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Diabetic Ketoacidosis among Patients Receiving Clozapine: A Case Series and Review of Socio-Demographic Risk Factors

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Background. *Diabetic ketoacidosis (DKA) has been associated with clozapine. The purpose of this study is to examine the clinical-demographic correlates of DKA among outpatients receiving clozapine.*

Methods. *A literature search was conducted from 1966 to present using Medline to identify 23 case reports of clozapine-associated DKA. In addition, a cohort of twenty-six patients with clozapine-associated diabetes at the University of Rochester Medical Center Department of Psychiatry were examined for histories of DKA through review of medical records. Based on a total sample of 26 case reports including three unpublished cases at University of Rochester, associations between clinical and demographic variables and DKA were examined.*

Results. *African American patients were significantly more likely than other patients to have DKA ($p < 0.0001$). Clozapine treatment duration was significantly shorter among patients with DKA than those without DKA ($p < 0.0001$), with 61.5% of patients developing DKA within three months of clozapine initiation. Also, presence of antidiabetic medications was negatively correlated with DKA ($p < 0.0001$). Trends were noted toward an association between low doses of clozapine ($p < 0.0583$) and toward a negative association between family history of diabetes ($p < 0.0696$).*

Conclusion. *Clozapine is associated with DKA that usually presents in patients who have not previously been diagnosed with diabetes. DKA typically occurs early in the course of treatment, when clozapine treatment duration is short and doses are low.*

Keywords Clozapine, Diabetes, Diabetic Ketoacidosis, Prevalence, Risk Factors, Schizophrenia

INTRODUCTION

Clozapine is the most effective antipsychotic drug available and is currently recommended for the treatment of drug refractory schizophrenia (1). Growing evidence suggests that antipsychotic drugs are associated with an increased risk for developing diabetes mellitus, with clozapine imposing an especially high risk (2). It is generally assumed that antipsychotic drug associated diabetes is consistent with type II diabetes due to its adult onset and the propensity of antipsychotic drugs to induce weight gain (3,4,5,6). However, 23 reports of diabetic ketoacidosis (DKA) have been reported with the use of clozapine (7–24) (Table 1).

Diabetic ketoacidosis (DKA) is a serious metabolic disturbance that is typically associated with type I diabetes mellitus. DKA may be the initial symptom complex that leads to a diagnosis of diabetes, but more frequently it occurs in individuals with established type I diabetes mellitus. DKA is a result of the body's transition from glucose to lipid oxidation due to a deficiency of insulin (25). While it can occasionally present in patients with severe type II diabetes, DKA occurs far more often in patients

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Table 1 Clozapine-Associated DKA-Summary of Cases

Reference	Age in Yrs	Race	Obesity Status	Diabetes Status before Clozapine	Family History of Diabetes	Dose of Clozapine	Duration of Clozapine Treatment	Concomitant Medications
Kamran et al. (7)	41	AA.	–	Negative.	No.	Started 50 mg/d built upto 450 mg bid over 2 months.	60 days.	Ranitidine and Benztropine.
Koval et al. (8)	34	AA.	–	Negative.	Yes. Type 1 DM.	Started at 25 mg/d built gradually to 250 mg/d, reintroduced dosage unknown	6 weeks. After reintroduction 3 days.	Lithium 1200 mg/d. Benztropine 2 mg/d.
Kostakoglu et al. (9)	42	–	Obese man-130 kg (mildly obese).	Negative.	Yes type 2 DM.	25 mg/d increased to 200 mg bid decreased to 350 mg/d.	4 weeks.	–
Peterson et al. (10)	46	AA.	Weight stable for two yrs (not obese).	Negative.	Yes.	500 mg/d.	5 weeks.	Clozapine, Lithium, Bethnechol, Verapamil.
Pierides et al. (11)	50	–	–	Negative.	–	Started at 25 mg/d increased to 100 mg qam and 200 mg qpm.	7 days.	All medications stopped before clozapine was started.
Popli et al. (12)	32	AA.	11% over ideal weight, after clozapine 8 pounds weight gain over 5 weeks (moderate obese).	Negative.	Yes. Father and brother had 1 and 2 respectively at same age.	Titrated to 425 mg/d over 6 weeks.	8 weeks.	Ephedrine 25 mg/d. Propanolol 5 mg/d. Clonidine 0.2 mg/d.
Popli et al. (12)	44	AA.	42% over body weight ideal for him. 3 pounds weight gain after starting clozapine (severely obese-BMI>40).	Negative.	No.	Titrated to 450 mg/d over 8 weeks. Built up to 675 mg/d over 6 months.	5 weeks.	Risperidone 6 mg/d. Hydrochlorthiazide 25 mg/d. Lithum 1200 mg/d. Clonidine 0.1 mg/d.
Popli et al. (12)	51	White.	Stable weight.	One year history of diabetes type 2 stable with 12.5 mg/d of glyburide.	–	200 mg/d for 20 days, stopped then reintroduced 200 mg/d and stabilized on that.	2 weeks.	All were stopped before clozapine was started.
Popli et al. (12)	51	AA.	–	Well controlled diabetes type II with glyburide 20 mg/day.	–	900 mg/d.	–	Lisinopril 30 mg/d. Glyburide 20 mg/d.
Wirshing et al. (13)	32	AA.	No history of obesity. Gained 37% body weight after starting clozapine.	Negative.	No.	–	18 months.	–

