The use of diazoxide in the management of spontaneous hypoglycemia in patients with ESRD

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Abstract

Although diabetes remains the number one cause of renal failure nationwide, spontaneous hypoglycemia in patients with CKD has also been described in the absence of exogenous insulin or any other diabetes treatment. Decreased renal gluconeogenesis and impaired renal insulin clearance are underlying mechanisms of hypoglycemia in individuals with ESRD. Diazoxide was originally approved as an anti-hypertensive medication, but also is known to bind ATP-sensitive K channels in the beta cells of the pancreas, ultimately leading to inhibition of insulin release. We detail six cases of ESRD-associated hypoglycemia which responded to treatment with diazoxide therapy.

Keywords Hypoglycaemia · ESRD · Diazoxide

Introduction

According to population estimates, over 44 million Americans have chronic kidney disease (CKD). Close to 500,000 of these patients receive dialysis [1]. Diabetes remains the number one cause of renal failure nationwide [2]. End-stage renal disease (ESRD) patients with diabetes, who are receiving insulin or oral hypoglycemic agents are at high risk for developing hypoglycemia, due to reduced insulin clearance and alterations in glucose metabolism [3]. Spontaneous hypoglycemia in patients with CKD has also been described in the absence of exogenous insulin or any other diabetes treatment [4]. It is estimated that the kidneys contribute up to 25% of gluconeogenesis occurring in the body [5], which is compromised in ESRD. In addition, it is believed that changes in carbohydrate metabolism such as impaired counter-regulatory mechanisms of cortisol and growth hormone, malnutrition, and poor appetite can also contribute to hypoglycemia in ESRD patients [6]. In other reported cases, concomitant presence of liver failure and lactic acidemia have led to hypoglycemia in nondiabetic-ESRD

patients on hemodialysis [7]. Furthermore, guanidino compounds—uremic substrates that accumulate in the body and cause several adverse clinical outcomes such as uremic encephalopathy—are thought to act like biguanide agents and improve insulin sensitivity, possibly contributing to the increased risk of hypoglycemia [2]. Often, adequate dialysis using high-performance membranes and extending dialysis time may reduce uremic substrates, thus decreasing the risk of hypoglycemia [8, 9]. However, not all individuals respond to these measures and a remaining subset of individuals have ongoing episodes of hypoglycemia despite adequate dialysis.

Evaluation and management of spontaneously occurring hypoglycemia in ESRD in the absence of exogenous insulin or hypoglycemic agents have not been well established. Cases of hypoglycemia in this group of patients have been reported, but large studies do not exist outlining optimal treatment approaches. Typical evaluation for excess endogenous insulin production (insulinoma) includes fulfilment of Whipple's Triad (documented hypoglycemia on serum glucose, symptoms of hypoglycemia, and improvement in symptoms with glucose administration) as a starting point. If a patient cannot attain serum hypoglycemia spontaneously, a prolonged fast of up to 72 h may be pursued to provoke hypoglycemia and allow collection of critical specimens [10]. This workup in a patient with ESRD may prove challenging as many of these metrics are abnormal at baseline in this population given altered metabolism of insulin. Finally, imaging (CT vs MRI vs uptake scan) is used to localize a

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mass that can potentially be surgically resected [10]. Failure to localize a mass and inability to control hypoglycemia through conservative measures—including dietary changes, adjustments in medications, and optimization of dialysis/dialysate—necessitate treatment alternatives in these individuals.

From July 2015 and August 2019, we encountered six subjects with ESRD during their admission to a tertiary referral medical center who suffered from episodes of unexplained hypoglycemia, some requiring continuous infusion of dextrose solution to maintain normal blood sugars. None of the patients were actively being treated with hypoglycemic agents and they all were receiving adequate, regular dialysis sessions. No obvious modifiable cause could be determined for their hypoglycemia. We postulate that hypoglycemia was caused by relative hyperinsulinism secondary to poor renal clearance of endogenous insulin, which has been exacerbated by their acute illness, malnutrition, and other comorbidities; decreased renal gluconeogenesis; and, possibly increased guanidino compounds which enhance insulin sensitivity in the setting of hyperinsulinemia.

