Clozapine: Diabetes Mellitus, Weight Gain, and Lipid Abnormalities

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Clozapine remains the most effective agent for treatment-resistant patients with schizophrenia. Recently, treatment with clozapine has been linked to a number of metabolic disturbances, including weight gain, diabetes mellitus, and serum lipid abnormalities. Despite the potential risks of medical morbidities, clozapine continues to have a major role in the care of treatment-resistant patients with schizophrenia. This article discusses the diagnosis and significance of the above metabolic abnormalities and potential mechanisms for these abnormalities as well as recommendations for monitoring and treatment.

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The clozapine program discussed in this article began with 10 outpatients with schizophrenia who had been institutionalized for several years before initiation of clozapine therapy. Over the years, the patient population grew to more than 100 patients, with most initiating treatment with clozapine in the outpatient clinic.[23] My colleagues and I became interested in glucose metabolism because of early clinical observations that clozapine-treated patients with chronic schizophrenia had a high incidence of diabetes mellitus and gained a great deal of weight, resulting in a classic "Santa Claus" (abdominal obesity) appearance. As a result, guidelines were implemented several years ago to more closely monitor patients with schizophrenia for medical disorders such as obesity and diabetes mellitus.

There are several different types of diabetes mellitus. Type 1 diabetes mellitus is believed to be due to complete pancreatic β-cell destruction with lack of insulin production. Type 2 diabetes mellitus is characterized by insulin resistance (i.e., a decreased response to circulating insulin) with some insulin deficiency and can result in a reduction in β-cell functioning, but the body is still able to make insulin. The Expert Committee on the Diagnosis and Classification of Diabetes Mellitus[1] lists the criteria for the diagnosis of diabetes as follows: symptoms of diabetes plus random plasma glucose concentration ≥ 200 mg/dL, fasting blood glucose concentration ≥ 126 mg/dL, or a 2-hour blood glucose concentration ≥ 200 mg/dL during an oral glucose tolerance test (OGTT).

There are other types of diabetes mellitus, including genetic defects in β-cell function, pancreatic diseases, gestational diabetes, and drug- and chemical-induced diabetes mellitus. A number of medications have been implicated as potentially impairing glucose metabolism, including centrally acting α-blockers, β-blockers, corticosteroids, cyclosporine, phenytoin, phenothiazines, thiazide diuretics, and oral contraceptives containing norgestrel.[2–8] Glucocorticoids are believed to impair glucose utilization, with insulin resistance appearing to occur at both receptor and postreceptor sites.[9,10] Valproate has been found to induce a metabolic syndrome characterized by centripetal obesity, hyperinsulinemia, lipid abnormalities, polycystic ovaries, and hyperandrogenism in women with epilepsy.[11,12]

Patients with diabetic ketoacidosis, a potentially life-threatening illness, present with hyperglycemia, serum glucose levels usually > 300 mg/dL, high levels of ketones, HCO_3 level ≤ 15 mEq/L, and acidosis with a pH of 7.3 or less. Clinical symptoms of diabetic ketoacidosis include nausea, vomiting, abdominal pain, shortness of breath, fever, depression of the central nervous system, and infection. Diabetic ketoacidosis was once believed to occur only in patients with type 1 diabetes mellitus; however, in certain conditions (e.g., infections, large glucose load), it is possible for patients with type 2 diabetes mellitus to have episodes of diabetic ketoacidosis.[13,14] Many cases of diabetic ketoacidosis in the general population are also associated with other acute medical problems.[14]

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Little is known regarding risk factors for clozapine-associated diabetes mellitus or diabetic ketoacidosis. Potential risk factors include obesity or weight gain, age, family history, hypertension, elevated serum lipid levels, diet, inactivity, and race. Many of the reported cases in the literature, particularly the early cases, involved black patients; thus, race may be an important factor. Many patients with schizophrenia may have some of the above risk factors for diabetes mellitus. However, regardless of other risks and medications, patients with schizophrenia may experience high rates of diabetes mellitus compared with the general population.[15]