Wirshing et al. (13)	41	AA.	No obesity before clozapine but after clozapine 38% above body wt (severely obese-BMI>40).	Negative.	No.	–	5 weeks.	–
Ai et al. (14)	30	Afro- Caribbean.	–	Negative.	No.	150 mg bid over 5 months.	5 months.	Minocycline.
Smith et al. (15)	40	Afro-Caribbean.	Mildly obese	Negative.	No.	Standard regime.	16 days.	Chlorpromazine 200 qid. Flupenthaxol decanoate 400 mg weekly.
Colli et al. (16)	31	White.	3 kg wt gain on clozapine. BMI-29 (mildly obese).	Negative.	No.	200 mg/d.	3 months.	–
Maule et al. (17)	50	White.	–	Negative.	Family his of type 2 DM.	400 mg/d.	30 days.	Valproate 1000mg/d.
Mohan et al. (18)	30	AA.	–	Negative.	No.	325 mg/d.	90 days.	–
Rigalleau et al. (19)	38	–	3 kg wt loss on clozapine. BMI-27.	Negative.	No.	–	6 months.	–
Avram et al. (20)	33	White.	Ideal wt should be 65 kg was 92.7 kg. Increased after to 106.6 kg,BMI increased from 32.5 to 37.4 (moderate obese).	Negative.	No.	50 mg bid.	8 months.	Sertraline 50 mg poqd. Trihexphenidyl 2 mg bid. Ranitidine 150 mg bid.
Nicolai et al. (21)	33	Indian.	–	Negative.	–	450 mg/d	4 yrs.	Valproate 500 mg bid.
Wilson et al. (22)	26	AA.	Obesity (mildly obese).	Negative.	No.	50 mg in am and 125 mg at night.	10 days.	Risperidone 3 mg/d. Venlaflaxine. Lithium.
Wilson et al. (22)	33	AA.	–	Negative.	No.	550 mg/d over 6 weeks.	One month.	Olanzapine 10 mg/d.
LaFayette et al. (23)	22	Italian Hispanic.	BMI 30–40, 33 kg-moderately obese.	Negative.	Family history two maternal aunts with NIDDM.	125 mg/d.	10 weeks.	Lorezepam 3 mg/d. Risperidone 2 mg/d. Benztropine 1 mg/d. MVI and calcium.
Lamberti et al. (28)	51	White.	–	Non-compliant as he had a high HbA1c throughout.	No.	600 mg/d.	76 months.	Depakote 1750 mg/d. Claritin 10 mg po qam as needed. Ambien 10 mg po qhs as needed. Zantac 150 mg po qam as needed
Lamberti et al. (28)	58	White.	Slightly obese.	Unable to treat with insulin due to non-compliance.	No.	350 mg/d.	43 months.	Metformin 500 bid. Glyburide 5 mg po bid.
Lamberti et al. (28)	51	AA.	–	Poor compliance.	Mother had DM.	175 mg/d.	–	Risperidone 2 mg po hs. Glyburide 2.5 mg am and 10 mg hs. Prolixin 20 mg po q6h as needed.
Koren et al. (24)	37	Ashkenazi Jew.	–	–	No.	Started 12.5 mg/d increased 25 mg/d over 3 days.	11 weeks.	–

