Metabolic Syndrome in Patients With Major Depressive DisorderAssociated Risk Factors

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Although most studies have focused on the risk of metabolic syndrome for patients with schizophrenia exposed to atypical antipsychotics, other psychiatric patients appear to be at risk for metabolic disturbances as well.7-9 Major depressive disorder (MDD) may be of particular interest because it is much more common than schizophrenia and is treated with a broad range of psychotropics.

It has long been recognized that certain metabolic conditions are associated with cardiovascular disease and increased risk for morbidity and mortality.[1,2] These alterations in metabolic functions often occur in clusters, a presentation known as metabolic syndrome.[3,4] There is ongoing debate about how best to conceptualize and define metabolic syndrome, but most authorities now accept that central obesity or visceral adiposity, altered glucose and lipid metabolism, and hypertension are critical health indicators.[4-6]

CHECK POINTS

- ✓ Persons with major depressive disorder (MDD) may be at greater risk for metabolic syndrome than previously thought. In fact, a history of MDD doubles the odds of developing metabolic syndrome.
- ✓ There is considerable variability in risk factors for metabolic syndrome as well as variability in its presentation.
- ✓ Concern about metabolic syndrome should not be limited to patients with schizophrenia or to those treated with atypical antipsychotics. The presence of even one criterion for metabolic syndrome is of potential concern and may be an early warning signal that can prevent progression to the full syndrome.

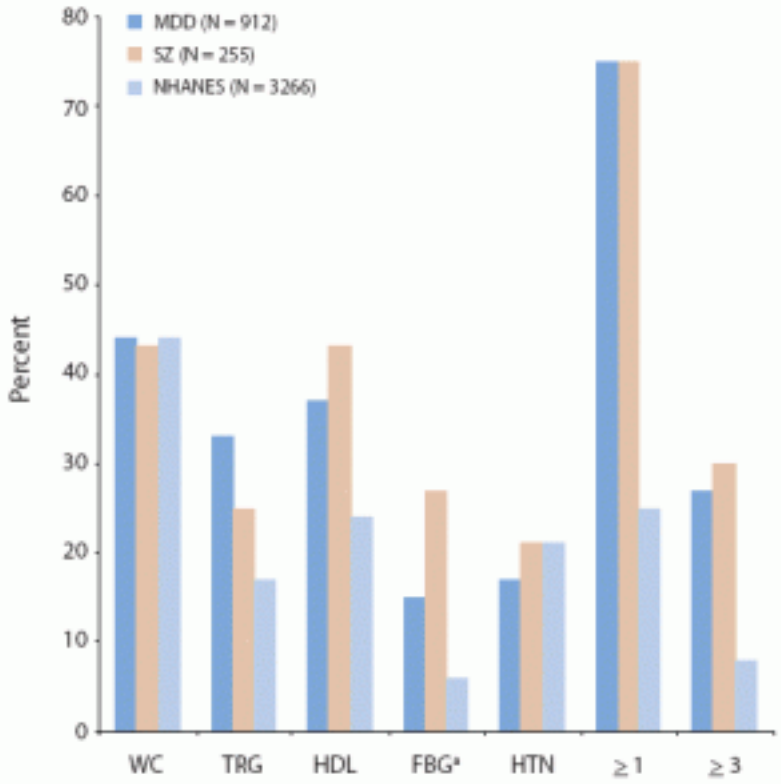
Although most studies have focused on the risk of metabolic syndrome for patients with schizophrenia exposed to atypical antipsychotics, other psychiatric patients appear to be at risk for metabolic disturbances as well.[7-9] Major depressive disorder (MDD) may be of particular interest because it is much more common than schizophrenia and is treated with a broad range of psychotropics.