METABOLIC DISTURBANCES ASSOCIATED WITH CLOZAPINE

Diabetic Ketoacidosis and Diabetes Mellitus

The interest in clozapine and glucose metabolism began with case reports of clozapine-treated patients developing diabetic ketoacidosis, because few medications have been directly linked to diabetic ketoacidosis. The reports of diabetic ketoacidosis and the increased incidence of type 2 diabetes mellitus with clozapine therapy may represent 2 separate populations of patients with varying risks. There have been a number of cases of diabetic ketoacidosis associated with clozapine and olanzapine, with most resulting in partial or complete remission when the drug was discontinued.[16–29] Additionally, several cases of diabetic ketoacidosis resolved after treatment with clozapine or olanzapine was discontinued, only to have hyperglycemia return on reinstitution of the drug.[18,19,22,29] Patients with diabetic ketoacidosis have been taken off treatment with clozapine or olanzapine and achieved remission, which strongly suggests that insulin secretion is affected.[20,25–27,29] This is an important area of knowledge, because there is a significant risk of mortality associated with diabetic ketoacidosis.

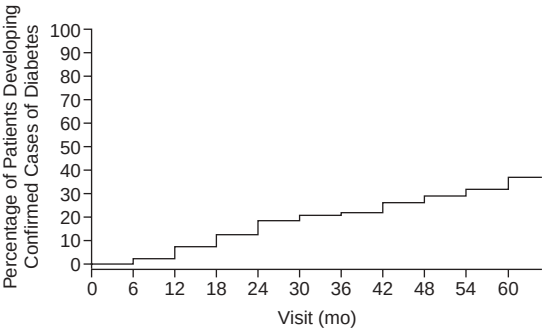
Using an OGTT, Hägg and colleagues[30] reported that 12% of patients treated with clozapine developed type 2 diabetes mellitus and 10% developed impaired glucose tolerance compared with 6% and 3%, respectively, for patients treated with conventional depot neuroleptics. Although the increased rates of diabetes mellitus and impaired glucose tolerance with clozapine did not achieve statistical significance, patients in the conventional neuroleptic group were older, which may have influenced the results.

In the clozapine protocol my colleagues and I conducted, patients had monthly weight, blood pressure, pulse, and temperature measurements.[23] Additionally, baseline screening of serum electrolyte levels, fasting glucose levels, liver function tests, and lipid profiles were instituted and then repeated every 6 months. This allowed close monitoring of clozapine-treated patients over time and careful examination of different factors causing concern.

The most striking finding in our 5-year naturalistic study[23] is that 30 (36.6%) of the 82 patients developed diabetes mellitus (Figure 1). Patients were identified by an abnormal fasting serum glucose value and referred to their primary care clinician for workup and confirmation of diabetes mellitus. Consistent with our clinical observation, the development of diabetes mellitus did not correlate with body mass index (BMI) or weight gain. Although weight gain was a contributing factor in the development of diabetes mellitus for many patients, some patients who did not gain weight still developed diabetes mellitus. However, weight gain correlated with an increase in triglyceride levels, and the development of diabetes mellitus correlated with an increase in serum triglyceride levels.

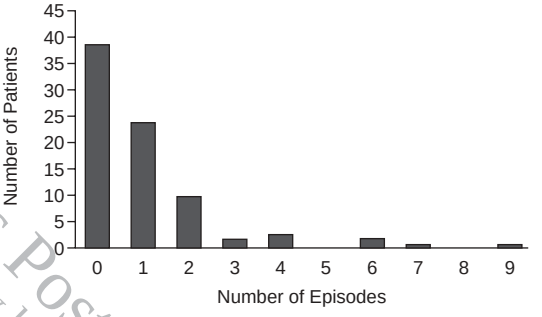
When fasting blood glucose data were examined using the "old" American Diabetes Association criterion for abnormal glucose level, a serum glucose level ≥ 140 mg/dL,[31] 39 (47.6%) of 82 patients had no abnormal fasting blood glucose values, 24 (29.3%) had 1 abnormal value, and 19 (23.2%) had more than 1 abnormal value (Figure 2). Because patients continued to develop diabetes mellitus during the entire 60-month study period, it appears that, as