with type I diabetes because the latter is associated with absolute insulin deficiency. Type I diabetes is usually seen in children and adolescents as there is an inborn deficiency of insulin secretion due to B cell malfunction of the pancreas (26).

In DKA, marked hyperglycemia causes osmotic diuresis, excessive urinary losses of water, NA and K and volume contraction with ketosis resulting from increase in hepatic ketone formation leading to a state of metabolic acidosis (25). Some signs and symptoms include nausea, vomiting, abdominal pain, Kussmaul respirations, acetone odor on the patient's breath, tachycardia, postural hypotension and ketonuria. Lethargy and central nervous system depression may evolve into coma with severe DKA (27). The mortality rate of DKA is as high as 10% (25,27).

Another serious complication of diabetes is the non-ketotic hyperosmolar state (NKHS). NKHS is a condition that also consists of hyperglycemia and subsequent osmotic diuresis leading to intravascular volume depletion. It is important to distinguish DKA from NKHS because the treatments differ somewhat as hydration is the cornerstone of NKHS treatment while insulin plays a major role in the treatment of DKA (28). Clinically both states share the presentation of dehydration, delirium and coma at the end stage. However, usually the blood sugars are higher in NKHS and there is an absence of acidosis, the cardinal feature that differentiates NKHS from DKA. DKA can be reliably distinguished from NKHS by laboratory tests that show a normal pH, an absence of ketones in the blood and an absence of abnormality in potassium and phosphate levels (27).

Our current understanding of clozapine-associated diabetic ketoacidosis is limited by available data that primarily consists of case reports. There are some inherent methodological challenges in studying clozapine associated DKA. The rare occurrence of this complication limits conducting a prospective controlled study as it would require a large sample size to generate statistically significant findings. Use of a placebo control group would raise ethical issues as clozapine candidates usually have a medication resistant form of schizophrenia or schizoaffective disorder, although use of a second generation antipsychotic as a comparison group is possible. This paper reviews all published case reports and three additional unpublished cases in order to examine the relationship between clozapine associated DKA, and possible clinical-demographic risk factors. Identification of risk factors could assist clinicians in identifying those patients at highest risk for DKA, with ultimate goal of reducing morbidity and mortality.

MATERIALS AND METHODS

Subjects and Data Collection

A literature search was conducted from 1966 to present using Medline to identify all English language case reports published on DKA and clozapine. The search terms used were clozapine, diabetes, DKA and atypical antipsychotics. Twenty three case reports were identified and included in the analysis.

A previous study (29) of clozapine-associated diabetes was conducted at the University of Rochester Medical Center's Department of Psychiatry. This study examined a sample of 101 patients receiving clozapine and identified a cohort of 26 patients with clozapine-associated diabetes. The study was approved by the University of Rochester Research Subject Review Board, and written informed consent was obtained from all subjects. In the present study, medical records from the cohort of 26 patients with clozapine-associated diabetes were examined for documented episodes of DKA. Three additional cases of DKA were identified in this database giving us a study group of 26 patients with clozapine-associated DKA. The remaining 23 cases of clozapine-associated diabetes without DKA (29) were used as the comparison group.

An a priori set of diagnostic criteria for DKA was established before the start of the study. Criteria were developed through consultation with an internist and review of standard criteria for DKA from Harrison's Principles of Internal Medicine (27) (Table 2). Each reported case of DKA was subsequently evaluated as to the presence or absence of these criteria.