Diazoxide was originally introduced as an anti-hypertensive agent in the 1960's [11]. It has also been used in the treatment of hyperinsulinemia caused by insulinomas, in refractory cases or in patients who are poor surgical candidates [12] and is described in the treatment of congenital hyperinsulinemic hypoglycemia [13]. Diazoxide acts by binding to ATP-sensitive K channels in the beta cells of the pancreas, leading to cell hyperpolarization and inhibition of insulin release [14]. The use of diazoxide in the treatment of spontaneous hypoglycemia in patients with ESRD has not been well-documented, and not mentioned in a recent review of the topic [6].

Materials and methods

This is a retrospective descriptive case series of six patients who were admitted to the University of Maryland Medical Center between July 2015 and August 2019. All six patients were evaluated by the endocrine consult service for recurrent or persistent hypoglycemia. All patients had ESRD and were receiving regular renal replacement therapy with hemodialysis (HD).

Results

Case 1

A 54-year-old woman, with a history of type 2 diabetes and hypertension was started on HD due to hypertensive nephropathy. After starting HD, diabetes medications were slowly tapered off over 6 months due to frequent hypoglycemic episodes. Two months after discontinuation of all diabetes medications serum blood sugar was 57 mg/dL, with inappropriately normal proinsulin and c-peptide levels. Hypothyroidism and adrenal insufficiency were ruled out (Table 1). Ultrasound of the abdomen did not show any gross pancreatic abnormalities. After starting diazoxide, 100 mg once daily, hypoglycemic episodes improved, as shown in Fig. 1.

Case 2

A 51-year-old woman with history of HIV/AIDS treated with anti-retroviral therapy, hypertensive nephropathy, on regular HD was admitted with a fracture of the cervical spine sustained after a fall. There was no prior history of

Fig. 1 Case 1 glucose levels before and after diazoxide (diazoxide given at time 0)

diabetes. Recurrent episodes of spontaneous hypoglycemia were treated with glucose tablets. During admission, recurrent episodes of hypoglycemia with blood glucoses in the 37–50 mg/dl range required intermittent treatment with continuous dextrose infusion. C-peptide, insulin, and proinsulin levels were done with a concurrent blood glucose of 46 mg/dl (finger stick) and were inappropriately elevated (Table 2). Computed tomography (CT) scan of the abdomen with and without contrast showed no evidence of a pancreatic mass. Diazoxide treatment with 100 mg per day was started with improvement in blood glucose levels noted (Fig. 2).

Case 3

A 60-year-old man with a history of hepatitis C, HIV infection, and ESRD was receiving regular sessions of HD, and had no prior history of diabetes. During a prior hospitalization, a diagnosis of “hyperinsulinemia” was made, with no identifiable pancreatic mass on imaging. He was started on diazoxide which kept his blood glucose levels within the normal range.

After discharge, he was re-admitted to the intensive care unit with loss of consciousness believed to be secondary to hypoglycemia (blood glucose on finger stick was 30 mg/dl). A methicillin sensitive *Staphylococcus Aureus* bacteremia was diagnosed, and treatment was initiated for septic shock. The patient had not been compliant on diazoxide in the ambulatory setting. Hypoglycemia workup was repeated, and hypothyroidism and adrenal insufficiency were ruled out (Table 3). Diazoxide was held on admission due to hypotension but then resumed at 100 mg per day after blood pressure improved. Blood glucose levels then stabilized, and dextrose drip was slowly weaned off (Fig. 3). CT scan of the abdomen and pelvis and subsequent endoscopic ultrasound showed no pancreatic lesions.