Figure 1. Cumulative Percentage of Patients Diagnosed With Diabetes Mellitus (N = 30) During a 60-Month Period Among 82 Patients Receiving Clozapine[a]



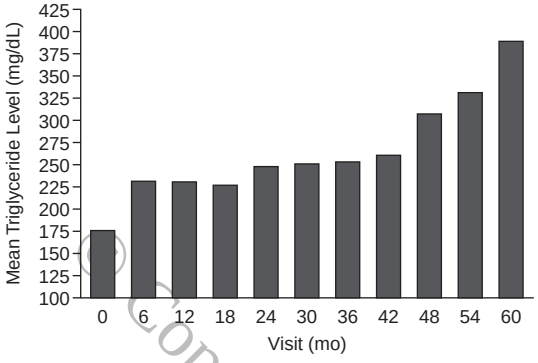
[a]Reprinted, with permission, from Henderson et al.[23]

Figure 2. Frequency of Abnormal Fasting Glucose Levels Using Old American Diabetes Association Criteria (fasting serum glucose level ≥ 140 mg/dL) Among 82 Patients Receiving Clozapine[a]



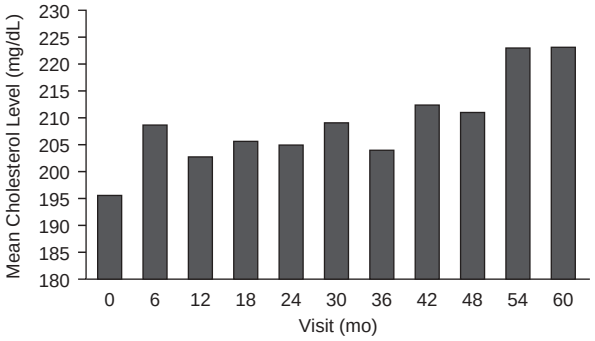
[a]Data from Henderson et al.[23]

Figure 3. Mean Triglyceride Levels At Baseline And 6-Month Intervals Among 82 Patients Receiving Clozapine[a]



[a]Data from Henderson et al.[23]

Figure 4. Mean Serum Cholesterol Levels at Baseline and 6-Month Intervals Among 82 Patients Receiving Clozapine[a]



[a]Data from Henderson et al.[23]

long as patients are receiving clozapine, they may be at a higher risk for developing diabetes mellitus.

Weight Gain

Several studies have reported substantial weight gain with clozapine,[32–39] and there were significant correlations with clinical response in 2 of these studies.[34,39] Obesity is associated with an increased risk for hypertension, dyslipidemia, insulin resistance, type 2 diabetes mellitus, cardiovascular disease, respiratory dysfunction, and gallstones.[40]

In the 5-year study my colleagues and I conducted,[23] there was a significant increase in weight that continued for approximately 46 months in clozapine-treated patients. The weight gain was correlated with an increase in serum cholesterol and triglyceride levels. This highlights the fact that weight changes in clozapine-treated patients may be a chronic clinical problem that requires continuous monitoring and interventions.

Lipid Abnormalities

A study by Ghaeli and Dufresne[41] found increased serum triglyceride levels after initiation of treatment with clozapine without a significant change in serum cholesterol levels. My coworkers and I became concerned about clozapine and lipid abnormalities when the phlebotomist we were working with examined a tube of blood just obtained from one of our patients who was being treated with clozapine. Seen floating in the plasma were clearly visible lipids that were not measurable by the laboratory. This patient's serum triglyceride level was normal before initiation of treatment with clozapine; however, the patient had a family history of hypertriglyceridemia, which may have been triggered or exacerbated by treatment with clozapine.