The following data was obtained and entered into a secure Microsoft Access database: demographic data, obesity status, family history of diabetes, presence or absence of diabetes diagnosis before introduction of clozapine, diabetes treatment, dosage of clozapine, duration of clozapine, duration of hyperglycemia, treatment of hyperglycemic episode, presence of concomitant medications before the onset of the hyperglycemic episode, whether clozapine was discontinued after the hyperglycemic episode and number of DKA criteria fulfilled by each case.

Concomitant medications for each case were divided into the following three groups. 1) Psychiatric medications associated with weight gain: Antipsychotics, antidepressants (including SSRIs) lithium and depakote. 2) Anti-diabetic medications. 3) Other medications: antihypertensives, anticholinergics, benzodiazepines, multivitamins, calcium, claritin, ranitidine, bethnechol and minocycline.

Data Analysis

Data analysis was conducted using SAS version 8.2. The two groups compared were 1) Clozapine-associated DKA

Table 2 Criteria for Differentiation of DKA and NKHS

	DKA	NKHS
Blood sugars (mmol/L (mg/dL)	16.7–33.3 (300–600)	33.3–66.6 (600–1200)
Plasma/Urine ketones	++++	+/–
Arterial pH	6.8–7.3	More than 7.3
Potassium levels (meq/L)	Normal to ↑↑	Normal

(26 cases) and 2) Clozapine-associated diabetes (23 cases). The following continuous variables were examined: age, primary diagnosis, duration of clozapine treatment and clozapine dose. To determine whether means of the continuous variables differed between DKA and non-DKA groups, T-tests were preformed on each variable. Categorical variables examined were gender, race/ethnicity, family history, obesity status, antidiabetic medications, psychotropic medications, and other treatments. Fisher's Exact Tests were used to test for associations between the categorical variables and DKA status. All tests preformed were two-sided, with significance level a=.05 unless noted otherwise. A stepwise selection logistic regression model with the response variable DKA (yes/no) was used to determine all significant predictors of the presence of DKA.

RESULTS

None of the cases fulfilled all the criteria for DKA, while majority of the cases fulfilled either one or two (20 cases) of the four criteria delineated. One possibility is that they did fulfill the factors, but did not mention them in the case reports due to editorial or other constraints. The possibility that some of the cases could have been NKHS rather than DKA cannot be ruled out.

Twenty-one out of 26 cases of DKA were new onset cases and did not have any history of diabetes before being treated with clozapine while the remaining five cases were exacerbation of previously existent diabetes. Mean (SD) age of subjects was 40.2 (9.83) years and 21 (80.7 %) were male. Six (23%) were Caucasian, 14 (53.8%) were African American and three (11.5%) were other race/ethnicity. Diagnostically, 16 (61.5%) carried a diagnosis of schizophrenia, seven (27%) were diagnosed as schizoaffective disorder and two (7.5%) were diagnosed as other (one patient was diagnosed as delusional disorder and the other as bipolar illness). Subjects had received an average (SD) dose of clozapine of 340 mg/d (211 mg/d) for an average (SD) duration of 295 days (573 d). The most commonly co-prescribed psychiatric medication was lithium in 4 (15%) cases. Depakote was co-prescribed in 3 (11.5%) cases. The most commonly used second antipsychotic was risperidone in 4 (15%) cases.

Of the 26 subjects diagnosed with DKA 16 (61.5%) presented with DKA within the first three months of clozapine treatment. Analyses of the aforementioned predictors resulted in four significant associations. Race, duration of clozapine, antidiabetic medications and other medications were statistically significant factors which correlated with DKA. African American patients had a significantly increased risk of having a DKA ($p < 0.0001$) diagnosis while Caucasian patients had a significantly lower risk. Clozapine duration was significantly shorter ($p < 0.0001$) in the DKA cohort. Presence of antidiabetic medications and presence of other medications were negatively correlated with the presence of DKA ($p < 0.0001$ and $p < 0.0003$ respectively). The other medications were antihypertensives, anticholinergics, benzodiazepines, ranitidine, claritin, calcium, MVI, bethnechol and minocycline. Two other variables were almost statistically significant. A trend was noted for a negative correlation between family history of diabetes and the diagnosis of DKA ($p < 0.0696$). Also, the current dose of clozapine in the DKA group tended to be lower ($p < 0.0583$) than in the clozapine-associated diabetes cohort.

