Elevated Hemoglobin A1c as a Possible Indicator of Diabetes Mellitus and Diabetic Ketoacidosis in Schizophrenia Patients Receiving Atypical Antipsychotics

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Objective: We conducted a retrospective epidemiologic study assessing the incidence of new-onset diabetes mellitus presenting as diabetic ketoacidosis in patients with schizophrenic disorders (ICD-9 295.0–295.9; referred to as "schizophrenia patients" hereafter) treated with atypical antipsychotic agents.

Method: The identification of patients and the review of records were achieved by using an electronic database linking administrative and clinical laboratory data between January 1, 1995, and December 31, 2001. The main outcome measure was the incidence of diabetic ketoacidosis or hyperosmolar hyperglycemic syndrome per 10,000 patient years in patients with new-onset or existing diabetes mellitus. We also determined the incidence of diabetic ketoacidosis associated with the use of atypical antipsychotics and calculated the mean hemoglobin A1c (HbA1c) level for all patients.

Results: During the 7-year period, 18.4% of schizophrenia patients were diagnosed with diabetes mellitus, compared with 6.6% in the general hospital population ($p < .001$). After chart review, 23 schizophrenia patients were identified with diabetic ketoacidosis: 11 had diabetes presenting as diabetic ketoacidosis, 8 had diabetic ketoacidosis with known diabetes mellitus, 2 had new-onset diabetes mellitus–hyperosmolar hyperglycemic syndrome, and 2 had hyperosmolar hyperglycemic syndrome with known diabetes mellitus. The incidence of diabetes presenting as diabetic ketoacidosis in schizophrenia patients was more than 10-fold higher than that reported in the general population: 14.93 per 10,000 patient years in schizophrenia patients versus 1.4 per 10,000 patient years in the general population ($p < .000001$) and versus the 1.98 per 10,000 patient years in the general hospital population ($p < .000001$). The incidence of diabetic ketoacidosis for each of atypical antipsychotic drugs over the 7-year period was as follows: clozapine, 2.2%; olanzapine, 0.8%; and risperidone, 0.2% (no incidence with ziprasidone or quetiapine). Of the 11 patients with diabetes presenting as diabetic ketoacidosis, the mean HbA1c level at admission was 13.3% ± 1.9% (10.4%–16.9%).

Conclusions: The incidence of diabetes mellitus presenting as diabetic ketoacidosis in schizophrenia patients is higher than in the general hospital population and differs across atypical antipsychotic agents. Elevated HgbA1c levels observed suggests that patients had undiagnosed diabetes mellitus for at least several weeks before the diabetic ketoacidosis episode.

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There have been several reports of diabetic ketoacidosis associated with treatment with atypical antipsychotic agents, most notably clozapine and olanzapine.[1–14] Additionally, several cases of diabetes mellitus resolved after clozapine or olanzapine was discontinued, only to have hyperglycemia to return upon reinstitution of the drug.[15,16] The observation that patients treated with atypical antipsychotic agents and without prior history of diabetes present with diabetic ketoacidosis, and when taken off the drugs achieve remission of their diabetes, suggests that the drugs may affect insulin secretion and/or action.

Griffiths and Springuel,[17] using the Canadian Adverse Drug Reaction Monitoring Program, reported 37 cases of suspected glucose metabolism disorders associated with atypical antipsychotic agents. The majority (8 of 12) cases with diabetic ketoacidosis were associated with clozapine use, and half (5 of 10) of the patients with new-onset

diabetic ketoacidosis were taking clozapine. In addition, 3 of 10 patients with new-onset diabetic ketoacidosis died. Olanzapine was the agent associated with the second most reports of diabetes mellitus and diabetic ketoacidosis. Case reports filed with the U.S. Food and Drug Administration have implicated clozapine, olanzapine, and, to a lesser degree, risperidone and quetiapine[15,16,18,19] in the development of type 2 diabetes. In a review of 45 published cases of new-onset diabetes mellitus or exacerbation of existing cases, Jin and colleagues[20] noted that 50% had gained no weight and 42% of new-onset cases presented with diabetic ketoacidosis, an unusually high incidence.

