

# Severe Recurrent Hyperinsulinemic Hypoglycemia Associated with Quetiapine in a Patient with Schizophrenia: A Case Report

Inês Grenha <sup>1,\*</sup>, Mariana Maia Marques <sup>1</sup>, Soraia Rodrigues <sup>1</sup>, Leonor Lopes <sup>1</sup>, Juliana Lima Freixo <sup>1</sup>, Mercedes Alvarez <sup>1</sup>

<sup>1</sup> Department of Psychiatry and Mental Health, Local Health Unit of Alto Minho (ULSAM), Viana do Castelo, Portugal.

\* Correspondence: ines.grenha@hotmail.com.

**Abstract:** Atypical antipsychotics are frequently associated with metabolic disturbances such as weight gain, insulin resistance, and hyperglycemia. In contrast, drug-induced hypoglycemia is rarely described, particularly with quetiapine. We report a case of severe, recurrent hyperinsulinemic hypoglycemia temporally associated with quetiapine use in a patient with schizophrenia, with resolution following drug withdrawal. A 72-year-old man with schizophrenia was admitted for acute psychotic decompensation while receiving long-term haloperidol and quetiapine 150 mg/day. Shortly after admission, he developed recurrent, predominantly postprandial hyperinsulinemic hypoglycemia, with plasma glucose reaching 20–40 mg/dL, repeatedly asymptomatic. During a documented episode (glucose of 48 mg/dL), insulin and C-peptide were inappropriately elevated, confirming endogenous hyperinsulinemia. Adrenal insufficiency, hypothyroidism, insulinoma, IGF-2-secreting tumors, nesidioblastosis, hepatic dysfunction, and factitious hypoglycemia were systematically investigated, with no findings supporting these alternative diagnoses. Hypoglycemia resolved promptly after quetiapine discontinuation and recurred upon rechallenge. Replacement with tiapride led to full metabolic stabilization, with no further hypoglycemic events. This case highlights a rare but potentially life-threatening adverse effect of quetiapine. Clinicians should remain vigilant for hypoglycemia in susceptible individuals, particularly older patients or those with underlying glucose dysregulation, as early recognition and drug withdrawal can prevent serious complications.

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## 1. Introduction

Atypical antipsychotics are widely used in the management of schizophrenia and related psychiatric disorders. Their metabolic adverse effects, particularly weight gain, insulin resistance, dyslipidemia, and type 2 diabetes, are well documented and are mediated predominantly by antagonism of serotonergic (5-HT<sub>2A/C</sub>), histaminergic (H<sub>1</sub>), and muscarinic receptors, which impair insulin sensitivity and promote adiposity [1–3]. In contrast, hypoglycemia induced by atypical antipsychotics is exceedingly rare, and evidence is largely limited to isolated case reports. Among these agents, quetiapine is more commonly associated with hyperglycemia, diabetic ketoacidosis, or new-onset diabetes mellitus than with hypoglycemia [4].

Proposed mechanisms for antipsychotic-induced postprandial hypoglycemia include enhanced pancreatic  $\beta$ -cell insulin secretion through antagonism of  $\alpha$ <sub>2</sub>-adrenergic and muscarinic M<sub>3</sub> receptors, increased insulin signaling, and individual susceptibility in



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patients with pre-existing glucose dysregulation [5–7]. Importantly, quetiapine has relatively lower affinity for  $\alpha$ 2-adrenergic and muscarinic M3 receptors compared with clozapine or olanzapine, suggesting that additional factors such as active metabolites or individual vulnerability may contribute to this rare adverse effect. Recurrent postprandial hyperinsulinemic hypoglycemia, particularly with glucose levels below 40 mg/dL, warrants thorough evaluation for life-threatening causes such as insulinoma, IGF-2-producing tumors, adrenal insufficiency, hepatic dysfunction, and critical illness [8]. Drug-induced causes are also part of the differential diagnosis, but antipsychotics are seldom recognized as potential culprits.

We present a case of severe, recurrent, asymptomatic postprandial hyperinsulinemic hypoglycemia temporally associated with quetiapine in an older patient with schizophrenia. The severity of hypoglycemia, with repeated glucose values below 40 mg/dL, and the advanced age of the patient underscore the potential clinical impact of this rare adverse reaction. Resolution after discontinuation and recurrence on rechallenge strongly support a causal relationship, illustrating a rare but clinically relevant adverse effect.

## 2. Case Report

A 72-year-old man with a more than 30-year history of schizophrenia was admitted to a psychiatric inpatient unit due to a three-month progression of behavioral disorganization and auditory hallucinations. According to his wife, he had become increasingly dependent on basic activities of daily living, refusing to eat, and expressing suicidal intent. There was no report of recent infections, substance misuse, or acute medical events. His long-term psychiatric regimen included haloperidol depot 100 mg monthly, quetiapine 150 mg/day, amisulpride 50 mg/day, mirtazapine 30 mg/day, and alprazolam 1 mg/day. Past medical history was notable for chronic respiratory disease, benign prostatic hyperplasia, dyslipidemia, and a parotid nodule under evaluation. He had no diagnosis of diabetes mellitus and was not taking any hypoglycemic agents. A prior oral glucose tolerance test (OGTT) 2 years before had documented post-load hypoglycemia (43 mg/dL) despite normal fasting values, but this finding had not been further investigated. At the time of this OGTT, the patient was already receiving quetiapine as part of his chronic antipsychotic regimen.