Case 4

A 56-year-old man with history of ESRD was receiving hemodialysis for 4 months. The cause of CKD was presumed to be secondary to long-standing hypertension. Other past medical history was significant for untreated HCV, and CML with pancytopenia. The patient was admitted with hospital acquired pneumonia, and the inpatient stay was complicated by respiratory failure requiring mechanical ventilation. Recurrent episodes of hypoglycemia with point of care glucose values between 46 and 69 mg/dl required continuous dextrose infusion. Hypoglycemia was confirmed by serum glucose, and serum proinsulin and C-peptide levels were inappropriately non-suppressed (Table 4). CT scan of the abdomen and pelvis with contrast failed to show any pancreatic abnormality. Diazoxide was started at 100 mg twice daily. Two days later, the blood glucose levels had increased to the normal range without the dextrose infusion (Fig. 4).

Case 5

A 50-year-old man with history of ESRD secondary to HUS since childhood was admitted after being found unresponsive during dialysis with a finger stick of 46 mg/dl. There was no prior history of diabetes mellitus or taking diabetes medications. A continuous dextrose infusion was required to maintain euglycemia. Elevated c-peptide levels were seen with concurrent glucose of 51 mg/dl (Table 5). Adrenal insufficiency and hypothyroidism were ruled out. A CT scan of the abdomen and pelvis with contrast showed a 1.9 × 2.6 cm mass along the tail of the pancreas. Endoscopic ultrasound guided FNA revealed that the mass was consistent with an accessory spleen. Diazoxide was started at 100 mg twice daily and blood sugars remained stable off

Fig. 2 Case 2 glucose levels before and after diazoxide (diazoxide given at time 0)

Fig. 3 Case 3 glucose levels before and after diazoxide (diazoxide given at time 0)

Fig. 4 Case 4 glucose levels before and after diazoxide (diazoxide given at time 0)

of dextrose drip. **Note: Blood glucose trends were not available for this patient.

Case 6

A 75-year-old man with history of ESRD presumed secondary to diabetes mellitus was admitted from his nursing home after found being unresponsive with fingerstick of 58 mg/dL. He was not on any regular antidiabetic medications, but would receive occasional insulin as part for hyperglycemia greater than 250 mg/dL. He had not received any doses of insulin for at least 5 days prior to admission. Multiple boluses of dextrose were required to treat recurrent hypoglycemia. C-peptide and pro-insulin levels were inappropriately normal during episodes of hypoglycemia (Table 6) and a previous CT abdomen and

pelvis revealed diffusely atrophic pancreas but no focal mass/lesion. Diazoxide was started at 70 mg TID, and patient was discharged. He was readmitted 4 days later with altered mental status, hypoglycemia, and pneumonia and was transitioned to comfort care. It was unclear if he continued diazoxide during nursing home stay. After readmission dextrose infusion was required to maintain his blood glucose levels. After restarting diazoxide, dextrose infusion was discontinued, and blood glucoses remained stable until time of discharge to hospice (Fig. 5).

Fig. 5 Case 6 glucose levels before and after diazoxide during two separate admissions (diazoxide given at time 0 on each admission)

Table 1 Case 1 hypoglycemia-related laboratory results

Blood glucose	52 mg/dl
C-peptide	1.2 ng/ml (Ref 1.1–4.4 ng/ml)
Pro-insulin	2.6 pmol/l (Ref 0.0–10.0 pmol/l)
Sulfonylurea screen	Negative
AM cortisol	18.3 mcg/dl
TSH	0.35 mIU/L (Ref 0.47–4.68 mIU/L)
Free T4	2.1 ng/dl (Ref 0.60–2.5 ng/L)

Table 2 Case 2 hypoglycemia-related laboratory results

Blood glucose (finger stick)	46mg/dl
C-peptide	12.9 ng/ml (Ref 1.1–4.4 ng/ml)
Proinsulin	6.6 pmol/l (Ref 0.0–10.0 pmol/l)
Insulin	9.3 mIU/ml (Ref 2.6–24.9 mIU/ml)
Sulfonylurea screen	Negative
AM cortisol (on a separate day)	16.1 mcg/dl
TSH	2.4 mIU/L (Ref 0.47–4.68 mIU/L)