Viewed broadly, diabetic ketoacidosis is a life-threatening acute complication of diabetes mellitus and accounts for approximately 10% of deaths in patients with diabetes mellitus between the ages of 45 and 64 years.[21] Diabetic ketoacidosis is the result of an absolute or relative insulin deficiency usually associated with increased levels of counter-regulatory hormones such as catecholamines, glucagon, cortisol, and growth hormone. It is characterized by hyperglycemia, metabolic acidosis, and elevated blood ketones. It usually occurs in type 1 diabetes (being the initial manifestation of the disease in 20%–30% of cases), but can occur in type 2 diabetes, usually under the stress of a parallel acute illness.[22–24] Usually, insulin deficiency in patients with type 2 diabetes mellitus is relative. Occasionally, levels of insulin may not be enough to prevent the diabetic ketoacidosis. Physical or mental stress promotes the release of glucose counter-regulatory hormones, which may lead to diabetic ketoacidosis in the presence of limited beta cell response. Insulin deficiency decreases peripheral utilization of glucose by skeletal muscle and adipose tissue and increases lipolysis and proteolysis. Lipolysis provides the free fatty acids for ketone body production in the liver, and proteolysis provides the amino acids for increased gluconeogenesis.[22–24]

Diabetic ketoacidosis and hyperosmolar hyperglycemia syndrome both are life-threatening acute complications of diabetes mellitus. They differ from each other by the magnitude of hyperglycemia, severity of acidosis/ketonemia, and degree of dehydration. While diabetic ketoacidosis can occur in type 1 diabetes mellitus and type 2 diabetes mellitus, hyperosmolar hyperglycemic syndrome typically develops in type 2 diabetes mellitus.[22–24]

Diabetic ketoacidosis is usually characterized by hyperglycemia (usually ≥ 300 mg/dL), metabolic acidosis (HCO_3 ≤ 18 mmol/L, pH ≤ 7.3), dehydration, and elevated ketones. Hyperosmolar hyperglycemic syndrome is usually characterized by hyperglycemia (usually > 600 mg/dL), mild metabolic acidosis (HCO_3 ≥ 15 mEq/L, pH ≥ 7.3), and dehydration. A number of medical factors may predispose to or precipitate diabetic ketoacidosis and hyperosmolar hyperglycemic syndrome including acute illness, infections, cerebrovascular accidents, myocardial infarction, pancreatitis, pulmonary emboli, severe burns, renal failure, and medications.[22,23]

We conducted a retrospective epidemiologic study assessing the incidence of diabetes mellitus presenting as diabetic ketoacidosis in schizophrenia patients treated with atypical antipsychotic agents. The hypotheses were that patients with schizophrenia treated with atypical antipsychotic agents experienced higher rates of new-onset diabetes mellitus presenting as diabetic ketoacidosis than the general population and general hospital population and that these occurrences were more likely associated with clozapine and olanzapine.

METHOD

The patient population studied included inpatients and outpatients who attended Massachusetts General Hospital (Boston, Mass.) between January 1, 1995, and December 31, 2001. Following institutional review board (IRB) approval, identification of the patients was achieved using the Research Patient Data Registry (RPDR), an electronic database linking administrative and clinical laboratory data.[25] The RPDR identifies diagnosis by ICD-9 criteria. A user has the ability to query diagnoses through the use of a hierarchical tree structure, thus eliminating the need for the user to know the exact ICD-9 code used by the RPDR. The RPDR gathers data from various hospital legacy systems and stores the data in one place. Users may query against data for aggregate totals, and with proper IRB approval they may access medical records. The RPDR project data warehouse contains patient demographic data, diagnoses, and procedure data; pharmacy data; inpatient and outpatient encounter information; provider information; and laboratory data. All patient identifiers are encrypted throughout the database. The RPDR data warehouse is a Microsoft SQL 2000 database and is housed in a Windows 2000 server (Microsoft Corporation, Redmond, Wash.).

Queries were made using the diagnosis of schizophrenic disorders (ICD-9 295.0–295.9), diabetes mellitus (250), and diabetic ketoacidosis and hyperosmolar hyperglycemic syndrome (250.1–250.3) and record of atypical antipsychotic agents (clozapine, olanzapine, risperidone, quetiapine, and ziprasidone). The control group were queried for diabetes mellitus (250) and diabetic ketoacidosis and hyperosmolar hyperglycemic syndrome (250.1–250.3), while excluding schizophrenic disorders (ICD-9 295.0–295.9) and atypical antipsychotic agents (clozapine, olanzapine, risperidone, quetiapine, and ziprasidone). After patients were identified through RPDR, their complete medical records were reviewed by an endocrinologist (E.C.) and a psychiatrist (D.C.H. and P.M.L.).

Statistical Methods

The total person years of observation time were calculated by adding up the time each person was followed in the database from January 1, 1995, to December 31, 2001. For schizophrenia or schizoaffective disorder patients, the time each person received an atypical antipsychotic agent was added. The total number of patients receiving treatment with each atypical antipsychotic drug and duration of treatment during the 7-year period was tabulated. For patients who had the event (diabetic ketoacidosis or hyperosmolar hyperglycemic syndrome), only the time preceding the event was added per year of observation. The total number of events was divided by total observation time. The time to the event per year was calculated, and the number of events was tallied. The incidence per 10,000 patient years was calculated.[26] We tested for equality comparing the 1.4/10,000 patient years of diabetes presenting as diabetic ketoacidosis in the general population[26] and the incidence in the general hospital population with the incidence in patients with schizophrenia using the χ^2 test. The comparisons between diabetes presenting as diabetic ketoacidosis and diabetic ketoacidosis in known diabetes mellitus patients were performed using the Student t test. All statistical tests were 2-tailed, and p values of less than .05 were considered statistically significant.

