Severe hypoglycemia with endogenous hyperinsulinemia in a nondiabetic hemodialysis patient following parathyroidectomy

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Abstract
Insulin resistance and abnormal carbohydrate metabolism is a recognized complication in patients with advanced chronic kidney disease. We describe a rare case of severe hypoglycemia with inappropriate endogenous hyperinsulinemia in a hemodialysis patient following parathyroidectomy for severe secondary hyperparathyroidism. The patient required intravenous dextrose infusions for 3 days to prevent neuroglycopenic symptoms. Extensive workup for hypoglycaemia revealed high C-peptide and insulin levels in the absence of insulinoma. It is postulated that reversal of parathyroid hormone (PTH)-mediated inhibition of insulin secretion, along with large doses of 1,25-dihydroxyvitamin D3 (calcitriol) were responsible for the increase in insulin secretion and consequent hypoglycemia in this patient.

Keywords: dialysis; hyperinsulinemia; hypoglycemia; parathyroidectomy

Introduction
Insulin resistance and glucose intolerance is much more common than hypoglycemia in end-stage renal disease (ESRD) patients. Both secondary hyperparathyroidism and vitamin D deficiency are involved in the pathophysiology of abnormal glucose and insulin metabolism in ESRD. We report a dramatic case of hypoglycemia in a nondiabetic hemodialysis patient following surgical parathyroidectomy (PTX). The abrupt fall in parathyroid hormone (PTH) levels in combination with high doses of calcitriol used in this patient may have caused this rare complication.
Case history

A 50-year-old well-nourished Asian man with ESRD on hemodialysis for last 15 years underwent PTX for severe secondary hyperparathyroidism, which could not be adequately controlled with phosphate binders and oral calcitriol. He could not afford cinacalcet therapy. He suffered fractures of the radial and fibular bones and had bone pains along with radiographic changes of renal osteodystrophy. His serum intact PTH level was 546 pmol/L (5200 pg/mL) (range 9.0–18 pmol/L or 85–170 pg/mL), corrected serum calcium 2.6 mmol/L (10.4 mg/dL) (range 2.20–2.60 mmol/L or 8.8–10.4 mg/dL), serum phosphate 1.72 mmol/L (5.3 mg/dL) (range 0.80–1.4 mmol/L or 2.5–4.5 mg/dL) and alkaline phosphatase 450 U/L (range 40–150 U/L).

Three and one-half gland PTX was performed and postoperatively the serum calcium decreased to 1.66 mmol/L (6.6 mg/dL). He required large doses of oral and intravenous calcium (15 g/day) along with oral calcitriol 2 μg/day. He remained in hospital after surgery due to prolonged severe hypocalcemia requiring continued intravenous (IV) calcium. His PTH level postoperatively was undetectable.

On the first postoperative day, the patient was prescribed clear fluids, which was liberalized to a 60 g protein diet (the patient weighed 60 kg) by the next day. He continued to receive thrice-weekly hemodialysis, with a dialysate glucose concentration of 11.1 mmol/L. Seven days after surgery, he was found to be diaphoretic, tachycardic and drowsy. Blood work showed a random blood glucose of 1.9 mmol/L (34.2 mg/dL). His symptoms resolved promptly with intravenous (IV) 50% dextrose. On the day he developed hypoglycemia, blood work was repeated fifteen times. Serum bicarbonate varied between 17 and 21 mmol/L. An arterial blood gas showed pH 7.38, pCO2 30 mm Hg and pO2 101 mm Hg. Serum phosphorus was measured eight times that day and was always normal, varying between 0.98 and 1.25 mmol/L. IV fluid used for the management of his metabolic abnormalities until the hypoglycemia supervened was normal saline. However, he continued to show severe hypoglycemia for the next 3 days, complicated by a grand mal seizure on one occasion with a simultaneous blood glucose of 1.6 mmol/L (28.8 mg/dL) despite continuous IV 10% dextrose infusion. He also received multiple doses of IV glucagon 1 mg each. Only after 4 days of continuous dextrose infusion did his blood glucose levels stabilize and he was carefully weaned off the IV dextrose, with frequent attendant blood glucose monitoring and frequent meals (Figure 1).