Table 3 Case 3 hypoglycemia-related laboratory results

Blood glucose	41 mg/dl
C-peptide	8.2 ng/ml (Ref 1.1–4.4 ng/ml)
Insulin	37.2 mIU/ml (Ref 2.6–24.9 mIU/ml)
Proinsulin	6.7 pmol/l (Ref 0.0–10.0 pmol/l)
Sulfonylurea screen	Negative
AM cortisol (on a separate day)	19.1 mcg/dl
TSH	16.4 mIU/L (Ref 0.47–4.68 mIU/L)
Free T4	1.4 ng/dl (Ref 0.60–2.5 ng/L)

Table 4 Case 4 hypoglycemia-related laboratory results

Blood glucose	34 mg/dl
C-peptide	2.9 ng/ml (Ref 1.1–4.4 ng/ml)
Insulin	0.3 mIU/ml (Ref 2.6–24.9 mIU/ml)
Proinsulin	3.4 pmol/l (Ref 0.0–10.0 pmol/l)
Sulfonylurea screen	Negative
AM Cortisol (on a separate day)	19.5 mcg/dl
TSH	4.22 mIU/L (Ref 0.47–4.68 mIU/L)

Table 5 Case 5 hypoglycemia-related laboratory results

Blood glucose	51 mg/dl
C-peptide	5.1 (Ref 1.1–4.4 ng/ml)
Proinsulin	1.9 (Ref 0.0–10.0 pmol/l)
Insulin	0.3 (Ref 2.6–24.9 mIU/ml)
Sulfonylurea screen	Negative
AM cortisol level	14.7 mcg/dl

Table 6 Case 6 hypoglycemia-related laboratory results

Blood glucose	75 mg/dl
C-peptide	0.9 (Ref 0.8–3.5 ng/ml)
Proinsulin	2.1 pmol / l (Ref 0.0–8.0 pmol/l)
AM cortisol level	16.5 mcg/dl
TSH	1.07 mIU/L (Ref 0.47–4.68 mIU/l)

Discussion

Hypoglycemia in non-diabetic ESRD patients on renal replacement therapy has been previously described but has not been extensively studied. Spontaneous hypoglycemia in this population is thought to be multifactorial. Malnutrition, infections, and alcohol abuse can all disturb the delicate energy balance in these patients and cause hypoglycemia. Primary or secondary adrenal insufficiency and hypothyroidism are two important treatable conditions that contribute to the development of hypoglycemia and should be excluded in all patients with this presentation [15]. We have observed that in all six patients in our series serum insulin, c-peptide and pro-insulin were not appropriately suppressed during the confirmed episodes of hypoglycemia (Table 7). After failing to find a direct cause of hypoglycemia, we concluded that hypoglycemia can largely be attributed to relative hyperinsulinemia caused by poor renal clearance of endogenous insulin. This is exacerbated by the patients' acute illnesses, state of malnutrition, and infection.

CT imaging has good sensitivity (78%) in detecting pancreatic lesions; however, endoscopic ultrasound is more advantageous in detecting smaller lesions [16]. There are previously three case reports of hypoglycemia caused by an insulinoma in patients with chronic renal failure. In our series, the patient in Case 3 underwent endoscopic ultrasonography because of considerably high levels of plasma insulin which raised the suspicion of a pancreatic pathology. In Case 5, the patient was found to have a pancreatic tail mass on abdominal CT, and subsequently underwent endoscopic ultrasonography to obtain a biopsy, which confirmed that this mass was in fact an accessory spleen. Due to the rare incidence of insulinomas in ESRD, our suspicion of an insulinoma was low, and we found that it was best to not subject most of these patients to invasive imaging techniques.

As demonstrated in all of six cases, spontaneous hypoglycemia in ESRD can be refractory, and a continuous

dextrose infusion was often required to maintain euglycemia. This especially occurred in the setting of an acute insult such as infection, trauma, or a gastrointestinal bleed. We have observed that in some cases, hypoglycemia can persist even after the improvement of the acute illnesses, and the patients often needed to remain in the critical care unit until they are no longer dependent on the dextrose drip making their care more resource consuming.

