Clinical Correlates of Oral Glucose Tolerance Test Performance in Olanzapine-Treated Patients with Schizophrenia or Schizoaffective Disorder

To the Editor: While olanzapine is frequently associated with glucoregulatory abnormalities, the underlying pathophysiologic mechanisms remain unclear.[1] Because olanzapine's superior therapeutic profile frequently renders switching to more metabolically safe antipsychotics a clinically undesirable option,[2] understanding how olanzapine is involved in metabolic disturbances may be important for preventing negative health consequences and for improving treatment adherence.

Oral glucose tolerance test (oGTT) is the "gold standard" for diagnosing diabetes, reliably determining insulin sensitivity, and is a better predictor of morbidity and mortality than fasting plasma glucose (FPG).[3,4] There is a relative paucity of olanzapine oGTT studies, none of which have addressed the role of treatment duration or insulin sensitivity. The present study aimed to fill this gap. To that end, we employed the Matsuda index, which analyzes dynamic glucose/insulin interactions during oGTT (encompassing both hepatic and peripheral insulin sensitivities) and has been demonstrated to be superior to other commonly used indices for determining glucose intolerance such as homeostasis model assessment (HOMA), which only assesses peripheral insulin resistance.[5,6]

Method. Two-hour oGTT was performed in olanzapine-treated nondiabetic patients with a Structured Clinical Interview for *DSM-IV* Axis I Disorders diagnosis of schizophrenia or schizoaffective disorder (N = 35) from June 2008–February 2010. Detailed selection methodology and clinical trial data are reported elsewhere.[7] Separate multiple linear regression analyses were performed for FPG (to determine hepatic glucose production), Matsuda index, HOMA-IR (insulin resistance), and HOMA-β (β-cell function)[5,6] as dependent variables, employing a model in which independent variables were age, olanzapine dose, treatment duration, body mass index (BMI), fasting plasma cholesterol, and triglycerides. Post hoc correlative analyses were conducted using the Pearson product-moment correlation coefficient. All analyses were 2-tailed with $\alpha < .05$ for statistical significance.

Results. Seven previously undiagnosed patients fulfilled American Diabetes Association diagnostic criteria[3] based on oGTT (≥ 200 mg/dL), but only 1 would have been identified by FPG alone (≥ 126 mg/dL). Multiple regression analyses (Table 1) revealed that Matsuda index significantly correlated with BMI (corresponding Pearson correlation: $r_{33} = 0.62$, $P = .00007$) and triglycerides ($r_{33} = 0.41$, $P = .0146$), but not with age, dose, duration, or cholesterol. Using the same independent variables in multiple regression analyses, HOMA-IR and FPG glucose each correlated with triglycerides only ($r_{33} = 0.65$, $P = .00002$; and $r_{33} = 0.62$, $P = .00005$, respectively), while HOMA-β had no significant correlations.

Table 1. Regression Analyses for Dependent Variables (Matsuda Index, HOMA-IR, Fasting Glucose)

Variable	β	SE of β	B	SE of B	t_{28}	*P* Value[a]
Matsuda index						**.0013**
Age	−0.0639	0.1384	−0.0239	0.0518	−0.4619	.6478
Olanzapine treatment duration	−0.0901	0.1542	−0.0865	0.1481	−0.5842	.5638
Olanzapine dose	0.1234	0.1441	0.0502	0.0586	0.8566	.3989
BMI	−0.6012	0.1407	−0.3979	0.0932	−4.2718	**.0002**
Cholesterol	−0.0659	0.1672	−0.0054	0.0136	−0.3942	.6964
Triglycerides	−0.3092	0.1344	−0.0060	0.0026	−2.2995	**.0291**
HOMA-IR						**.0010**
Age	0.0501	0.1367	0.0209	0.0569	0.3665	.7167
Olanzapine treatment duration	−0.2161	0.1522	−0.2311	0.1627	−1.4198	.1667
Olanzapine dose	−0.0824	0.1423	−0.0373	0.0644	−0.5789	.5673
BMI	0.2337	0.1390	0.1722	0.1024	1.6816	.1038
Cholesterol	−0.1484	0.1651	−0.0135	0.0150	−0.8989	.3764
Triglycerides	0.6273	0.1328	0.0136	0.0029	4.7248	**<.0001**
Fasting glucose						**.0088**
Age	0.1767	0.1516	0.3478	0.2985	1.1653	.2534
Olanzapine treatment duration	0.0823	0.1619	0.4312	0.8483	0.5083	.6151
Olanzapine dose	−0.0157	0.1543	−0.0355	0.3483	−0.1018	.9196
BMI	0.0436	0.1511	0.1601	0.5550	0.2886	.7750
Cholesterol	−0.0294	0.1763	−0.0130	0.0783	−0.1665	.8689
Triglycerides	0.6405	0.1444	0.0692	0.0156	4.4368	**.0001**

[a]Boldface indicates statistical significance.
Abbreviations: BMI = body mass index, HOMA-IR = homeostasis model assessment of insulin resistance.

In addition to the alarming rates of undiagnosed diabetes in olanzapine-treated patients, our data suggest that both triglycerides and BMI may be implicated in olanzapine-related glucoregulatory abnormalities. The lack of correlation with treatment duration or dose may suggest preexisting metabolic alterations in schizophrenia spectrum patients, at least partially independent of antipsychotic effects[8,9] (eg, conditions predisposing schizophrenics to develop diabetes), and/or metabolic alterations arising early in the course of treatment[10,11] (eg, insulin receptor damage/loss). Our finding that 20% of participants had undiagnosed diabetes suggests that oGTT is advantageous for clinically monitoring antipsychotic-treated patients. This is consistent with findings that about 70% of antipsychotic-treated patients are not adequately screened for diabetes.[12]

Although more costly and time-consuming than FPG, oGTT measures glucose and insulin sensitivity related to food intake, which is more realistic (ie, diabetics spend little time in a fasting state). Our findings suggest that all antipsychotic prescribers (psychiatric and primary care alike) should screen/monitor patients for diabetes, possibly with oGTT (or at least BMI and triglycerides)—especially those with obesity or hypertriglyceridemia.

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