Research Article

Associations Between Components of Metabolic Syndrome and Cognition in Patients With Schizophrenia

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The metabolic syndrome and cognitive dysfunctions are common in patients with schizophrenia, yet there is no general consensus concerning the effects of the components of the metabolic syndrome on various cognitive domains. The goal of this study was to investigate the relationship between components of the metabolic syndrome and cognition in patients with schizophrenia. Components of the metabolic syndrome and neurocognitive functioning were assessed in 68 patients with schizophrenia. The Brief Assessment of Cognition in Schizophrenia (BACS) was used to assess neurocognition. Hyperglycemia and hypertension were the only components of the metabolic syndrome found to be associated with cognitive functioning. Patients with schizophrenia who were hypertensive showed cognitive impairments in 2 domains, with a negative association found between hypertension and verbal memory ($P = 0.047$) and verbal fluency ($P = 0.007$). Hyperglycemia was associated with higher scores on verbal memory ($P = 0.01$) and verbal fluency ($P < 0.001$). It appears that medical treatment of certain components of the metabolic syndrome could affect cognitive performance in patients with schizophrenia.
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The metabolic syndrome and its components, including abdominal obesity, dyslipidemia, hyperglycemia, and hypertension, are very prevalent in patients with schizophrenia.[1,2] The prevalence of the metabolic syndrome in patients with schizophrenia in the United States and Canada has been reported as 43% and 46%, respectively.[1,3] Genetic risk factors, increased cortisol level, unhealthy diet, lack of exercise, and antipsychotic treatment are factors that contribute to the etiology of the metabolic syndrome in schizophrenia.[4–6]

The performances of patients with schizophrenia are 1.5 to 2.0 SDs below healthy controls on a range of neurocognitive tasks, including verbal memory, verbal fluency, working memory, motor speed, attention, and executive function.[7] Studies have also shown that cognitive deficits may be a cause of poor social and occupational functioning.[8,9] Consequently, cognitive deficits have become a potential pharmacological target to improve quality of life and functional capacity in patients with schizophrenia.[7,10]

Recently, attention has focused on the effects of the metabolic syndrome on cognitive functioning. Some studies have shown that the metabolic syndrome and its components may lead to poorer cognitive functioning in the general population.[11] However, a recent study challenged the notion that the metabolic syndrome and its components have a negative effect on cognition.[12] Those researchers found that elderly participants with metabolic syndrome had better cognitive functions than those without metabolic syndrome.

A few studies have investigated the effects of the components of metabolic syndrome on cognitive domains in schizophrenia, but the results have been contradictory.[13–18] Although 1 study demonstrated that patients with schizophrenia, hypertension, and increased body mass index had more cognitive deficits than the control group,[15] other studies found a

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relationship only between hyperglycemia, but not hypertension or abdominal obesity, and cognitive impairments in schizophrenia.[14,16] Another study reported that high levels of triglycerides, abdominal obesity, and low levels of high-density lipoprotein (HDL) cholesterol were the only metabolic factors that were associated with memory impairment in schizophrenia.[17] The Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) study failed to find any association between metabolic syndrome and cognitive domains.[18] One explanation for these negative results in the CATIE study may be that the patients were divided into 2 groups, those who met and those who did not meet any 3 of the 5 criteria for the metabolic syndrome. This dichotomization may have masked the effects of individual components of the metabolic syndrome on cognition.

The study described here was designed to examine the association between the individual components of the metabolic syndrome and cognitive dysfunctions in patients with schizophrenia. To assess various cognitive domains, the Brief Assessment of Cognition in Schizophrenia (BACS) was used.[19,20] The BACS was specifically designed to assess cognitive function in schizophrenia, and time required to administer (approximately 35 min) and score it is brief. Studies have shown acceptable reliability and concurrent validity of the BACS with a standard cognitive battery.[19,20]