Contributing factors

In a recent study presented at the 160th Annual Meeting of the American Psychiatric Association, we examined the prevalence of metabolic syndrome and each of the 5 criteria for this syndrome (**Table 1**) in psychiatric inpatients aged 18 through 64 years with a clinical diagnosis of MDD (N = 912).10 These findings were compared with data from a similar sample of patients who had schizophrenia (N = 255). **Table 2** presents demographic data. A total of 30.3% (n = 296) of the MDD sample had psychotic features, and 19.2% (n = 175) had recurrent depression. Alcohol or other substance abuse/dependence was comorbid in 57.3% of the patients with MDD and in 39.6% of the patients with schizophrenia. **Table 3** lists the psychotropics that were being prescribed at index admission. The investigators found that in the MDD sample, 22% of patients met the Adult Treatment Panel (ATP) III criteria for metabolic syndrome and that at least 1 of the 5 criteria for the syndrome was present in 75% of the patients.[10] The Figure shows the proportion of the MDD patients who met each ATP criterion compared with patients who had schizophrenia and with the general population.[10,11] There was no difference in the prevalence of metabolic syndrome in the 2 patient groups nor in the

proportion of patients who had at least 1 of the 5 criteria, but these rates were much higher than in the general population.

Figure
Prevalence of each metabolic measure



MDD, major depressive disorder; SZ, schizophrenia; NHANES, National Health and Nutrition Examination Survey; WC, waist circumference (men: > 120 cm; women: > 88 cm); TRG, triglycerides (≥ 150 mg/dL); HDL, high-density lipoprotein cholesterol (men: < 40 mg/dL; women: < 50 mg/dL); FBG, fasting blood glucose (≥ 110 mg/dL); HTN, hypertension; ≥ 1, 1 or more of the above 5 measures present; ≥ 3, metabolic syndrome.
* MDD vs schizophrenia, $P < .001$.

Patients in the MDD and schizophrenia samples were statistically different only on the fasting blood glucose criterion (14.9% vs 26.9%, respectively; x2 = 18.67; P < .001); there was a trend toward a greater prevalence of elevated triglycerides in MDD patients (32.7% vs 24.5%; x2 = 3.76; P = .053). For the MDD sample, logistic regression was used to determine the association of each of a number of independent variables with the syndrome and with each metabolic syndrome criterion. Three demographic but no treatment variables, including receiving an atypical antipsychotic, were associated with an increased risk of at least 1 of the 5 criteria:

- Age 40 years or older: odds ratio (OR) = 1.73; confidence interval (CI), 1.15 - 2.60
- Female sex: OR = 1.52; CI, 1.01 - 2.27
- Latino ancestry: OR = 2.23; CI, 1.30 - 3.84

Patients 40 years or older (OR = 1.91; CI, 1.39 - 2.61) and women (OR = 4.46; CI, 3.22 - 6.18) were at increased risk for visceral adiposity. Patients 40 or older who were at double the risk (OR = 2.09; CI, 1.47 - 2.98) on the triglyceride measure, were at moderately lower risk on the high-density lipoprotein criterion (OR = 0.70; CI, 0.50 - 0.99), and were more likely to meet the glucose (OR = 2.82; CI, 1.87 - 4.24) and hypertension (OR = 13.27; CI, 7.84 - 22.47) criteria than patients younger than 40 years.

Patients at highest risk

Previous reports suggested that metabolic syndrome is common in persons with a history of depression as well as in patients with current MDD.[12] Findings from our study indicate that the prevalence may be as high as that found in patients with schizophrenia.[10] However, it must be noted that this study was limited to inpatients, almost all of whom were receiving an SSRI. This class of drugs has been associated with abdominal obesity (OR = 1.40), increased body mass index, and elevated cholesterol levels.[13,14] Depression has also been found to be associated with insulin resistance.[13-16] Any reported prevalence of metabolic syndrome is, in part, a function of the diagnostic and demographic mix of the sample. In our study, the participants in the MDD and schizophrenia groups did not differ by age (38.8 ± 12.1 vs 39.6 ± 11.9, respectively), but the

proportion of women was significantly greater. This sex difference is noteworthy because women were more likely to meet the waist circumference criterion and to have at least 1 of the 5 criteria. Perhaps related is the finding that in women, but not in men, a history of MDD doubles the odds of having metabolic syndrome.15 The ages of individuals in a sample may also affect study results. For example, although the prevalence of diabetes is higher in patients with schizophrenia than in the general population, this finding holds true only for patients younger than 50 years.[17,18]