RESULTS

During the 7-year period, 819,308 inpatients and outpatients attended the hospital. Of these, 417,847 (51%) were female and 53,942 (6.6%) received the diagnosis of diabetes mellitus. There were 4850 patients with the diagnosis of schizophrenia or schizoaffective disorder who attended the hospital during this time period; these patients represented only 0.6% of the general hospital population. Among patients with schizophrenia or schizoaffective disorder, 2231 (46%) were female and 2619 (54%) were male, with 3584 (74%) white, 631 (13%) black, 326 (7%) Hispanic, and 69 (1%) Asian. Five hundred fifteen (11%) of the schizophrenia or schizoaffective disorder patients died during the 7 years. Of patients with the diagnosis of schizophrenia or schizoaffective disorder, 893 (18.4%) were also diagnosed with diabetes mellitus, compared with 6.6% in the general hospital population ($p < .001$).

An initial search for the concurrent diagnosis of schizophrenia and diabetic ketoacidosis yielded a result of 51 patients. In the general hospital population, 1132 (0.138%) of 819,308 patients received the diagnosis of diabetic ketoacidosis, while 1.1% of patients (51/4850) with schizophrenia or schizoaffective disorder received the diagnosis of diabetic ketoacidosis. Schizophrenia or schizoaffective disorder diagnosis represented 4.5% (51/1132) of the diabetic ketoacidosis cases treated in the hospital during the 7-year period.

Upon thorough chart review, 24 of the 51 schizophrenia or schizoaffective disorder patients did not meet ICD-9 or DSM-IV criteria for the diagnosis of schizophrenia or schizoaffective disorder and diabetic ketoacidosis/hyperosmolar hyperglycemic syndrome. Additionally, 1 patient was eliminated because of steroid-induced hyperosmolar hyperglycemic syndrome and 3 were eliminated because of chronic pancreatitis or cirrhosis. Of 23 patients with schizophrenia or schizoaffective disorder identified as having diabetic ketoacidosis, 11 had new-onset diabetes mellitus presenting as diabetic ketoacidosis (Table 1), 8 were known diabetes mellitus patients (in 5 of these patients, diabetic ketoacidosis was due to medication noncompliance) (Table 2), 2 had hyperosmolar hyperglycemic syndrome without prior history of diabetes mellitus, and 2 had hyperosmolar hyperglycemic syndrome and a known history of diabetes mellitus. Thus, the incidence of diabetic ketoacidosis in schizophrenia or schizoaffective disorder patients was 19 of 1132, or 1.67% of all cases of diabetic ketoacidosis in the hospital during the 7-year period. Three patients with new-onset diabetes mellitus presenting as diabetic ketoacidosis went on to have additional episodes of diabetic ketoacidosis within the 7-year period of follow-up.

Among the 11 patients with new-onset diabetes mellitus presenting as diabetic ketoacidosis, the mean ± SD age was 42 ± 12 years (range, 26–64), the mean body mass index was 30 ± 5 kg/m^2 (range, 24–35 kg/m^2); 6 (55%) were female, 8 (73%) were white, 2 (18%) were black, and 1 (9%) was Hispanic (Table 1). Eight (73%) were diagnosed with chronic schizophrenia and 3 (27%), with schizoaffective disorder. The mean glucose level at the time of presenting with diabetic ketoacidosis was 795 ± 328 mg/dL; the HCO_3 level was 13.1 ± 5.4 mmol/L (range, 5–21 mmol/L); the mean anion gap was 20.1 ± 4.6 mmol/L (range, 15–30 mmol/L); the mean pH was 7.22 ± 0.17; and the mean hemoglobin A1c (HbA1c) was 13.3% ± 1.9% (range, 10.4%–16.9%) (Table 1). There was a known family history of diabetes mellitus in 27% of patients with diabetes presenting as diabetic ketoacidosis. The incidence of diabetic ketoacidosis in schizophrenia or schizoaffective disorder patients without a prior diagnosis of diabetes was more than 10-fold higher than that reported in the general population: 14.93 per 10,000 patient years (schizophrenia or schizoaffective disorder) vs. 1.4 per 10,000 patient years ($p < .000001$).[26] The incidence was also significantly higher than the 1.98 per 10,000 patient years found in the Massachusetts General Hospital general hospital population ($p < .000001$).

