Refractory Hypoglycemia Associated with End-Stage Renal Disease and Therapeutic Role of Diazoxide

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Received Date: 09 October 2020; Accepted Date: 19 October 2020; Published Date: 26 October, 2020

Abstract

Background: Refractory hypoglycemia commonly occurs in End-Stage Renal Disease (ESRD). Extent of work-up of this kind of hypoglycemia and its treatment are not well-studied.

Objective: To report a case of refractory hypoglycemia in the setting of ESRD and describe its causes and management.

Methods: PUBMED search of English literature up to October 8, 2020. Search terms included hypoglycemia, insulin, C-peptide, hemodialysis, end-stage renal disease, treatment, diazoxide. All relevant studies and case reports were reviewed.

Results: We present a case of refractory hypoglycemia in a patient receiving hemodialysis. Our review of literature revealed 10 patients with ESRD presenting with similar condition. In only one patient, insulinoma was confirmed. In many cases of ESRD, plasma insulin and C-peptide concentrations may be markedly elevated due to delayed renal clearance. In addition, circulating insulin levels may be elevated due to compensatory hyperinsulinemia in the face of prevailing insulin resistance. The increased circulating insulin and C-peptide values in ESRD frequently lead to diagnostic confusion and extensive invasive work-up to rule out insulinoma. In all patients reported, diazoxide therapy was effective in the control of hypoglycemia.

Conclusions: ESRD is frequently complicated by refractory hypoglycemia, which is effectively treated by diazoxide. Both circulating insulin and C-peptide levels are commonly increased in ESRD and may lead to erroneous diagnosis of insulinoma. Therefore, caution should be exercised in interpretation of these tests to avoid unnecessary invasive investigations.

Keywords: Hypoglycemia; End-stage renal disease; Diazoxide; Insulin; C-peptide

Introduction

Hypoglycemia is a common complication of ESRD frequently encountered in hospitalized patients. However, the exact prevalence of hypoglycemia in patients with ESRD is unknown and is likely underreported. The etiology of this type of hypoglycemia is multifactorial including reduced insulin clearance, poor oral intake, medications, and altered renal gluconeogenesis. In fact, the kidneys are the second organ of gluconeogenesis after the liver [1]. The contribution of the kidney to overall glucose release is variable, with reported proportions ranging from 5 to 28% (mean 20%; 95% CI, 8-32%) [1]. Other diseases may co-exist with ESRD causing or worsening hypoglycemia such as adrenal insufficiency and hypothyroidism.

The purpose of this case report is to clarify the interpretation of laboratory results in hypoglycemia associated with ESRD, and to review the most effective way of its pharmacological treatment.

Case Report

A thirty-one-year-old man with a history of Human Immunodeficiency Virus (HIV) and ESRD on hemodialysis presented with persistent hypoglycemia with no history of diabetes or medication causing hypoglycemia. The patient was initially admitted for sepsis due to disseminated histoplasmosis requiring intubation for impending respiratory failure. He was started on amphotericin B for histoplasmosis and intravenous fluids with dextrose for volume resuscitation and hypoglycemia. After he was extubated and the intravenous fluids were discontinued, he was found to have persistent fasting hypoglycemia with low blood glucose levels averaging 25 mg/dL each morning. The hypoglycemia persisted despite altering the patient’s meal schedule to include additional nighttime snacks at 10 PM and 3 AM, and administration of intravenous 5% dextrose. Laboratory tests during a fasting hypoglycemic episode featured inappropriately normal fasting insulin of 1.2 µIU/ml (normal <19.6 µIU/ml) and C-peptide of 7.5% of the arterial plasma C-peptide levels at 7.5% of the arterial plasma C-peptide levels. It is not uncommon to find increased serum insulin levels in ESRD even in presence of hypoglycemia i.e. hyperinsulinemic hypoglycemia. Miyamoto, et al. [2], have shown that mean circulating insulin levels were approximately 3.7 times higher in 9 patients with ESRD compared with age- and body mass index-matched control subjects with normal renal function. In a group of 107 patients with ESRD (90 on hemodialysis and 17 on peritoneal dialysis), Guthoff, et al. [3], have demonstrated that basal serum insulin levels were increased, albeit to a lesser extent compared with the study of Miyamoto, et al. [2], median levels being 69 and 48 pmol/L in patients with ESRD and control subjects, respectively (P<0.001). The cause of hyperinsulinemia in ESRD is attributed to both delayed renal insulin clearance and insulin resistance as result of uremic toxins [4]. In fact, the studies of Guthoff, et al. [3], confirmed the existence of insulin resistance in ESRD and suggested that hyperinsulinemia might be result of increase insulin secretion to counteract the prevailing insulin resistance in ESRD.

