergic symptoms postoperatively, and often sent these patients to the intensive care unit [37].

Additional challenges of the immediate postoperative period are blood pressure instability and heart rate control, necessitating close patient monitoring for at least 24–48 h [36]. Since patients are being closely monitored for hemodynamic instability for prolonged periods of time, it only makes sense to routinely monitor patients for hypoglycemia, at least for the first five critical postoperative hours where studies have shown most patients present with this complication.

Despite the well-documented complication of postoperative hypoglycemia after pheochromocytoma resection, all of these studies have limitations associated with either being case studies, case reports, retrospective reviews, or prospective studies with small patient samples. As a result, all of the current available research on postoperative hypoglycemia falls under the GRADE format study design category of observational studies, which places the initial quality of evidence rating as low. Further review of the quality of evidence reveals that it should not be downgraded since there are no serious doubts about the indirectness of evidence, no serious imprecisions, and an unlikely probability of publication bias. The recommendation however can be upgraded because it is likely that there are plausible biases from the observational studies. In particular, the relatively rare nature of this complication often inherently leads to biased results which may actually underestimate the benefit of routine monitoring of hypoglycemia. Thus, the actual treatment effect is likely to be larger than what the data suggests. An overall GRADE of 1C is therefore recommended in favor of routine postoperative glucose monitoring after pheochromocytoma resection. This grade corresponds to a strong recommendation from low quality evidence and clinically fits the GRADE 1C risk/benefit category since the benefits of identifying and treating early hypoglycemia appear to outweigh the risks of severe neurologic consequences if episodes of hypoglycemia are missed. Additionally, this benefit appears to override the burden of routine monitoring [38, 39].

Overall, since no current consensus guidelines exist on routine postoperative glucose monitoring after pheochromocytoma resection, we propose the following guidelines with a GRADE 1C recommendation:

- All postoperative pheochromocytoma patients should have routine glucose monitoring for at least 5 h.
- Patients with preoperative risk factors for hypoglycemia such as elevated urine metanephrine levels or large tumors with an anticipated prolonged operative time should be considered for monitoring in the intensive care unit or monitored setting with a similar level of acuity [29].
- Patients who remain intubated, are hemodynamically unstable, or have delayed emergence from anesthesia should go to the intensive care unit for prolonged routine glucose monitoring on a case by case basis or until institution-dependent discharge criteria from the intensive care unit are met.

To increase the strength of the recommendation, a large multisite prospective randomized control study would prove useful to identify additional factors predictive of this complication and how to preemptively avoid this complication.

Intraoperative or postoperative real-time monitoring of serum insulin, glucagon, and glucose levels may help to anticipate and treat postoperative hypoglycemia before complications arise [29].

References

1. Manger WM, Gifford RW. Clinical and experimental pheochromocytoma. Hoboken: Blackwell Science; 1996.
2. Därr R, Lenders JW, Hofbauer LC, Naumann B, Bornstein SR, Eisenhofer G. Pheochromocytoma - update on disease management. Ther Adv Endocrinol Metab. 2012;3(1):11–26.
3. Prejbisz A, Lenders JW, Eisenhofer G, Januszewicz A. Cardiovascular manifestations of phaeochromocytoma. J Hypertens. 2011;29:2049–60.
4. La Batide-Alanore A, Chatellier G, Plouin PF. Diabetes as a marker of pheochromocytoma in hypertensive patients. J Hypertens. 2003;21:1703–7.
5. Witteles RM, Kaplan EL, Roizen MF. Safe and cost-effective preoperative preparation of patients with pheochromocytoma. Anesth Analg. 2000;91:302–4.
6. Bravo EL, Tagle R. Pheochromocytoma: state-of-the-art and future prospects. Endocr Rev. 2003;24:539–53.
7. Kinney MA, Narr BJ, Warner MA. Perioperative management of pheochromocytoma. J Cardiothorac Vasc Anesth. 2002;16:359–69.
8. Kocak S, Aydintug S, Canakci N. Alpha blockade in preoperative preparation of patients with pheochromocytomas. Int Surg. 2002;87:191–4.
9. Prys-Roberts C, Farndon JR. Efficacy and safety of doxazosin for perioperative management of patients with pheochromocytoma. World J Surg. 2002;26:1037–42.
10. Tokioka H, Takahashi T, Kosogabe Y, Ohta Y, Kosaka F. Use of diltiazem to control circulatory fluctuations during resection of a phaeochromocytoma. Br J Anaesth. 1988;60:582–7.
11. Gray RJ. Managing critically ill patients with esmolol. An ultra short-acting Beta-adrenergic blocker. Chest. 1988;93:398–403.
12. Reach G, Thibonnier M, Chevillard C, Corvol P, Milliez P. Effect of labetalol on blood pressure and plasma catecholamine concentrations in patients with phaeochromocytoma. Br Med J. 1980;280:1300–1.
13. Van Stratum M, Levarlet M, Lambilliotte JP, Lignian H, De Rood M. Use of labetalol during anesthesia for pheochromocytoma removal. Acta Anaesthesiol Belg. 1983;34:233–40.
14. Yabe R, Suenaga K, Niimura S, Itoh N, Tani M, Kunii N, et al. Treatment of pheochromocytoma with dilevalol. J Med. 1987;18:147–52.
15. Briggs RS, Birtwell AJ, Pohl JE. Hypertensive response to labetalol in phaeochromocytoma. Lancet. 1978;1:1045–6.
16. Akiba M, Kodama T, Ito Y, Obara T, Fujimoto Y. Hypoglycemia induced by excessive rebound secretion of insulin after removal of pheochromocytoma. World J Surg. 1990;14:317–24.
17. Yamaguchi N. Sympathoadrenal system in neuroendocrine control of glucose: mechanisms involved in the liver, pancreas, and adrenal gland under hemorrhagic and hypoglycemic stress. Can J Physiol Pharmacol. 1992;70:167–206.
18. Steiner KE, Stevenson RW, Green DR, Cherrington AD. Mechanism of epinephrine's glycogenolytic effect in isolated canine hepatocytes. Metab Clin Exp. 1985;34:1020–3.
19. Ahrén B, Veith RC, Taborsky GJ. Sympathetic nerve stimulation versus pancreatic norepinephrine infusion in the dog: 1. Effects on basal release of insulin and glucagon. Endocrinology. 1987;21:323–31.
20. Porte D, Williams RH. Inhibition of insulin release by norepinephrine in man. Science. 1966;152:1248–50.