Comparing New-Onset Diabetic Ketoacidosis and Diabetic Ketoacidosis in Known Diabetes Mellitus

For schizophrenia patients with a known history of diabetes mellitus who experienced a diabetic ketoacidosis episode, the mean ± SD age was 44 ± 12 years, the mean

Table 1. Demographics, Medical History, Basic Laboratory Values, and Medications of Schizophrenia Patients With New-Onset Diabetes Mellitus That Presented as Diabetic Ketoacidosis or Hyperosmolar Hyperglycemia Syndrome

Patient ID	Age, y	Sex	Race	BMI, kg/m^2	Psychiatric Diagnosis	Medical Problems	DM Family History	DKA or HHS	Medications at Admission	Acetone Positive (ratio) or Negative	Ketones Positive or Negative	Glucose, mL/dL[a]	HCO_3, mmol/L[b]	Anion Gap, mmol/L[c]	pH[d]	HbAlc Level, %[e]
1	42	F	White	35	SCA	Polycystic ovary disease, UTI	Yes	DKA	Olanzapine 10 mg/d, divalproex sodium	Positive	Serum (1:4)	1274	16.3	…	7.35	11.6
2	34	M	White	29	SCA	HL	No	DKA	Olanzapine 20 mg/d, lithium, lamotrigine, carbamazepine	…	Urine (3+)	832	19	15	7.3	12.4
3	26	F	Black	32	SC	…	Yes	DKA	Clozapine 175 mg/d	Trace	Urine (3+)	512	8.2	21	7.27	12.2
4	45	M	White	…	SCA	Cardiomyopathy, HL	Unknown	DKA	Clozapine 400 mg/d, lisinopril, warfarin, furosemide	Positive (1:4)	Serum (1:4)	1158	7.9	30	7.24	14.3
5	41	F	White	24	SC	Hypothyroidism	Unknown	DKA	Olanzapine 10 mg/d	Positive (1:16)	Serum (1:4)	1160	5	19	6.82	13.7
6	43	M	White	35	SC	Morbid obesity	Yes	DKA	Olanzapine 20 mg/d, fluoxetine	…	Urine (2+)	833	21	…	…	13.1
7	40	F	White	…	SC	…	Unknown	DKA	Clozapine 350 mg/d	Negative	Urine (3+)	450	19	20	7.37	…
8	29	M	Hispanic	…	SC	HTN, appendicitis	No	DKA	Clozapine 400 mg/d, divalproex sodium	Positive (1:8)	Serum (1:4)	374	10	16	7.28	…
9	63	F	White	26	SC	…	Unknown	DKA	Olanzapine 15 mg/d	…	Serum (1:4)	539	9.1	21.6	7.22	14.8
10	36	M	Black	33	SC	HTN, HL, hyperthyroidism	No	DKA	Clozapine 550 mg/d, risperidone 2 mg/d, sertraline, metoprolol, nifedipine	Positive blood	Urine (3+)	544	16	…	7.43	10.4
11	64	F	White	25	SC	Pancreatitis, pneumonia, acute renal failure, HTN, HL	Unknown	DKA	Haloperidol, olanzapine 10 mg/d, chlorpromazine 150 mg/d, propranolol, hydrocortisone, atorvastatin	(> 300 mg/dL)	Urine (3+)	1065	12	18	7.24	16.9
12	55	M	White	31	SC	HTN, HL, CAD, CABG	Yes	HHS	Olanzapine 15 mg/d	Negative	Negative	776	26	…	7.33	16.1
13	29	M	White	32	SC	Obesity, HL	Yes	HHS	Olanzapine 20 mg/d, thiothixene	Negative	Negative	931	21	…	7.31	…

[a]Reference range, 70–110 mL/dL.
[b]Reference range, 23–30 mmol/L.
[c]Reference range, 8–12 mmol/L.
[d]Reference range, 7.32–7.45.
[e]Reference range, 3.8%–6.4%.
Abbreviations: BMI = body mass index, CABG = coronary artery bypass graft, CAD = coronary artery disease, DKA = diabetic ketoacidosis, DM = diabetes mellitus, HbA1c = hemoglobin A1c, HHS = hyperosmolar hyperglycemic syndrome, HL = hyperlipidemia, HTN = hypertension, SC = schizophrenia, SCA = schizoaffective disorder, UTI = urinary tract infection.
Symbol: … = data not available.