He had never experienced any prior hypoglycemic episodes and his random blood glucose levels before surgery ranged from 5 to 8 mmol/L (90–140 mg/dL). He was not receiving insulin, oral hypoglycemic agents or beta blockers and extensive review of nursing notes did not reveal any medication error. The other patients in the same room were nondiabetic and none were receiving hypoglycemic medications. He was eating well during this period and there was no evidence of sepsis or liver dysfunction.

Diagnostic workup revealed normal thyroid function tests, normal 8 AM serum cortisol levels as well as a normal ACTH stimulation test. Sulfonylurea screen was negative. However, an insulin level obtained during a hypoglycemic episode was markedly elevated at 589 pmol/L (normal range for fasting 50–250 pmol/L) and concurrent C-peptide level was 13 330 pmol/L, (normal range 370–1470 pmol/L) (Figure 2).

His insulin levels decreased over the next 7 days to 53 pmol/L, and C-peptide levels also declined to 1425 pmol/L. He underwent a supervised fasting test in consultation with endocrine services to diagnose insulinoma. The test was terminated at 48 h since he did not develop hypoglycemia during this observation period and his fasting insulin levels were appropriately suppressed at <15 pmol/L. Contrast Computerized tomographic scan of his pancreas ruled out any mass lesion.

Commensurate with the fall in his insulin levels, his blood glucose normalized on discharge. On follow-up for the next 6 months in the hemodialysis unit, his blood glucose levels remained normal.

Discussion

Abnormal carbohydrate metabolism and insulin resistance is almost universal in patients with ESRD [1–3]. About 50% of patients can elevate their insulin secretion suf-
sufficiently to maintain normal glucose tolerance despite insulin resistance. However, in the remaining 50% of patients, pancreatic beta cell dysfunction and inhibition of glucose-stimulated insulin secretion results in glucose intolerance [3].

Spontaneous hypoglycemia is uncommon in ESRD patients and its mechanism is unclear. It likely involves impaired renal gluconeogenesis and reduced renal clearance of insulin. Associated chronic liver disease, malnutrition, sepsis, lactic acidosis, glucose free dialyzate and drugs have also been implicated. In these patients, however, insulin levels are appropriately suppressed [4–6].

Severe hypoglycemia with inappropriate endogenous hyperinsulinemia following PTX in a dialysis patient has been reported only once before [7].

There is evidence from animal studies and in patients with chronic kidney disease that secondary hyperparathyroidism inhibits glucose-mediated insulin secretion and contributes to insulin resistance in peripheral tissues [8–13]. The action of PTH on glucose metabolism and insulin secretion was examined by hyperglycemic clamp studies in hemodialysis patients with secondary hyperparathyroidism [12]. Before PTX, patients were insulin resistant and glucose intolerant. Following surgery, insulin secretion increased with correction of glucose intolerance and without change in insulin sensitivity [12].

Similar results have been achieved with medical therapy of secondary hyperparathyroidism [13] with phosphate binders and vitamin D. In pediatric pre-dialysis patients, PTX has led to an increase in glucose disposal rate by 32% and insulin secretion increased by 34%, but glucose sensitivity remained unchanged during glucose clamp studies [13]. Studies in uremic animals demonstrated similar results following PTX [8–10].

These studies also showed that the effect of PTH on insulin secretion was due to chronically high intracellular calcium levels in pancreatic beta cells and not related to changes in cyclic AMP levels [11].

Based on the above studies, it can be postulated that the abrupt decline in PTH levels after PTX may have led to a reduction of intracellular calcium in the beta cells, leading to an increase in insulin secretion and consequent hypoglycemia.

Large doses of calcitriol used postoperatively to treat severe hypocalcemia may also have contributed to hypoglycemia in our patient.