On admission, the patient appeared perplexed, with marked psychomotor retardation, increased latency of speech, echolalia, verbigeration, and probable auditory hallucinations. He described feeling “very sad” but had difficulty elaborating. Physical examination showed a thin elderly man (body mass index around 19 kg/m<sup>2</sup>), normotensive and afebrile, without focal neurological deficits. Laboratory studies revealed normal blood count and normal electrolytes, renal and hepatic function. A CT scan of the brain showed chronic small-vessel ischemic changes, without acute ischemia, hemorrhage, or mass lesions. Given the severity of behavioral disorganization, he was admitted for stabilization. His usual antipsychotic regimen initially continued, with close monitoring.

On the second day of hospitalization, a random capillary glucose measurement revealed hypoglycemia of 42 mg/dL, which was asymptomatic. Over the following days and weeks, he developed recurrent episodes of hypoglycemia, predominantly in the postprandial period, with venous or capillary glucose values between 20 and 50 mg/dL. Remarkably, he often exhibited no adrenergic or neuroglycopenic symptoms, remaining clinically silent during many of these episodes. This relative paucity of adrenergic symptoms was notable given the severity of hypoglycemia. Fasting glucose values were consistently within the normal range, whereas postprandial measurements were frequently low. Several episodes required urgent administration of oral carbohydrates or intravenous glucose. Endocrinology and internal medicine were consulted.

During a documented hypoglycemic episode (plasma glucose 48 mg/dL), biochemical evaluation revealed an insulin level of 18.9  $\mu$ IU/mL (reference range 2.2–25  $\mu$ IU/mL) and a C-peptide level of 11.31 ng/mL (reference range 0.78–5.19 ng/mL), which are inappropriate in the context of hypoglycemia and diagnostic of endogenous hyperinsulinemia.

Beta-hydroxybutyrate levels were suppressed, further supporting an insulin-mediated mechanism. Insulin-like growth factor 1 (IGF-1), cortisol levels and thyroid function tests were normal. Further imaging with CT of the abdomen and thorax revealed no pancreatic mass, adrenal or hepatic pathology, or evidence of malignancy. A formal sulfonylurea toxicology screen was not available at the hospital but there was no known access to exogenous insulin or sulfonylureas, and there were no features suggestive of adrenal insufficiency, severe infection, or hepatic failure. Taken together, the findings were compatible with postprandial hyperinsulinemic hypoglycemia in a patient with pre-existing dysglycemia.

After multidisciplinary discussion, drug-induced hyperinsulinism was considered. Quetiapine, which had been part of the patient's long-term antipsychotic regimen and was continued during hospitalization, emerged as a likely contributor based on temporal association, pharmacological plausibility, and the absence of a more likely alternative explanation. Quetiapine was therefore discontinued and replaced by risperidone. Acarbose was introduced as an adjunctive measure to address underlying postprandial dysglycemia. Over the following days, hypoglycemic episodes resolved completely, with normalization of postprandial glucose levels. However, due to persistent psychotic symptoms and behavioral instability, quetiapine was later reintroduced after clinical risk-benefit consideration. Within 48 hours, recurrent postprandial hypoglycemia reappeared, with values as low as 35 mg/dL.

This positive dechallenge-rechallenge pattern strongly supported a causal relationship between quetiapine and hyperinsulinemic hypoglycemia. Quetiapine was definitively discontinued and replaced with tiapride. No further hypoglycemic episodes occurred during the remaining six weeks of hospitalization. At discharge, the patient showed improved organization of thought, reduction of psychotic symptoms, and stable metabolic control. He maintained follow-up in outpatient psychiatry and endocrinology, with no further episodes of hypoglycemia recorded.

### 3. Discussion

This case illustrates a rare but clinically relevant adverse effect: severe, recurrent hyperinsulinemic hypoglycemia associated with quetiapine use in an older patient with schizophrenia. The association is supported by temporal proximity, systematic evaluation for alternative etiologies, and a clear dechallenge-rechallenge pattern. Metabolic side effects of atypical antipsychotics, particularly weight gain, insulin resistance, and hyperglycemia, are well established [1-4]. Quetiapine is commonly associated with impaired glucose tolerance and, in some reports, diabetic ketoacidosis. In contrast, hypoglycemia is rarely described. Existing reports typically involve older patients, polypharmacy, or underlying metabolic vulnerability [6,9-12].