METHODS

Participants

A convenience sample of 68 patients with schizophrenia (46 male and 22 female patients) was recruited over a period of approximately 3 months. All of the patients had been receiving treatment as inpatients for at least 2 years in the psychiatry clinic at the Golestan Mental Health Hospital. In this sample, the average age was 42.4 years (SD 9.5y), the average educational level completed was 10.1 years (SD 5.2 y), and the average duration of illness was 16.3 years (SD 8.1 y). Patients enrolled in the study were receiving antipsychotic medication and were clinically stable. The inclusion criteria included: (1) age 18 to 65 years; (2) DSM-IV[21] diagnosis of schizophrenia (all subtypes) or schizoaffective disorder with illness duration ≥2 years; (3) auditory and visual acuity adequate to complete the cognitive tests; (5) stable dose of primary typical or atypical antipsychotic for at least 4 weeks; (6) no physical health problem requiring frequent changes in medications; and (7) capacity and willingness to give written informed consent. Exclusion criteria included: (1) inability to read or speak; (2) documented disease of the central nervous system; (3) intellectual disability; (4) a clinically significant or unstable cardiovascular, renal, hepatic, gastrointestinal, pulmonary, or hematological condition; (5) a medical problem that might affect cognition (eg, human immunodeficiency virus infection, an episode of anoxia, head injury, cerebrovascular accident, Parkinson disease, Alzheimer disease, seizure disorders); and (6) a diagnosis of substance dependence.[21] All patients gave informed consent and were administered a set of comprehensive fasting metabolic measures and a set of neurocognitive measures (BACS) during the baseline period of the study. The study was approved by the Ethics Committees of Kerman University of Medical Sciences.

Measures

Assessment of Metabolic Syndrome

The components of the metabolic syndrome were defined according to the National Cholesterol Education Program–Adult Treatment Panel III criteria (NCEP-ATPIII),[22] as follows:

- Central obesity: waist circumference ≥102 cm or 40 inches (male) or ≥88 cm or 36 inches (female).
- Dyslipidemia: triglyceride level ≥1.7 mmol/L (150 mg/dL).
- Dyslipidemia: HDL-C<40 mg/dL (male) or <50 mg/dL (female).
- Blood pressure ≥130/85 mm Hg.
- Fasting plasma glucose ≥5.6 mmol/L (100 mg/dL).

In addition, patients receiving antidiabetic agents, antihypertensive agents, or specific treatment for dyslipidemia were generally considered as meeting the component criterion for glucose, blood pressure, or triglycerides/HDL, respectively.

Waist circumference was measured at the midpoint between the lower rib margins and the iliac crest. Arterial blood pressure was recorded using a standard mercury sphygmomanometer. Using standard enzymatic techniques, a comprehensive

battery of metabolic measures was assessed at baseline, including fasting blood samples (drawn fasting between 6:00 and 8:00 AM) for glucose, total cholesterol, total triglycerides, HDL, and low-density lipoprotein levels. Chlorpromazine equivalent doses were also calculated for each patient.[23]

Assessment of Cognitive Function

Neurocognitive assessments were performed by trained physicians who were unaware of the study hypothesis. All of the participants were tested using the Persian version of the BACS, which has been validated in a sample of patients with schizophrenia who spoke Persian.[24] The battery of tests in the BACS includes brief assessments of verbal memory, working memory, motor speed, verbal fluency, reasoning and problem-solving, and attention.

List Learning (verbal memory): Patients were presented with 15 words and then asked to recall as many as possible. This procedure was repeated 5 times.

Digit Sequencing Task (working memory): Patients were presented with clusters of numbers of increasing length. They were asked to tell the experimenter the numbers in order, from lowest to highest.

Token Motor Task (motor speed): Patients were given 100 plastic tokens and asked to place them into a container as quickly as possible for 60 seconds.

Verbal Fluency: Patients were given 60 seconds to name as many words as possible within a given category (semantic fluency). Also, in 2 separate trials, patients were given 60 seconds to generate as many words as possible beginning with a certain letter (letter fluency). The total number of words from the 3 trials was the outcome measure.