21. Ostenson CG, Cattaneo AG, Doxey JC, Efendic S. Alpha-adrenoceptors and insulin release from pancreatic islets of normal and diabetic rats. Am J Phys. 1989;257:439–43.
22. Ahrén B. Autonomic regulation of islet hormone secretion—implications for health and disease. Diabetologia. 2000;43:393–410.
23. Deibert DC, DeFronzo RA. Epinephrine-induced insulin resistance in man. J Clin Investig. 1980;65:717–21.
24. Wiesner TD, Blüher M, Windgassen M, Paschke R. Improvement of insulin sensitivity after adrenalectomy in patients with pheochromocytoma. J Clin Endocrinol Metab. 2003;88:3632–6.
25. Martin R, St. Pierre B, Moliner OR. Phaeochromocytoma and postoperative hypoglycaemia. Can Anaesth Soc J. 1979;26(4):260–2.
26. Meeke RI, O'Keefe JD, Gaffney JD. Phaeochromocytoma removal and postoperative hypoglycaemia. Anaesthesia. 1985;40(11):1093–6.
27. Kato Y, Saga Y, Hou K, Yamaguchi S, Hashimoto H, Kaneko S, Yachiku S. Postoperative hypoglycemia after resection of pheochromocytoma: a case report. Hinyokika Kiyo. 2004;50(7):479–83.
28. Plouin PF, Duclos JM, Soppelsa F, Boublil G, Chatellier G. Factors associated with perioperative morbidity and mortality in patients with pheochromocytoma: analysis of 165 operations at a single center. J Clin Endocrinol Metab. 2001;86:1480–6.
29. Chen Y, Hodin RA, Pandolfi C, Ruan DT, McKenzie TJ. Hypoglycemia after resection of pheochromocytoma. Surgery. 2014;156(6):1404–8.
30. Chernow B, Alexander HR, Smallridge RC, et al. Hormonal responses to graded surgical stress. Arch Intern Med. 1987;147:1273–8.
31. Tsujimoto G, Honda K, Hoffman BB, Hashimoto K. Desensitization of postjunctional alpha 1- and alpha 2-adrenergic receptor-mediated vasopressor responses in rat harboring pheochromocytoma. Circ Res. 1987;61:86–98.
32. Tsujimoto G, Manger WM, Hoffman BB. Desensitization of beta-adrenergic receptors by pheochromocytoma. Endocrinology. 1984;114:1272–8.
33. Cremer GM, Molnar GD, Taylor WF, et al. Studies of diabetic instability. II. Tests of insulinogenic reserve with infusions of arginine, glucagon, epinephrine, and saline. Metab Clin Exp. 1971;20:1083–98.
34. Costello GT, Moorthy SS, Vane DW, Dierdorf SF. Hypoglycemia following bilateral adrenalectomy for pheochromocytoma. Crit Care Med. 1988;16:562–3.
35. Pacak K, Eisenhofer G, Lenders JWM. Pheochromocytoma: diagnosis, localization, and treatment. Birmingham: Blackwell Pub; 2007.
36. Mannelli M. Management and treatment of pheochromocytomas and paragangliomas. Ann N Y Acad Sci. 2006;1073:405–16.
37. Yanaru T, Sugi Y, Higa K, Katori K, Shono S, Nitahara K. Postoperative profound hypoglycemia after resection of adrenaline-predominant pheochromocytoma. Masui. 2007;56(12):1419–21.
38. Guyatt GH, Oxman AD, Kunz R, Falck-Ytter Y, Vist GE, Liberati A, Schünemann HJ, GRADE Working Group. Going from evidence to recommendations. BMJ. 2008;336(7652):1049–51.
39. Guyatt GH, Oxman AD, Vist G, Kunz R, Brozek J, Alonso-Coello P, Montori V, Akl EA, Djulbegovic B, Falck-Ytter Y, Norris SL, Williams JW Jr, Atkins D, Meerpohl J, Schünemann HJ. GRADE guidelines: 4. Rating the quality of evidence-study limitations (risk of bias). J Clin Epidemiol. 2011;64(4):407–15.