Several mechanisms may explain how quetiapine could precipitate hyperinsulinemic hypoglycemia. First, antagonism of  $\alpha$ 2-adrenergic receptors on pancreatic  $\beta$ -cells removes an inhibitory signal on insulin secretion, leading to increased insulin release in response to meals [5,6]. Second, muscarinic M3 receptor antagonism may paradoxically enhance insulin secretion in sensitized  $\beta$ -cells, particularly in the context of pre-existing postprandial glucose dysregulation [7]. Third, individual differences in  $\beta$ -cell responsiveness and counterregulatory hormones, along with coexisting factors such as age, nutritional status, and comorbidities, might modulate the net effect of the drug on glucose homeostasis [10]. Notably, quetiapine has lower affinity for  $\alpha$ 2-adrenergic and muscarinic M3 receptors than clozapine or olanzapine, which are more strongly associated with metabolic dysregulation, suggesting that active metabolites such as norquetiapine or patient-specific vulnerability may play a contributory role even at relatively low doses [11].

In this patient, a prior oral glucose tolerance test had already demonstrated post-load hypoglycemia, indicating an underlying dysregulation of glucose metabolism. Quetiapine may have acted as a trigger or exacerbating factor, contributing to the emergence of severe, recurrent hyperinsulinemic episodes. The absence of fasting hypoglycemia and

the predominance of postprandial episodes further support this interpretation. Another striking feature of this case is the relative lack of adrenergic or neuroglycopenic symptoms despite very low glucose levels. Older adults with chronic mental illness may have blunted autonomic responses to hypoglycemia, impaired awareness due to cognitive deficits or psychotic symptoms, and reduced capacity to report internal states. Concomitant psychotropic medications, including benzodiazepines, may further dampen autonomic warning signs; the sedative and antihistaminic properties of quetiapine itself may further mask early warning symptoms of hypoglycemia. As a result, severe hypoglycemia may go unrecognized unless glucose is actively monitored.

The differential diagnosis of hyperinsulinemic hypoglycemia in adults includes insulinoma, functional  $\beta$ -cell disorders such as nesidioblastosis, IGF-2-secreting tumors, autoimmune insulin syndrome, adrenal insufficiency, severe liver disease, sepsis, renal failure, and factitious hypoglycemia [8]. In this case, extensive evaluation found no evidence of structural pancreatic lesions, malignancy, endocrine insufficiency or critical illness; there was no known access to exogenous insulin or sulfonylurea exposure. A formal sulfonylurea toxicology screen could not be performed because it was not available at the hospital, which represents a limitation of this case. Taken together, the temporal pattern—characterized by the onset of hypoglycemic episodes during hospitalization, resolution after quetiapine discontinuation, and recurrence upon rechallenge—supports a drug-associated mechanism.

Although causality cannot be proven without a controlled rechallenge, the Naranjo adverse drug reaction probability scale would likely classify this association as “probable” rather than merely “possible”, given the dechallenge–rechallenge pattern and the lack of alternative explanations [9]. Previous case reports have described similar presentations of quetiapine-related hypoglycemia, particularly in older patients and in those with comorbidities or concomitant medications affecting glucose metabolism [10,12,13]. However, reports remain scarce, and the true incidence of this adverse effect is unknown. From a clinical perspective, this case underscores the importance of considering atypical antipsychotics among the potential causes of otherwise unexplained hypoglycemia, especially in vulnerable populations. Regular monitoring of glucose levels is already recommended when prescribing these agents because of the risk of hyperglycemia and diabetes [2–4]; however, clinicians should also be aware that paradoxical hypoglycemia can occur. Early recognition allows timely adjustment or discontinuation of the offending drug, preventing potentially life-threatening events.

In our patient, switching from quetiapine to alternative antipsychotics provided adequate psychiatric control without further metabolic decompensation. This highlights the possibility of choosing antipsychotics with a more favorable metabolic profile in patients with pre-existing glucose dysregulation or a history of unexplained hypoglycemia. Although acarbose was used as an adjunctive measure during hospitalization, metabolic stabilization was temporally linked to quetiapine withdrawal rather than to carbohydrate absorption modulation.

#### 4. Conclusion

We report a case of severe, recurrent hyperinsulinemic hypoglycemia associated with quetiapine use in an older patient with schizophrenia, in whom extensive investigation did not identify a more likely alternative cause. The temporal relationship, positive dechallenge–rechallenge pattern, and pharmacological plausibility support a probable causal association between quetiapine exposure and hypoglycemia. Although atypical antipsychotics are more commonly linked to hyperglycemia and insulin resistance, clinicians should be aware that they may also precipitate hypoglycemia in metabolically susceptible individuals.

Careful metabolic monitoring should be considered when prescribing quetiapine and other atypical antipsychotics, particularly in older adults and in patients with pre-existing or suspected glucose dysregulation. Early recognition and prompt withdrawal of

the offending agent can prevent serious complications and allow safe transition to alternative treatments with a more favorable metabolic profile.

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