Table 2. Demographics, Medical History, Basic Laboratory Values, and Medications of Schizophrenia Patients With Known Diabetes Mellitus Presenting as Diabetic Ketoacidosis or Hyperosmolar Hyperglycemia Syndrome

Patient ID	Age, y	Sex	Race	Psychiatric Diagnosis	Medical Problems	Type of DM	DKA or HHS	Medications at Admission	Ketones Positive or Negative	Glucose, mL/dL[a]	HCO_3, mmol/L[b]	pH[c]	HbAlc Level, %[d]
1	64	F	White	SCA	Neuropathy, retinopathy, HTN, hypothyroidism, obesity	Type 1	DKA	Quetiapine 500 mg/d, insulin, levothyroxine, valproate	Positive	809	14.9	7.24	8.8
2	23	F	Hispanic	SCA	Multiple DKA, medication noncompliance	Type 2	DKA	Olanzapine 30 mg/d, quetiapine 100 mg/d, insulin, gabapentin, trazodone	Positive	890	10	7.28	10.4
3	41	F	White	SCA	HTN	Type 2	DKA	Quetiapine 500 mg/d, insulin, levothyroxine, valproate	Positive	572	12.5	7.13	7.6
4	61	F	Black	SC	Neuropathy, retinopathy, nephrotic syndrome, HTN, hypothyroidism, HL	Type 2	DKA	Haloperidol 20 mg/d, insulin	Positive	727	12.1	7.26	17.4
5	43	M	White	SC	HTN, HL, OHA discontinued	Type 2	DKA	Olanzapine 15 mg/d	Positive	450	6	7.17	12.8
6	39	M	White	SC	Medication noncompliance (insulin), multiple DKA	Type 2	DKA	Olanzapine 25 mg/d	Positive	553	14.8	7.28	…
7	39	M	Black	SC	Medication noncompliance, (insulin)	Type 1	DKA	Medication noncompliant	Positive	623	16.2	7.29	…
8	43	M	White	SCA	Medication noncompliance (insulin), foot ulcer, WBC count = 29,000	Type 1	DKA	Medication noncompliant	Positive	672	5.1	6.99	7.8
9	46	M	Black	SC	Stopped medications, HTN	Type 2	HHS	Unknown	Negative	915	16.5	7.32	…
10	82	F	Hispanic	SC	HTN	Type 2	HHS	Olanzapine 20 mg/d, OHA	Negative	462	17.7	7.38	…

[a]Reference range, 70–110 mL/dL.
[b]Reference range, 23–30 mmol/L.
[c]Reference range, 7.32–7.45.
[d]Reference range, 3.8%–6.4%.
Abbreviations: DKA = diabetic ketoacidosis, DM = diabetes mellitus, HbA1c = hemoglobin A1c, HHS = hyperosmolar hyperglycemic syndrome, HL = hyperlipidemia, HTN = hypertension, OHA = oral hypoglycemic agent, SC = schizophrenia, SCA = schizoaffective disorder, WBC = white blood cell.
Symbol: … = data not available.

glucose level at the time of diabetic ketoacidosis was 690 ± 158 mg/dL, the mean pH was 7.21 ± 0.17, and the mean HbA1c level was 11.2% ± 3.6% (Table 2). There were no differences between patients with new-onset diabetes mellitus presenting as diabetic ketoacidosis and patients with known diabetes mellitus presenting as diabetic ketoacidosis in age ($p = .55$), glucose level at the time of diabetic ketoacidosis ($p = .81$), pH ($p = .80$), or HbA1c level ($p = .20$).

Antipsychotic Agents and Risk of Diabetic Ketoacidosis

The incidence of new-onset diabetes mellitus presenting as diabetic ketoacidosis was assessed for each atypical antipsychotic agent. In the RPDR system, patients were identified by the diagnosis of schizophrenia or schizoaffective disorder and treatment with particular antipsychotic agents. There were 776 olanzapine-treated schizophrenia or schizoaffective disorder patients, 585 risperidone-treated schizophrenia or schizoaffective disorder patients, 479 quetiapine-treated schizophrenia or schizoaffective disorder patients, 226 clozapine-treated schizophrenia or schizoaffective disorder patients, and 57 ziprasidone-treated schizophrenia or schizoaffective disorder patients. The incidence of diabetic ketoacidosis for each drug over the 7-year period was clozapine, 2.2%; olanzapine, 0.8%; risperidone, 0.2%; and no incidence for quetiapine or ziprasidone. If hyperosmolar hyperglycemic syndrome cases were included, the incidence with olanzapine rose to 1.0%. There was a significant difference in incidence of diabetes presenting as diabetic ketoacidosis between clozapine and risperidone ($p < .00001$) but not between clozapine and olanzapine ($p = .117$) or between olanzapine and risperidone ($p = .18$). The one case associated with risperidone was in combination with clozapine. Of note, no cases of quetiapine-, ziprasidone-, or aripiprazole-associated new-onset diabetes mellitus presenting as diabetic ketoacidosis were found in the database. However, 2 cases of diabetic ketoacidosis in patients with known diabetes mellitus were observed with quetiapine (Table 2). Finally, 1 pa-