Tower of London (reasoning and problem-solving): Patients looked at 2 pictures simultaneously. Each picture showed 3 balls of different colors arranged on 3 pegs, with the balls in a unique arrangement in each picture. The patients were told about the rules in the task and were asked to provide the least number of times the balls in one picture would have to be moved to make the arrangement of balls identical to that of the other picture.

Symbol Coding (attention and processing speed): Patients received a key explaining how unique symbols correspond to the individual numerals 1 to 9. They were asked to fill in the corresponding number beneath a series of symbols as quickly as possible for 90 seconds.

Statistical Analysis

χ^2 and t tests were applied to analyze the demographic and clinical data. To examine the relationship between the components of the metabolic syndrome and cognitive domains (as outcome variables), multivariate linear regression was used. P values <0.05 were considered significant. IBM SPSS 21 software was used for the statistical analyses.

RESULTS

Table 1 summarizes the demographic and clinical characteristics of all patients using the individual components of the metabolic syndrome. The prevalence rate for individual components of the metabolic syndrome in this sample was 20.6% for hyperglycemia, 23.5% for hypertension, 47.1% for low HDL cholesterol, 64.7% for high triglycerides, and 54.4% for abdominal obesity. Seventeen of the 46 men (37%) were current smokers; however, none of them was allowed to smoke >5 cigarettes per day. Twelve of the 16 patients with hypertension (75%) were on antihypertensive treatments (ie, metoprolol, nitrates, losartan, or propranolol). Seven of these patients with hypertension (44%) were receiving first-generation antipsychotics, and 13 (81%) were receiving second-generation antipsychotics (some patients were receiving >1 type of antipsychotic). Eight of the 14 patients with hyperglycemia (57%) were on oral antihyperglycemic agents (ie, glyburide or metformin). None of the patients was receiving insulin therapy. Five of the patients with hyperglycemia (36%) were receiving first-generation antipsychotics, and 12 (86%) were receiving second-generation antipsychotics (some patients were receiving >1 type of antipsychotic).

The results of the multivariate analyses are shown in Table 2. Our models were all adjusted for sex, age, educational levels, duration of disease, and chlorpromazine dose equivalents. After these adjustments, the diagnosis of hypertension predicted a poorer score on the cognitive domains of verbal memory ($P = 0.047$) and verbal fluency

TABLE 1. Demographic Characteristics of Groups With Components of the Metabolic Syndrome

	FBS≥100 mg/dL or Diabetic		*Blood Pressure≥130/85 mm Hg or Hypertensive*		*HDL<40 mg/dL in Male or HDL<50 mg/dL in Female*		*TG≥150 mg/dL*		*Waist Circumference ≥102 cm in Male, ≥88 cm in Female*	
	Yes (n=14)	*No (n=54)*	*Yes (n=16)*	*No (n=52)*	*Yes (n=32)*	*No (n=36)*	*Yes (n=44)*	*No (n=24)*	*Yes (n=37)*	*No (n=31)*
Sex										
Male n [n (%)]	10 (71.4)	36 (66.7)	13 (81.3)	33 (63.5)	17 (53.1)	29 (80.6)	27 (61.4)	19 (79.2)	22 (59.5)	24 (77.4)
Female [n (%)]	4 (28.6)	18 (33.3)	3 (18.8)	19 (36.5)	15 (46.9)	7 (19.4)	17 (38.6)	5 (20.8)	15 (40.5)	7 (22.6)
Age mean (SD) (y)	51.2 (7.1)	38.6 (9.2)	48.8 (8.6)	38.9 (9.5)	39.1 (8.4)	43.1 (11.3)	41.3 (9.0)	41.0 (12.2)	43.3 (9.2)	38.8 (10.7)
Education, mean (SD) (y)	10.1 (1.8)	10.0 (2.9)	10.6 (2.3)	9.8 (2.8)	10.9 (2.9)	10.0 (2.5)	10.1 (2.7)	10.0 (2.7)	10.4 (2.7)	9.6 (2.7)
Disease duration, mean (SD) (y)	19.1 (10.1)	15.1 (8.6)	18.5 (10.1)	15.2 (8.5)	14.2 (7.9)	17.5 (9.6)	15.9 (8.9)	16.0 (9.2)	17.6 (9.2)	14.0 (8.4)
CED (SD) (mg)	261 (154)	333 (184)	250 (152)	340 (184)	310 (208)	326 (153)	320 (185)	316 (174)	299 (189)	341 (168)

CED indicates antipsychotic dose in chlorpromazine equivalents; FBS, fasting blood sugar; HDL, high-density lipoprotein cholesterol; TG, triglycerides.