In our study,[23] the mean baseline serum triglyceride level was 175 mg/dL. Serum triglyceride levels showed a significant and persistent increase over the 60-month period (Figure 3). There was a nonsignificant increase in serum cholesterol levels that was consistent with reports in the literature (Figure 4). Many patients were placed on treatment with lipid-lowering drugs, with varying effect. In patients with a family history of lipid disorders, the lipid-increasing process may accelerate with the use of clozapine and consequently should be monitored more closely.

POTENTIAL MECHANISMS

Clozapine-Associated Impairment of Glucose Metabolism

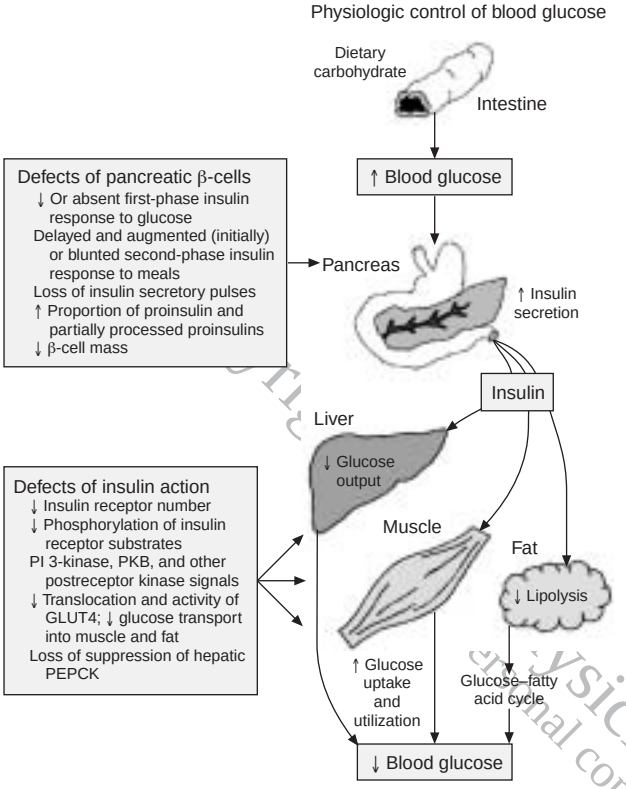
Insulin resistance is a characteristic feature of patients with impaired glucose tolerance and particularly of those with type 2 diabetes mellitus. Insulin resistance can be due to abnormalities at any step in the entire sequence of events initiated by insulin (e.g., receptor defects or postreceptor defects in insulin action; Figure 5[42]). It is possible that treatment with atypical antipsychotic agents decreases insulin-sensitive glucose transporters (GLUT) or results in an inability to stimulate recruitment of GLUT from microsomes to the plasma membrane. GLUT4 is a transporter that mediates the bulk of insulin-stimulated transport activity.[43,44]

Long-term exposure to high concentrations of glucose and insulin reduces the subsequent ability of insulin to maximally stimulate glucose transport by inhibiting GLUT translocation.[45] In fact, a reduction in glucose effectiveness is a common finding in patients with type 2 diabetes mellitus, regardless of their insulin sensitivity. Alternatively, it may be that antagonism at serotonin 5-HT_{1A} receptors by atypical antipsychotic agents decreases pancreatic β-cell responsiveness to blood glucose levels, resulting in impairment of glucose metabolism.[28]

Clozapine-Associated Weight Gain

The potential mechanisms of weight gain associated with atypical antipsychotics are discussed in greater detail in other articles within this supplement and may include an antihistamine effect, sedation, decreased physical activity,

Figure 5. Defects of Insulin Secretion by Pancreatic β-Cells and Defects of Insulin Action in Liver, Muscle, and Fat in Type 2 Diabetes Mellitus[a]



[a]Reprinted, with permission, from Bailey.[42] Abbreviations: GLUT4 = insulin-stimulated glucose transporter isoform 4, PEPCK = phosphoenolpyruvate carboxykinase, PI = phosphatidylinositol, PKB = protein kinase B. Symbols: ↑ = increase, ↓ = decrease.

serotonin antagonism, and an effect on serum leptin levels. However, because there may be a number of factors involved, there may also be a number of effective interventions.