Table 3. Follow-Up Post-DKA or Post-HHS for Schizophrenia Patients With New-Onset Diabetes Mellitus That Presented as DKA or HHS

Patient ID	Follow-up HbAlc, % (time)	DKA/HHS Follow-Up	Medications Changed	Treatment With OHA or Insulin	Diabetes Resolved	Comment
1	…	Treated with insulin	Psychiatric medications unchanged, insulin	Insulin	No	
2	5.5 (9 mo)	3 mo after DKA, patient no longer required insulin. At 6 mo post-DKA, OHA discontinued	Risperidone 6 mg	Insulin, then OHA, then OHA discontinued	Yes	
3	…	Insulin discontinued	Psychiatric medications unchanged	Insulin, then OHA	…	
4	…	Deceased	Psychiatric medications unchanged	Insulin, then OHA	No	
5	8.1 (6 mo)	Deceased	Olanzapine discontinued, risperidone 2 mg qd	Insulin, then OHA, then OHA discontinued	Yes	Died: 2nd DKA episode (on olanzapine treatment again) and heparin-induced thrombocytopenia
6	7.7 (9 mo)	Patient eventually started on treatment with clozapine and OHA	Psychiatric medications unchanged	Insulin, then OHA	No	
7	6.2 (7 mo)	Treated with insulin	…	Insulin	…	
8	11 (12 mo)	2 y later, patient was still taking clozapine and insulin	Psychiatric medications unchanged, insulin	Insulin	No	2 DKA episodes, died from myocardial infarction
9	…	…	Switched to risperidone	Insulin, then OHA, then OHA discontinued	Yes	
10	5.1 (11 mo)	Insulin for 2.5 y Then rosiglitazone and metformin, clozapine 500 mg, and risperidone 6 mg	Psychiatric medications unchanged, insulin	Insulin, then OHA	No	
11	…	…	Psychiatric medications unchanged	Insulin, then OHA	No	CVA 9 days after admitted for DKA
12	5.3 (24 mo)	Oral agent olanzapine, eventually switched to aripiprazole and DM resolved (oral agent discontinued)	Switched to aripiprazole	Insulin, then OHA, then OHA discontinued	Yes	DM resolved completely after switch to aripiprazole
13	…	Treated with insulin	Psychiatric medications unchanged, insulin	…	…	

Abbreviations: CVA = cerebrovascular accident, DKA = diabetic ketoacidosis, DM = diabetes mellitus, HbA1c = hemoglobin A1c, HHS = hyperosmolar hyperglycemia syndrome, OHA = oral hypoglycemic agent.
Symbol: … = data not available.

tient experienced diabetes presenting as diabetic ketoacidosis while receiving treatment with haloperidol decanoate, olanzapine, and chlorpromazine.

After up to 6 years of follow-up, 8 of 11 patients were able to discontinue insulin therapy, thus excluding the diagnosis of type 1 diabetes mellitus (Table 3). In 3 of 11 patients with diabetes mellitus presenting as diabetic ketoacidosis, the diabetes mellitus resolved completely on switching antipsychotic agents. In 1 case, 2 weeks after the diagnosis of diabetic ketoacidosis and discontinuation of olanzapine, anti-islet cell antibodies were negative and fasting and stimulated C-peptide levels were within normal limits, thus ruling out the diagnosis of type 1 diabetes mellitus. The patient was switched to risperidone 6 mg/day, and 18 months after presentation, his glucose control was entirely within normal limits, his HbA1c level was 5.5%, and he was taking no antidiabetic agents (Table 3). Additionally, in 1 of 2 diabetes mellitus patients presenting as hyperosmolar hyperglycemic syndrome, the diabetes mellitus also resolved completely on switching from olanzapine to aripiprazole. Another patient had complete resolution of diabetes mellitus after olanzapine was discontinued. However, following a psychiatric decompensation, olanzapine was restarted and she experienced a second diabetic ketoacidosis episode and died in the hospital from heparin-induced thrombocytopenia. Finally, diabetes mellitus resolved completely in another patient in whom treatment was switched from olanzapine to risperidone following a diabetic ketoacidosis episode.