C-peptide levels are even more increased than those of insulin in ESRD. Indeed, Zavaroni, et al. [5], showed that the kidney removed 25.7 ± 7.5% of the arterial plasma C-peptide. Moreover, they found that more than 85% of C-peptide was metabolized by the kidney [5]. Furthermore, Miyamoto, et al. [2], have shown that mean C-peptide levels are 7 times higher than those in control subjects of similar age and body mass index and normal renal function, 13.6 and 1.9 ng/ml, respectively. Likewise, more recently, Guthoff, et al. [3], have shown that plasma C-peptide levels were significantly higher in patients with ESRD on hemodialysis (n=90) and peritoneal dialysis (n=17) than in control subjects with normal renal function both at basal state and during oral glucose tolerance test. In fact, baseline C-peptide levels were almost 5 times greater in patients with ESRD compared with individuals with normal renal function [3].
Clinical implications of elevated plasma levels of insulin and C-peptides

Interpretation of elevated insulin and C-peptide levels can be problematic during the laboratory evaluation of hypoglycemia in patients with ESRD and can be confused with other causes of hyperinsulinemia such as sulfonylurea ingestion, or insulinoma. For example, Shaer [6], reported an 85 year-old man with severe hypoglycemia and ESRD. Based on markedly elevated concentrations of C-peptide and insulin, the diagnosis of insulinoma was considered the primary diagnosis [6]. All imaging, including endoscopic ultrasound, failed to demonstrate insulinoma in that patient [6]. We speculate that the increased levels of C-peptide and insulin in the previous case are due to ESRD, and not insulinoma.

Diazoxide treatment of hypoglycemia

Diazoxide inhibits insulin secretion by opening of ATP-sensitive K⁺ channels and reduced opening of Ca²⁺ channels [7]. Diazoxide is excreted by the kidneys [8]. Its half-life (24-36 h) and duration of action are prolonged in kidney dysfunction but the extent of prolongation is unknown [8]. Accordingly, diazoxide doses should be reduced in patients with impaired renal function, thus, whereas the usual daily dose of diazoxide is 3-8 mg/kg divided into 2-3 equal doses, it is wise to start with low dose e.g. 3 mg/kg/d in patients with ESRD [8]. It should be emphasized that sodium and fluid retention are frequent adverse effects of diazoxide and may precipitate heart failure [8]. Therefore, caution should be exercised to watch for clinical signs of volume overload. Our review of literature revealed 10 cases of refractory hypoglycemia associated with ESRD-on hemodialysis [6,9-12] (Table 1). In only one case, the diagnosis of insulinoma was confirmed [11]. In all patients, diazoxide therapy was effective in controlling hypoglycemia.

Table 1. Patients with end-stage renal disease and refractory hypoglycemia treated with diazoxide.

<table>
<thead>
<tr>
<th>Reference</th>
<th>Patient age &amp; gender</th>
<th>History of diabetes</th>
<th>Diazoxide dose</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Nakdarni, et al. [9]</td>
<td>51 year-old man</td>
<td>No</td>
<td>Not reported</td>
<td>Hypoglycemia started 6 days after parathyroidectomy</td>
</tr>
<tr>
<td>2. Shaer [6]</td>
<td>85 year-old male</td>
<td>No</td>
<td>75 mg q8h</td>
<td>Insulinoma was diagnosed based on elevated C-peptide (60 mg/ml, normal range 0.8-4) and insulin (227 uIU/ml, normal range 0-9)</td>
</tr>
<tr>
<td>3. Jimenez, et al. [10]</td>
<td>73 year-old woman</td>
<td>No</td>
<td>132 mg/d (3 mg/kg/d)</td>
<td>Insulinoma was suspected due to elevated C-peptide and insulin.</td>
</tr>
<tr>
<td>4. Shimizu, et al. [11]</td>
<td>63 year-old man</td>
<td>Type 2 diabetes</td>
<td>250 mg/day</td>
<td>Insulinoma was confirmed by biopsy, but patient declined pancreatectomy.</td>
</tr>
<tr>
<td>5. Mesmar, et al. [12]</td>
<td>54 year-old woman</td>
<td>Type 2 diabetes</td>
<td>100 mg/d</td>
<td></td>
</tr>
<tr>
<td>6. Mesmar, et al. [12]</td>
<td>51 year-old woman</td>
<td>Type 2 diabetes</td>
<td>100 mg/d</td>
<td></td>
</tr>
<tr>
<td>7. Mesmar, et al. [12]</td>
<td>60 year-old man</td>
<td></td>
<td>100 mg/d</td>
<td></td>
</tr>
<tr>
<td>10. Mesmar, et al. [12]</td>
<td>76 year-old man</td>
<td>Type 2 diabetes</td>
<td>70 mg tid</td>
<td></td>
</tr>
<tr>
<td>11. Current case</td>
<td>31 y/o man</td>
<td></td>
<td>100 mg bid</td>
<td>See text</td>
</tr>
</tbody>
</table>

Conflicts of Interest

The authors have no conflict of interest to declare.

References


Conclusions and Current Needs

Hyperinsulimemic hypoglycemia may commonly occur in ESRD due to inappropriately normal or frankly elevated plasma insulin and C-peptide levels in the face of hypoglycemia. This laboratory constellation may cause diagnostic confusion as it mimics laboratory results of insulinoma. Meanwhile, insulinoma is a rare disease characterized by fasting hypoglycemia relieved by constant caloric intake and is associated with weight gain, presence of a pancreatic tumor detected on physical exam or on imaging. In some cases, insulinoma may be a part of multiple endocrine neoplasia type 1. In absence of the previous findings, the authors recommend avoidance of unnecessary and invasive procedures to rule out insulinoma. Diazoxide proves to be the only pharmacologic treatment for hypoglycemia associated with ESRD. Unfortunately, the pharmacokinetics and pharmacodynamics of diazoxide were not studied in patients with ESRD. Studies are also required to evaluate the long-term efficacy and safety and optimum doses of diazoxide in the setting of ESRD.