DISCUSSION

Clozapine is the most effective antipsychotic drug available for drug-refractory schizophrenia (1). However, a recent consensus panel made up of the American Diabetes Association, American Psychiatric Association, American Association of Clinical Endocrinologists and North American Association for the Study of Obesity in 2004 concluded that clozapine is associated with an especially high risk for developing metabolic side effects (2). The actual level of risk of DKA associated with clozapine treatment is unclear. In 2001, Koller et al. (30) identified 80 cases of DKA in a cohort of 384 cases of clozapine-associated diabetes (20.8%). This prevalence is higher than the 2.35% rate observed in the general diabetic population (31). However, the rate of clozapine-associated DKA could be high because clinicians expect the occurrence of this rare complication and monitor their clozapine treated patients with greater scrutiny. Another factor is that the regular blood work required for treatment with clozapine increases the close follow up of these patients. We were unable to assess true prevalence rate of clozapine-associated DKA in this study, since we know the number of cases of DKA which have been reported in the literature but we do not know the total number of patients who were treated with clozapine.

It is generally assumed that clozapine is associated with type II diabetes (3–6). Clozapine causes significant weight gain, weight gain is an established risk factor for type II diabetes, and increased adiposity is known to lead to insulin resistance. However, other lines of evidence suggest that clozapine may cause insulin resistance directly in certain susceptible individuals rather than indirectly through increased adiposity. Ardizzone et al. (32) showed that clozapine was capable of blocking glucose accumulation at the GLUT 4 transporter protein in cells derived from peripheral and brain tissue. Furthermore, in a recent study in Sweden, the authors treated non-diabetic insulin resistant subjects with an oral hypoglycemic medication for three weeks and showed a reversal via the increased availability of the GLUT 4 protein in fat biopsy (33). These findings provide evidence of the importance of glucose transporters in the pathophysiology of insulin resistance. In addition, they suggest a possible mechanism by which a state of insulin resistance may be produced relatively quickly by clozapine via blockade of the GLUT 4 transporter in certain individuals. Also, the findings suggest the possibility of prevention through the use of oral hypoglycemic agents.

Other findings suggest that clozapine may induce DKA through mechanisms other than weight gain. As noted previously,

clozapine-associated DKA tends to be early in the course of clozapine treatment. Koller et al. (30) also found that 56% of the new onset diabetes cases and 64% of the exacerbation of diabetes cases occurred within the first three months of exposure to clozapine. In addition, evidence suggests that clozapine-associated metabolic disturbances are reversible in some patients, once the clozapine is discontinued. In the Koller study (30), the diabetic state was reversible in 78% of cases with discontinuation of clozapine. In 58% of cases, clozapine was discontinued in our study. The duration of hyperglycemia following clozapine discontinuation in these cases, ranged from 10 days to 2 years. There were two cases where clozapine was re-introduced and this again resulted in a DKA clinical picture within a matter of hours to days, (7,11) and these resolved with ultimate discontinuation of clozapine. The potential reversibility of clozapine-associated metabolic disturbances, the reemergence of DKA with repeated exposure to clozapine, and shorter duration of exposure point in the direction of an acute change in insulin resistance rather than the generally assumed mechanism of gradual weight gain and development of diabetes. This finding is clinically significant and may be a guide for further studies in the etiology and management of clozapine associated DKA.

Significant findings of our study among socio-demographic factors include race, family of history of diabetes and obesity status. Being African American statistically increased the chances further of developing DKA on clozapine. This finding is consistent with evidence that individuals form racial/ethnic minority groups are at increased risk for diabetes. The prevalence of diabetes is approximately twofold greater in African Americans, Mexicans, Hispanic, Asians, East Indians and Native Americans compared to non-Hispanic whites in the general population (34). The age-adjusted rate of hospital discharge of DKA in 1996 was 2.3 times higher for African Americans than whites (31). African American patients with a diagnosis of Schizophrenia receive less primary preventive health care and therefore the diagnosis of diabetes may have been missed before the presentation of DKA.