Table 1 ATP-III criteria for metabolic syndrome[a]

- Abdominal obesity (waist circumference)
  Men: > 120 cm (> 40 in)
  Women: > 88 cm (> 35 in)
- Triglycerides: ≥ 150 mg/dL
- HDL cholesterol (decreased)
  Men: < 40 mg/dL
  Women: < 50 mg/dL
- Blood pressure: ≥ 130/≥ 85 mm Hg[b]
- Fasting blood glucose: ≥ 110 mg/dL

ATP, Adult Treatment Panel; HDL, high-density lipoprotein.
[a] Metabolic syndrome is defined as the presence of 3 or more of these 5 measures.[7]
[b] In this study, a diagnosis of hypertension was substituted for a recorded blood pressure.

Drug exposure

In our sample of patients with MDD, no medication was associated with metabolic syndrome or with the presence of any individual criterion. Earlier studies have shown that even in schizophrenia at least some metabolic syndrome criteria appear to be independent of drug exposure.[8-10] While many drugs are associated with weight gain, other issues must also be considered in the pathogenesis of metabolic syndrome, including genetic predisposition and lifestyle variables.

Several recent studies have explored the link between metabolic syndrome, stress, and the hypothalamic-pituitary-adrenal axis.[9,19,20] Brown and colleagues[21] concluded that elevated cortisol levels are strongly associated with depression and abdominal obesity (and somewhat with diabetes and hypertension), but not with hyperlipidemia. Thus, among the many factors important in the etiology of metabolic syndrome there may be considerable variability in which metabolic measures are affected as well as variability in the mechanisms of action.

Table 2 Psychiatric inpatients at risk for metabolic syndrome: demographics by diagnosis[10]

	Major depressive disorder[a] No. (%)	Schizophrenia[b] No. (%)
Female	526 (57.7)	71 (27.8)
Race		
White	545 (59.8)	116 (45.5)
Black	116 (12.7)	75 (29.4)
Latino	217 (23.8)	49 (19.2)
Age: mean ± SD	38.8 ± 12.1	39.6 ± 11.9

[a] N = 912; [b] N = 255.

Summary

Future research may allow more precise delineation of risks and lead to more clinically useful risk profiles. The criteria for metabolic syndrome continue to evolve, and this debate may point to important areas for new research.[3] For example, some metabolic measures may be more important than others in psychiatric patients, and some risks may be negated by appropriate treatment (eg, statins, antihypertensives) or by a change in psychotropics.

The concern about metabolic syndrome should not be limited to patients with a diagnosis of schizophrenia or to those treated with atypical antipsychotics. The presence of even one criterion for metabolic syndrome is of potential concern and may be an early warning signal that can prevent progression to the full syndrome.

Table 3
Psychiatric inpatients at risk for metabolic syndrome: psychotropic agents prescribed at index admission[10]

	Major depressive disorder[a] No. (%)	Schizophrenia[b] No. (%)
Antipsychotic (any)	480 (52.6)	253 (99.2)
Antipsychotic (typical)	31 (3.4)	114 (44.7)
Antipsychotic (atypical)	472 (51.8)	213 (83.5)
> 2 Antipsychotics	16 (1.8)	67 (26.3)
Antidepressant	880 (96.5)	114 (44.)
Carbamazepine	10 (1.1)	2 (0.8)
Divalproex	40 (4.4)	53 (20.8)
Lithium	22 (2.4)	10 (3.9)

[a]N = 912; [b]N = 255.

Drugs Mentioned in This Article
Carbamazepine (Carbatrol, Tegretol, others)
Divalproex (Epival, Depakote)
Lithium (Eskalith, Lithane, Lithobid)

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