

Hypoglycemia associated with fluoxetine treatment in a patient with type 1 diabetes

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quirements progressively increased and returned to the patient's usual dose.

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Core tip: A patient with type 1 diabetes mellitus presented with hypoglycemia and a marked reduction in insulin requirements associated with fluoxetine treatment. Hypoglycemia accompanying treatment with fluoxetine has been reported in patients with type 1 or type 2 diabetes mellitus. Healthcare professionals should be aware of this association for the sake of patient safety.

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Abstract

We report on a patient with type 1 diabetes mellitus who presented with recurrent episodes of hypoglycemia and a marked reduction in her daily insulin requirements after introduction of fluoxetine. This 25-year-old Caucasian woman had been followed up at the outpatient clinic for type 1 diabetes mellitus and pre-pregnancy care. She used a continuous subcutaneous insulin infusion with lispro and her daily insulin dose was 0.5 IU/kg per day. She had no chronic diabetic complications or hypoglycemia unawareness. Fluoxetine at a daily dose of 20 mg had been started because of depressive symptoms and within one week, she presented recurrent hypoglycemic episodes that prompted a progressive reduction in the insulin dose down to 0.3 IU/kg per day. The reduced insulin requirements continued during the period of fluoxetine treatment while glycated hemoglobin remained stable. She had no concurrent additional cause to explain the reduced insulin requirements. After fluoxetine was stopped, insulin re-

INTRODUCTION

Diabetic patients have an increased risk of developing depression (8.5% to 20.0% higher than the general population)^[1-3]. Reports on the impact of antidepressant drugs on glucose homeostasis are diverse: hypoglycemic, hyperglycemic and neutral effects have been described depending on the specific drug^[4]. As to mechanisms, insulin sensitivity seems to be the main effector^[4], with some reports referring to an interaction with hypoglycemic agents^[5,6]. Specifically, fluoxetine has been associated with hypoglycemia^[7,8], hypoglycemia unawareness^[9] and increased insulin sensitivity^[9-11]. In addition, some case reports describe symptoms that suggest hypoglycemia although this was not confirmed on further analysis^[12,13].

Table 1 Summary of studies addressing fluoxetine and glucose metabolism

Reference	Study design	Results
Deeg <i>et al</i> ^[7]	Case report, patient with type 2 DM	Repeated episodes of hypoglycemia in a patient treated with glyburide. Fasting hypoglycemia (with hyperinsulinemia) continued 2 wk after glyburide was suspended and while receiving fluoxetine
Khoza <i>et al</i> ^[8]	Case reports, review of published reports	17 patients with glucose dysregulation (9 hyperglycemia; 8 hypoglycemia, one of them with fluoxetine) after initiation of treatment with antidepressant agents The authors concluded it was not clear whether changes in glucose regulation were due to antidepressants or to changes in mood and lifestyle
Sawka <i>et al</i> ^[9]	Case report, patient with type 1 DM	Reduced insulin requirements and hypoglycemia unawareness during treatment with fluoxetine
Maheux <i>et al</i> ^[10]	Experimental design, obese subjects with type 2 DM	Fluoxetine improved insulin sensitivity in a clamp study, independent of weight loss
Potter van Loon <i>et al</i> ^[11]	Experimental design, obese subjects with and without type 2 DM	Fluoxetine improved hepatic and peripheral insulin sensitivity in a clamp study
Lear <i>et al</i> ^[12]	Case report, patient with type 1 DM	Fluoxetine side effects mimicked hypoglycaemia
Fernández López <i>et al</i> ^[13]	Case report, non-diabetic woman	Clinical presentation with symptoms of hypoglycemia but without analytical confirmation
Briscoe <i>et al</i> ^[14]	Experimental design, patients with type 1 DM	6-wk administration of fluoxetine amplified autonomic nervous system and metabolic counter-regulatory mechanisms during moderate hypoglycemia.
Erenmemisoglu <i>et al</i> ^[15]	Experimental design, healthy and alloxan-induced diabetic mice	Fluoxetine and sertraline did not modify insulin concentrations but reduced plasma glucose
Gomez <i>et al</i> ^[16]	Experimental design, diabetic and non-diabetic rats	Sertraline prevented the increase in glycemia induced by an oral glucose load while fluoxetine had the opposite effect
Kesim <i>et al</i> ^[17]	Experimental design, healthy and diabetic mice	Paroxetine and fluoxetine had no significant or controversial effects on glycemia

DM: Diabetes mellitus.