DISCUSSION

The incidence of diabetes mellitus and new-onset diabetes mellitus presenting as diabetic ketoacidosis in

schizophrenia patients is much higher than in the general hospital population and differs across atypical antipsychotic agents. The mechanisms by which these agents can precipitate diabetic ketoacidosis in some individuals are unclear. Patients taking olanzapine and clozapine have been shown to have a significant degree of insulin resistance even in non-obese patients.[27,28] It is possible that the insulin resistance and the impairment in utilization of glucose may be the underlying cause of the diabetic ketoacidosis episodes.[27] The most striking finding was consistent: a grossly elevated HbA1c level in patients with diabetes presenting as diabetic ketoacidosis. This suggests that these patients had undiagnosed diabetes mellitus for at least several weeks before experiencing a diabetic ketoacidosis episode. Additionally, the fact that patients with known diabetes mellitus presenting as diabetic ketoacidosis had elevated HbA1c levels suggests poor compliance with diabetes treatment and monitoring. Noncompliance, discontinuation of diabetes treatment, or lack of monitoring of blood glucose may also place patients with schizophrenia and diabetes at increased risk for life-threatening events such as diabetic ketoacidosis. An effort to switch antipsychotic agents that may have contributed to the development of diabetes mellitus is warranted. Additionally, schizophrenia patients with diabetes mellitus may need more intensive diabetes treatment and training to improve monitoring of finger sticks for glucose and HbA1c.

Not surprisingly, the risk of diabetic ketoacidosis associated with each drug appears to mirror the risk of each drug's association with the development of type 2 diabetes mellitus, regarding which clozapine and olanzapine appear to be the most problematic. The reports of diabetic ketoacidosis with clozapine and olanzapine and increased incidence of type 2 diabetes mellitus in patients taking these drugs may reflect 2 separate populations with varying risks. For instance, many of the early published cases of diabetic ketoacidosis with clozapine were in African Americans, who appear to have a greater risk for type 2 diabetes mellitus. In fact, patients with undiagnosed diabetes mellitus experience diabetic ketoacidosis episodes that may resemble the Flatbush diabetes phenomenon. Flatbush diabetes mellitus was described in the African American population in New York City, where patients presented with new-onset type 2 diabetes mellitus in diabetic ketoacidosis.[29] Patients were usually insulin resistant and had acute defects in insulin secretion. Insulin secretory function appeared to recover following treatment for diabetic ketoacidosis.[29] Additionally, in the present study, several patients' diabetes mellitus resolved upon switching to different antipsychotic agents, suggesting that these patients may not always need insulin therapy following the diabetic ketoacidosis episode. This finding also suggests that schizophrenia patients who experience diabetic ketoacidosis or new-onset diabetes mellitus in association with antipsychotic agents should be given the opportunity to switch to a more metabolically neutral agent to attempt to reverse the diabetes mellitus.

Additionally, acute medical illnesses (urinary tract infection, pneumonia, appendicitis, acute pancreatitis) may increase the risk of diabetic ketoacidosis in schizophrenia patients in a manner similar to the way they increase that risk in the general population. Schizophrenia patients may not seek medical care as promptly or the health care system may not respond appropriately, as symptoms of diabetic ketoacidosis may be mistaken for other somatic or psychotic symptoms.[30] It is also possible that acute psychosis or agitation, which affect counter-regulatory hormones, may place vulnerable patients at risk.[31–33] However, there are no reports in the literature of diabetic ketoacidosis in unmedicated schizophrenia patients and few diabetic ketoacidosis reports in patients exposed to typical antipsychotic agents.[34] This argues against any disease state effect and more strongly for a drug effect (i.e., exposure to certain atypical antipsychotic agents). Additionally, the atypical antipsychotic–associated diabetic ketoacidosis reports have occurred predominantly in stable outpatients, which also argues against psychosis or agitation playing a significant role.

Our findings mirror nonpsychiatric general population studies. For patients with known history of diabetes mellitus, noncompliance with diabetes treatment was observed. In a community sample of 92 patients reported by Johnson et al.,[35] diabetic ketoacidosis was the initial presentation of diabetes mellitus in 23% of patients. The most common cause of diabetic ketoacidosis was infection, in 32%. Omission of therapy led to diabetic ketoacidosis in 13% (12/92), and a precipitating factor of diabetic ketoacidosis was unknown in 19% of cases. However, in our study, only 2 of the 13 patients with new-onset diabetes mellitus and 2 of 10 with known diabetes mellitus had an infection identified as a precipitant. In a study of acute care hospitals in Rhode Island by Faich et al.,[26] 20% of 137 patients had diabetic ketoacidosis as the initial presentation of diabetes mellitus; 9% of the patients died during the 152 diabetic ketoacidosis episodes in this population. The highest rates of diabetic ketoacidosis were found in the elderly, nursing home patients, and those living in one geographic region of the state. The annual incidence was 1.4 per 10,000 patient years for the total population and 46 per 10,000 patient years for diabetics. This group also found infections and noncompliance as the most common precipitants.