A number of animal and in vitro studies have demonstrated that vitamin D has a functional role in glucose tolerance through its effect on insulin secretion and insulin sensitivity [14]. These studies show the presence of specific vitamin D receptors (VDR) on pancreatic beta cells [15], expression of the 1-alpha-hydroxylase enzyme in beta cells [16], presence of the vitamin D response element in insulin gene promoter region [17] and the presence of VDR in skeletal muscles [18]. In addition, calcitriol directly activates transcription of the insulin receptor gene [19] and stimulates expression of the insulin receptor and insulin-mediated glucose uptake in vitro. Dietary vitamin D repletion in vitamin D-deficient rats markedly improved insulin secretion and glucose intolerance [20].

Mak [21,22] have shown that vitamin D deficiency in diabetes patients led to glucose intolerance due to inhibition of insulin secretion and IV calcitriol led to correction of glucose intolerance with an increase in insulin during hypoglycemic clamp studies without a change in PTH, calcium or phosphorus levels. Therefore, it is possible that the large doses of calcitriol administered to our patient may have caused hyperinsulinemia by a similar mechanism.

Conclusion

This is an exceptional case of life-threatening hypoglycemia due to hyperinsulinemia following PTX in a non-diabetic hemodialysis patient that has been reported only once before in the literature. We propose that this resulted from the rapid fall in PTH levels in combination with large doses of calcitriol. It also highlights the interesting and important role of PTH and vitamin D in insulin secretion, insulin resistance and glucose metabolism in ESRD patients.

Conflict of interest statement

None declared.

References

Scattered striated persistent nephrogram in sepsis

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Abstract

Persistent nephrogram, the hallmark of radiocontrast-induced kidney failure, is usually homogenous throughout the kidney and is considered as a generalized shutoff of glomerular filtration, the consequence of altered glomerular hemodynamics, affecting most glomeruli. Herein, we report an incidental finding of scattered persistent nephrogram that was noted in a septic prediabetic hypertensive patient during computerized tomography-guided drainage of a liver abscess. The peculiar patchy striated distribution pattern suggests more centrally altered renal hemodynamics, with hypoperfusion at the level of interlobar and intralobular arteries. Altered renal microcirculation in this case is likely related to the combined effects of prediabetes, sepsis and contrast medium upon renal blood flow regulation, perhaps with consequent focal hypoxic tubular damage.

Keywords: acute kidney injury; diabetes; dyslipidemia; hypertension; nephrogram; radiocontrast; sepsis

Background

The pathogenesis of acute kidney injury (AKI) is complex and only partially understood and often encompasses combinations of hypoxic and toxic components, in concert with altered renal microcirculation. For instance, reduced renal medullary blood flow with profound medullary hypoxia and enhanced generation of reactive oxygen species (ROS) plays a central role in the pathogenesis of radiocontrast-induced nephropathy (CIN) [1,2]. The propensity to develop CIN in patients with well-defined specific risk factors such as diabetes or preexisting renal disease underscores the complex interplay of these pathogenic mechanisms, which may be further activated in the predisposed patient [1,2]. Herein, we report an incidental finding of scattered persistent nephrogram that was noticed in a septic prediabetic patient during computerized tomography (CT)-guided drainage of a liver abscess. The peculiar patchy striated distribution pattern, illustrating altered renal blood flow conceivably at the level of interlobar and intralobular arteries, provides a new perspective regarding AKI in general and CIN in particular, in patients with sepsis and diabetes.

Case report

A 57-year-old woman with a history of hypertension, hyperlipidemia and impaired glucose tolerance presented with fever and right upper quadrant abdominal pain for 3 days. The patient underwent elective laparoscopic cholecystectomy for recurrent episodes of biliary colic 18 months previously. The postoperative course was complicated by bile leak from a dissected cystic duct entailing endoscopic retrograde cholangiopancreatography (ERCP) and stenting of the cystic duct. Post-ERCP, the patient suffered from acute pancreatitis which resolved with conservative treatment.