Family history is a well-established risk factor for diabetes mellitus within the general population (34). However, family history was negative in the majority of the DKA case reports. Research findings in this area have been inconsistent, with Henderson et al. reporting positive family history in only 2 out of the 82 cases studied (35) while Koller et al. reported a positive family history of diabetes in 56% of the cases studied (30). Our finding that most patients with DKA had a negative family history of diabetes is consistent with the notion that clozapine can induce DKA in susceptible individuals independent of the presence of diabetes. Another possibility is that due to absence of family history of diabetes, the vigilance for diabetes may have been lower in this group.

Obesity is a strong predictor of diabetes in the general population (34). We observed that although 79% of DKA cases indicated the presence of obesity, this association was not statistically significant. Henderson, Newcomer and Lindenmayer have also reported that the relationship of clozapine with glucose dysregulation is independent of weight or BMI status (35–37). However this lack of association may be a reflection of methodological limitations of these studies (29). The lack of association between obesity and DKA in our study could be due to the relatively small number of case reports, the lack of longitudinal data, and the lack of objective measurements of obesity.

The majority of the patients with diabetes in the general population who develop DKA are in the age group of 0–44 years (34.7/1000 diabetic population) (31). The mean age is 38–42 years for patients with new onset diabetes presenting with DKA (38). The average age in the DKA group in the present study was 40.2 ± 9.83 years, and the majority of patients (80%) presented with DKA as a symptom of new onset diabetes. Although age was not found to be statistically significant, these findings are consistent with the idea that clozapine-associated diabetes may best fit within the "other" category in the classification of diabetes (26).

The presence of anti-diabetic medications was negatively correlated to the presence of DKA. This finding may reflect a sampling bias since the majority of cases were new onset diabetes and hence were less likely to be receiving an anti-diabetic medication at the time of DKA. Interestingly, this finding is consistent with the observation that oral hypoglycemic agents may be helpful in decreasing insulin resistance even in non-diabetic patients (33).

As the results are obtained based on a retrospective study design, methodological limitations associated with such a design should be noted. The study is subjected to publication bias of previous case reports. We depend on the clinical conclusions of the authors of the case reports as they diagnosed DKA in the reported cases based on their clinical acumen regardless of the fulfillment of any specific criteria for DKA. As a result, our findings only establish associations in the risk factors studied, rather than causation as in a controlled randomized trial. Within the context of the current study, one potential factor that could bias our results is differential under-reporting of cases of DKA vs. DM due to the differences in monitoring and perceived risk associated with the use of other atypical antiopsychotic agents. However, since the four factors that are found to significantly differentiate the DKA and DM cases are highly unlikely to be responsible for the cause of differential reporting, they likely reflect true differences between the DKA and DM cases. Another common factor that limits most observational studies for causal interpretation is hidden bias. This source of bias refers to unmeasured or unobserved factors that could differentiate between the DKA and DM presentations. Without a controlled randomized trial, it is extremely difficult to address this issue. In the current study, we analyzed the data to the degree possible by controlling for all the available covariates from both data sources.

Another important factor to consider is that none of the cases reviewed fulfilled all the four criteria for DKA, established for this study. The possibility that some of the cases could have been NKHS rather than DKA cannot be ruled out.

CONCLUSION

Clozapine associated DKA is an emerging issue that challenges us to think about the pathophysiology of the disorder and how clozapine-associated diabetes should be categorized. African American patients were more susceptible to develop this complication with a majority of the patients developing DKA within three months of treatment with clozapine. The dose of clozapine tended to be smaller and duration of treatment with clozapine tended to be shorter in the DKA group. While the mechanism of clozapine-associated DKA is unclear, one possibility is that development of insulin resistance by blockage of the GLUT 4 transporter by clozapine may lead to the precipitation of DKA. Prospective studies with a rigorous methodological design examining insulin levels, insulin resistance and other parameters such as weight gain and BMI are required to elucidate the mechanism of clozapine-associated DKA.

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