TABLE 2. Linear Regression Analyses of Cognitive Test Scores

	Cognitive Domains of Brief Assessment of Cognition in Schizophrenia									
	*Verbal Memory**			*Verbal Fluency***			*Symbol Coding****			
	B	*Standardized β*	*P*	*B*	*Standardized β*	*P*	*B*	*Standardized β*	*P*
Sex	−0.124	−0.007	0.954	−3.91	−0.164	0.172	−2.24	−0.101	0.411
Age	−0.235	−0.289	0.087	−0.011	−0.063	0.950	−0.447	−0.435	0.012
Education	0.936	0.311	0.009	0.950	0.232	0.044	1.46	0.385	0.002
Duration of disease	−0.124	−0.136	0.306	−0.068	−0.421	0.675	−0.218	−0.187	0.162
Chlorpromazine dose equivalents	−0.011	−0.241	0.052	−0.018	−0.286	0.019	−0.017	−0.295	0.019
Waist circumference	1.77	0.108	0.474	−1.27	−0.057	0.699	0.044	0.002	0.989
Blood pressure	−4.64	−0.240	0.047	−9.61	−0.365	0.007	−4.05	−0.166	0.223
HDL cholesterol	2.48	0.151	0.254	−1.00	−0.045	0.728	−0.836	−0.040	0.761
Triglycerides	1.08	0.063	0.621	3.62	0.155	0.218	2.55	0.117	0.363
Fasting blood glucose	7.38	0.364	0.010	14.15	0.526	<0.001	5.78	0.225	0.105

*$P=0.006$; $R^2=0.333$.
**$P=0.002$; $R^2=0.362$.
***$P=0.008$; $R^2=0.324$.
HDL indicates high-density lipoprotein cholesterol.

($P=0.007$), whereas the diagnosis of hyperglycemia predicted better scores on the cognitive domains of verbal memory ($P=0.01$) and verbal fluency ($P<0.001$). Other aspects of the metabolic syndrome (ie, waist circumference and dyslipidemia) were not significant predictors for any of the individual cognitive domains (Table 2). The model was not fitted for working memory ($P=0.11$), motor speed ($P=0.28$), and reasoning and problem-solving ($P=0.08$). There was a significant relationship between poorer cognitive performance and lower levels of education and higher antipsychotic doses ($P<0.05$).

DISCUSSION

This study investigated the association between the components of the metabolic syndrome (hyperglycemia, dyslipidemia, hypertension, and abdominal obesity) and cognitive functioning in patients with schizophrenia. Our findings provided evidence for a correlation between hypertension and cognitive impairments in schizophrenia. Interestingly, the patients with schizophrenia and hyperglycemia showed significantly better cognitive functioning than the patients without hyperglycemia. We did not find any significant association between other components of metabolic syndrome and cognitive performance. Higher levels of education and lower antipsychotic doses, which may be representative of less severe psychosis, were also associated with better cognitive functioning.