Westphal[22] performed a retrospective chart review of adults presenting with diabetic ketoacidosis from 1987 through 1993. Sixty-two (27%) of 226 had diabetic ketoacidosis as the initial presentation of diabetes mellitus, and 52% of these were over the age of 40 years. A total of 47% were classified as having type 1 diabetes mellitus and 26%, as having type 2 diabetes mellitus. He also

found that 24% of patients with newly diagnosed diabetes mellitus and 8% of those with prior type 2 diabetes mellitus did not require insulin at follow-up. Finally, Leslie and Rosenheck[36] reported data from the U.S. Department of Veterans Affairs, which found that 4132 (7.3%) of 56,849 schizophrenia patients receiving monotherapy developed diabetes mellitus and 88 (0.2%) were hospitalized for diabetic ketoacidosis with a significantly elevated hazard ratio for clozapine- and olanzapine-treated patients.

Of note, there were no differences between patients with diabetes presenting as diabetic ketoacidosis and patients with known diabetes mellitus presenting as diabetic ketoacidosis on any demographic variable such as age, gender, race, glucose level, or HbA1c level at time of diabetic ketoacidosis episode. Again, this suggests that the diabetes presenting as diabetic ketoacidosis in schizophrenia patients treated with atypical antipsychotic agents represents undiagnosed diabetes mellitus that eventually culminates in an episode of diabetic ketoacidosis. Given the evidence for the effect of clozapine and olanzapine on glucose metabolism, one would expect higher rates of these occurrences in clozapine- and olanzapine-treated patients. However, by chance, there will most likely be reports of diabetic ketoacidosis following treatment with all antipsychotic agents, including more neutral agents such as ziprasidone and aripiprazole. If careful baseline screening is conducted, however, patients with undiagnosed diabetes mellitus will be detected and referred for appropriate treatment.

Among those with known diabetes mellitus presenting as diabetic ketoacidosis, a high proportion were noncompliant with their diabetes treatment and some with their antipsychotic medications prior to their diabetic ketoacidosis episode. It is possible that some atypical antipsychotic agents contribute to instability of glucose control in patients not compliant with their diabetes mellitus treatment.

There are several limitations to this study. It is possible that some patients in the database received treatment for diabetic ketoacidosis at other institutions that may not have been recorded in the medical records, and our results thus underestimate the occurrence of diabetic ketoacidosis. It is also possible that some patients were treated with antipsychotic agents that were not recorded in their inpatient or outpatient record. Additionally, prior antipsychotic agent exposure was not controlled for in the analysis.

Similar to monitoring the white blood cell count for clozapine-treated patients and lowering the risk and incidence of agranulocytosis, rigorous monitoring of fasting glucose and perhaps HgA1c with early interventions may prevent such occurrences of diabetic ketoacidosis. Published guidelines have recommended the monitoring of lipids, weight/waist measurements, and fasting glucose before initiating antipsychotic agents, at 12 weeks, and then yearly.[37] However, that frequency of monitoring of the fasting glucose may not be adequate to prevent the rare but dangerous episodes of diabetic ketoacidosis. A more frequent monitoring (every 3 to 6 months) may be more preventive. This report also highlights a potential role for HbA1c. Although HbA1c is not diagnostic of diabetes, increasing levels should sound an alarm. In this report, in diabetes presenting as diabetic ketoacidosis, the presenting HbA1c levels were elevated, which suggests a subacute onset of hyperglycemia. Additionally, patients with schizophrenia and known diabetes mellitus should have extensive education on diet, exercise, the importance of checking glucose, and monitoring of diabetes medications to assure compliance with their diabetes treatment and prevention. Partnerships between psychiatric clinicians, primary care physicians, and endocrinologists are necessary to appropriately address the numerous issues that may interfere with schizophrenia patients' benefiting from standard diabetes mellitus care.

Drug names: aripiprazole (Abilify), atorvastatin (Lipitor), carbamazepine (Carbatrol, Equetro, and others), chlorpromazine (Thorazine, Sonazine, and others), clozapine (Clozaril, FazaClo, and others), divalproex sodium (Depakote), fluoxetine (Prozac and others), furosemide (Lasix and others), gabapentin (Neurontin and others), haloperidol (Haldol and others), lamotrigine (Lamictal and others), levothyroxine (Tirosint, Synthroid, and others), lisinopril (Zestril, Prinivil, and others), lithium (Eskalith, Lithobid, and others), metformin (Riomel, Fortamet, and others), metoprolol (Topro-XL, Lopressor, and others), nifedipine (Procardia, Adalat, and others), olanzapine (Zyprexa), propranolol (Innopran, Inderal, and others), quetiapine (Seroquel), risperidone (Risperdal), rosiglitazone (Avandia), sertraline (Zoloft and others), thiothixene (Navane and others), warfarin (Coumadin, Jantoven, and others), ziprasidone (Geodon).

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