In one experimental study, it was shown that the autonomic nervous system and metabolic counter regulatory responses to moderate hypoglycemia were amplified by fluoxetine^[14], with symptoms mimicking hypoglycemia. A few studies have reported the influence of fluoxetine on glucose homeostasis to be neutral or hyperglycemic^[15-17].

As severe hypoglycemia is associated with both morbidity and mortality^[18], and non-severe episodes can be the harbinger of severe episodes. For the sake of patient safety, healthcare professionals need to be aware of potential drug interactions that could lead to hypoglycemia^[19].

CASE REPORT

The patient was a 25-year-old Caucasian woman who was diagnosed with type 1 diabetes mellitus when she was 15. At 23 years, she had an infant with a severe cardiac anomaly and at age 24 an insulin pump using lispro insulin was initiated to improve glycemic control as part of pre-pregnancy care. She had no chronic diabetic complications. The patient was receiving a total daily dose of 0.5 IU/kg per day. Her mean self-monitored blood glucose level was stable at 100-130 mg/dL, and she had around two non-severe hypoglycemic episodes per month but no episodes of severe hypoglycemia. Her most recent glycated hemoglobin measurement was 6.8% and her body mass index was 24.0 kg/m². The only previous relevant

event in her medical history was a minor depressive episode two years earlier, resolved without drug treatment.

Following a new depressive episode, the patient was started on fluoxetine, 20 mg *p.o.* a day. Approximately one week later, the frequency of hypoglycemic episodes increased to around 2 per week, prompting a decrease in her insulin requirements to 0.3 IU/kg per day. Over in this period, she reported no relevant modifications in her diet, exercise, and drug treatment or associated conditions. She did not have hypothyroidism or adrenal failure. Glycated hemoglobin decreased to 6.5% and 6.3% one and two months, respectively, after starting fluoxetine and stabilized again at 6.8% at 3 mo. Fluoxetine was stopped several months later and insulin requirements returned to previous values.

DISCUSSION

The mechanisms by which fluoxetine could induce hypoglycemia are listed in Table 1 and include pseudo-hypoglycemia^[12-14], increased insulin sensitivity^[9-11] and interference in the metabolism of sulphonylureas^[5,6]. Some studies, however, have reported that fluoxetine has no influence on glucose metabolism^[15-17]. Experimental studies have shown that fluoxetine improves insulin-mediated glucose disposal independently of weight loss^[10,11]. Nevertheless, the mechanism(s) underlying the association between fluoxetine treatment and increased insulin

sensitivity remain largely hypothetical. Some scientific evidence suggests that fluoxetine can act through a central mechanism^[4], decreasing triglycerides and free fatty acids^[11], or have an effect on glucose oxidation^[10] or on insulin binding to the insulin receptor^[10]. In the present case insulin requirements showed a substantial temporary modification, associated with fluoxetine treatment. This modification points to an effect of fluoxetine on insulin sensitivity, since an increase in insulin secretion would be highly unlikely in a patient with type 1 diabetes mellitus. The time interval did not allow the effect to be mediated through a decrease in body weight. A weakness of this report is that the drug was not reintroduced, and reintroduction is one of the criteria for establishing causality^[20].

Antidepressant drugs can have a variety of effects on glucose homeostasis. Selective serotonin-reuptake inhibitors have been associated with hypoglycemic episodes, as outlined in the technical data sheet of fluoxetine^[21]. The present case expands on these data. For the sake of patient safety, treatment of depression in diabetic patients must take into account the influence of antidepressant agents on glucose homeostasis.

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