MINIMAL MODEL ANALYSIS

Description of the Model

Bergman's minimal model[46,47] that interprets data gathered from a frequently sampled intravenous glucose tolerance test has been used to examine potential mechanisms of glucose metabolism impairment associated with atypical antipsychotic agents. With the minimal model approach, glucose is injected intravenously and is followed by an additional insulin secretagogue 20 minutes later. Twelve to 26 blood samples are collected during a 3-hour period. This model provides a sensitive and reliable method of measuring glucose effectiveness, insulin secretion, and insulin sensitivity, which are calculated from glucose and insulin concentrations measured during the test.[46,47]

Interstitial insulin acts to synergize the effect of glucose production suppression and increased utilization. Insulin sensitivity is a parameter that examines insulin resistance and is defined as the increase in net fractional glucose clearance rate per unit change in serum insulin concentration after an intravenous glucose load. Another parameter, glucose effectiveness, is defined as the net fractional glucose clearance rate due to the increase in glucose itself without any increase in circulating insulin concentration above baseline. Glucose effectiveness is the component of glucose disposal that is dependent on glucose transporters and independent of insulin receptor function. Glucose effectiveness also plays a major role in inhibiting endogenous glucose production.

Nondiabetic obese individuals have reduced insulin sensitivity and show insulin resistance with normal glucose effectiveness. When the body starts to show a degree of insulin resistance, more of the glucose disposal is handled by glucose effectiveness.[43,44] Although insulin has a job to do, serum glucose also plays a role in shutting down endogenous glucose production as well as stimulating uptake of glucose into the cells.

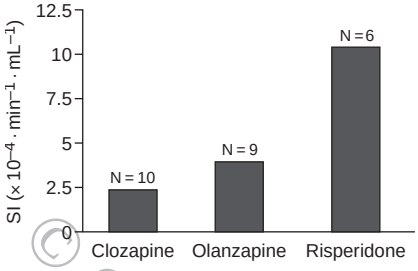
Preliminary Data Analysis

In a preliminary study[48] using the minimal model approach, nonobese patients with schizophrenia receiving treatment with clozapine, risperidone, or olanzapine were examined. Patients who were taking drugs that affect glucose metabolism or who had medical conditions that affect glucose metabolism were excluded. Patients were well matched in the 3 groups (clozapine, risperidone, olanzapine) as determined by a complete nutritional assessment including BMI, hip-waist ratio, skin fold, basal metabolic activity, and exercise levels.

Fasting serum glucose and fasting serum insulin levels were not statistically different among the 3 groups. There was a significant difference among the 3 treatment groups for insulin sensitivity (F value = 7.64, df = 2, $p = .0057$; Figure 6). For example, insulin sensitivity differed significantly between groups when comparing clozapine (mean = $2.44 \pm 2.55 \times 10^{-4} \cdot min^{-1} \cdot mL^{-1}$) with risperidone (mean = $10.45 \pm 7.00 \times 10^{-4} \cdot min^{-1} \cdot mL^{-1}$; $p = .0007$) and olanzapine (mean = $4.257 \pm 2.48 \times 10^{-4} \cdot min^{-1} \cdot mL^{-1}$) with risperidone ($p = .0051$). Differences among the 3 groups for glucose effectiveness were not significant after controlling for gender ($p = .15$), although clozapine (mean = 0.015 ± 0.005 min^{-1}) differed from risperidone (mean = 0.021 ± 0.0006 min^{-1}; $p = .067$) and olanzapine (mean = 0.016 ± 0.008 min^{-1}) differed from risperidone ($p = .09$) at trend levels (Figure 7).