As mentioned earlier, diazoxide has been used in the management of congenital hyperinsulinism, and in insulinoma cases that are not amenable to surgery, as well as hyperinsulinemic hypoglycemia after bariatric surgery [17]. Diazoxide is rarely reported as the treatment of choice for patients with spontaneous hypoglycemia in the setting of ESRD and other comorbidities, and the experience of using diazoxide for this purpose has been limited. There have been no data that specifies a certain dosage of diazoxide for the treatment of hypoglycemia in patients with ESRD. Depending on the baseline blood pressure, our starting dose was 100 mg daily which in some cases we titrated up to 150 mg twice daily to achieve normoglycemia as long as there were no adverse outcomes, most importantly hypotension. The exception was case 6, who at the recommendation of a clinical pharmacist was started on 3 mg/kg/day in divided doses. Studies have shown that diazoxide has sodium and chloride retaining qualities [18], so it was crucial to monitor these patients for signs and symptoms of fluid overload. There is one case report that mentioned successful treatment of hypoglycemia in a dialysis patient using 225 mg of diazoxide daily [19]. Another abstract reported the successful use of diazoxide in the treatment of spontaneous hypoglycemia in a peritoneal dialysis patient found to have endogenous hyperinsulinemia not attributed to an insulinoma [20]. We were able to observe significant improvement and stabilization of blood glucose levels in our patients; however, we were unable to perform post-discharge assessment as most of these patients were lost to follow up. The long-term safety of using diazoxide has been evaluated in the pediatric population with congenital hyperinsulinism. One report detailed a case where diazoxide was used for 4.5 years with no adverse

Table 7 Summary of laboratory results for Cases 1–6

	Ref range	Case 1	Case 2	Case 3	Case 4	Case 5	Case 6
Serum blood glucose	70–99 mg/dl	52	46	41	34	51	75
C-Peptide Level	1.1–4.4 ng/ml	1.2	12.9	8.2	2.9	5.1	0.9
Pro-Insulin Level	0.0–10.0 pmol/l	2.6	6.6	6.7	3.4	1.9	2.1
Insulin Level	2.6–24.9 mIU/mL	NA	9.3	37.2	0.3	0.3	NA
Sulfonylurea Screen	Negative	Negative	Negative	Negative	Negative	Negative	Negative
AM Cortisol	mcg/dl	18.3	16.1	19.1	19.5	14.7	16.5
TSH	0.47–4.68 mIU/l	0.35	2.4	16.4	4.22	NA	1.07
Free T4	0.60–2.5 ng/L	2.1	NA	1.4	NA	NA	NA

*NA Not available

events for treatment of persistent hyperinsulinemia hypoglycemia of infancy [21]. A cohort of 615 patients with congenital hyperinsulinism, 85% of which received long-term treatment with diazoxide, were evaluated. It was found that the mean duration of treatment was 57 months. The more common adverse events reported include hypertrichosis (52%), and fluid retention and electrolyte imbalance (30%). Bone marrow suppression, heart failure and renal failure had significantly lower incidences [13]. With the availability of various classes of anti-hypertensive medications, the use of diazoxide in treatment of hypertension has fallen out of favor. There are no large-scale studies, on our review of English literature, that have explored the safety of long-term diazoxide use in patients with chronic renal failure or ESRD.

In conclusion, although spontaneous hypoglycemia in ESRD patients has not been well characterized in terms of causality and management, it appears more prevalent than is reported in the literature. Focusing on nutrition strengthening, and improving other comorbidities is a key to management. Diazoxide should be considered as a reasonable add-on therapy that can ameliorate this condition by decreasing endogenous insulin release in the event other therapies including medication management, optimization of dialysis, and nutritional interventions have not worked. The cases described in this study demonstrated improvement in critically low hypoglycemia that previously had been refractory to these interventions. More studies are needed to evaluate the safety of its long-term use in this patient population.

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Compliance with ethical standards

Conflict of interest The authors have declared that no Conflict of interest exists.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the University of Maryland at which the patients were admitted and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

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