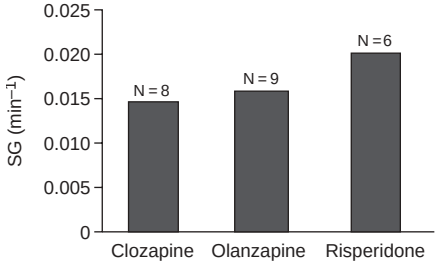
Of note, normal values with the minimal model analysis in the adult male population were $7.56 \pm 1.13 \times 10^{-4} \cdot min^{-1} \cdot mL^{-1}$ for insulin sensitivity and 0.026 ± 0.008 min^{-1} for glucose effectiveness.[46,47] The normal values for healthy women were $5.61 \times 10^{-4} \cdot min^{-1} \cdot mL^{-1}$ for insulin

Figure 6. Mean Insulin Sensitivity (SI) in Patients Receiving Clozapine, Olanzapine, or Risperidone[a]



[a]Adapted from Henderson et al.[48]

Figure 7. Mean Glucose Effectiveness (SG) in Patients Receiving Clozapine, Olanzapine, or Risperidone[a]



[a]Data from Henderson et al.[48]

sensitivity and 0.023 min^{-1} for glucose effectiveness, suggesting differences in insulin sensitivity between men and women.[46,47] Patients treated with clozapine appear to experience insulin resistance and possible impairment of glucose effectiveness, regardless of BMI. A reduction in both of these parameters (insulin sensitivity and glucose effectiveness) may predispose clozapine-treated patients to develop diabetes mellitus. Finally, impairment of glucose effectiveness suggests possible impairment or reduction in GLUT activity.

CONCLUSIONS AND RECOMMENDATIONS

Patients with schizophrenia receive poor medical care in general, and treating psychiatrists must play a major role in the patient's psychological and general medical health. Guidelines must be developed to aid psychiatrists in monitoring for potential medical morbidities associated with atypical antipsychotic drugs to assure patient safety. If diabetes mellitus develops, switching to another antipsychotic agent should be considered; however, this is not recommended in true treatment-resistant patients with schizophrenia who respond to clozapine.

My colleagues and I recommend baseline measurements before treatment and screenings at least every 6 months for fasting plasma glucose, glycohemoglobin, and lipid levels. Higher-risk patients (those with significant risk factors) should be monitored more frequently as clinically indicated. In the clozapine study my colleagues and I conducted, measurement of fasting plasma glucose values every 6 months allowed us to identify 29 of the 30 patients who developed diabetes.[23]

One problem, however, is that fasting plasma glucose values may be difficult to obtain in some patients unless extensive education and cooperation with families and halfway-house staff occur. Fasting plasma glucose levels are a more convenient measure than the OGTT, but the OGTT is more sensitive. Unfortunately, few psychiatrists actually order an OGTT. Measurement of glycohemoglobin may present an alternative to the above recommendations. However, no guidelines are in place to determine when intervention is needed (e.g., in the case of increasing but normal values of glycohemoglobin) until someone has reached diabetes mellitus levels. Physicians should aggressively monitor for weight change, educate patients, and consider weight loss and exercise programs for their patients. My colleagues and I have tried a number of weight-reduction interventions in schizophrenia patients with diabetes mellitus, with limited success. We are currently studying sibutramine, a U.S. Food and Drug Administration–approved weight-loss agent, as a possible treatment. As with the general population, behavioral approaches may work but appear to be short-lived. Consequently, psychiatrists need to be proactive regarding the potential side effects and medical morbidities of therapies for schizophrenia, and early patient education and interventions may prevent weight gain or the development of diabetes mellitus.

Drug names: clozapine (Clozaril and others), cyclosporine (Sandimmune and others), olanzapine (Zyprexa), phenytoin (Dilantin and others), risperidone (Risperdal), sibutramine (Meridia).

Disclosure of off-label usage: The author has determined that, to the best of his knowledge, no investigational information about pharmaceutical agents has been presented in this article that is outside U.S. Food and Drug Administration–approved labeling.

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