The prevalence of metabolic syndrome in our patients was 48.5% (n = 33), which is consistent with another study from Iran, which found a 40% prevalence of metabolic syndrome in patients with schizophrenia.[25] Moreover, our finding is consistent with reports from Western countries. For example, the prevalence of metabolic syndrome in patients with schizophrenia has been reported to be 43% and 46% in the United States and Canada, respectively.[1,3] The prevalence of the metabolic syndrome in the general population of Iran has been reported to range from 22.8% to >30% according to different studies.[26–28]

In this study, patients with schizophrenia and comorbid hypertension showed more deficits in the cognitive domains of verbal memory and verbal fluency than nonhypertensive patients with schizophrenia. Most of these patients (75%) were being

treated with antihypertensive agents. This finding is consistent with that of Friedman et al,[15] who reported in 2010 that hypertension had a negative impact on verbal memory in patients with schizophrenia being treated with antihypertensive medications. Our findings are also consistent with the results of nonpsychiatric studies that have similarly shown impaired verbal memory in hypertensive patients receiving antihypertensive treatment.[29] However, some studies have failed to show any association between high blood pressure and cognitive functioning in schizophrenia.[14,17,30] This discrepancy may be explained by variations in the populations and methodology used in these studies [eg, different cutoff points for hypertension (130 mm Hg in our study vs. 140 mm Hg), different races (white vs. Hispanic vs. African American), and different neurocognitive batteries used to assess the cognitive domains]. It is also important to note that these studies did not adjust their results for the duration of illness, lifestyle, diet, and dose of antipsychotic medications. All of these factors may affect assessments of both the components of the metabolic syndrome and cognitive functioning.[31–35] In our study, however, all participants had a relatively similar lifestyle, leisure activities, and diet as they were living in the same care center for chronic mental disorders. Finally, it has been suggested that different types of antihypertensive medications may have varying effects on cognitive function. For example, blockade of the renin-angiotensin system may prevent cognitive decline in hypertensive patients.[36–39]

Our results demonstrated that patients with schizophrenia who were hyperglycemic but not necessarily diabetic performed significantly better on verbal memory and verbal fluency than those without hyperglycemia. This finding is partially consistent with the results of the CATIE study,[13] in which it was found that diabetes had a negative effect on all cognitive domains except verbal memory and working memory in patients with schizophrenia. It should be mentioned that the cutoff point for hyperglycemia in our study was 100 mg/dL, whereas it was 126 mg/dL in the CATIE study. Among hyperglycemic patients in our study, 35.7% had fasting blood glucose <126, which may explain this discrepancy. However, our results are inconsistent with several other studies.[14,16,17] For example, in a study published in 2008, Dickinson and colleagues compared cognitive performance in 3 groups: patients with schizophrenia and comorbid diabetes, patients with schizophrenia without diabetes, and diabetic patients. Their results showed more cognitive impairment in the patients with schizophrenia and comorbid diabetes than in the other 2 groups, especially in the domains of processing speed and visual/spatial ability.[16] These discrepancies in results may be due to methodological and population differences in the studies, such as the different cutoff points for hyperglycemia and the duration of hyperglycemia. In particular, studies have shown that the duration of diabetes or hyperglycemia is related to cognitive functioning.[40,41] Future studies are needed to assess the effect of duration of diabetes on cognitive function in schizophrenia.

Our study failed to show any association between abdominal obesity or dyslipidemia and cognitive functioning. These results are consistent with a study that involved 1289 patients with schizophrenia and found no relationship between abdominal obesity or dyslipidemia and cognitive functioning.[13] However, 2 other studies found an association between abdominal obesity and cognitive deficits in patients with schizophrenia.[14,30] In a study published in 2012, Lindenmayer et al[14] found that greater waist circumference, lower HDL, and higher triglycerides were associated with impaired attention/vigilance. In a study published in 2013, Boyer et al[30] found a relationship between abdominal obesity and poor processing speed, and between hypertriglyceridemia and poor attention/vigilance, executive functioning, verbal memory, and processing speed. The explanation for the different results could be the duration of the metabolic syndrome, the ethnicity of the populations studied (mainly African American in the study by Lindenmayer and colleagues), and/or the mean age (relatively young average age in the study by Boyer and colleagues). Future studies are needed to explore the effect of the length of exposure to each component of the metabolic syndrome on cognition in schizophrenia.

In our study, higher antipsychotic doses were correlated with worse cognitive function. Studies have reported contradictory findings concerning the effects of antipsychotics on cognition in schizophrenia. On the one hand, antipsychotics may induce metabolic syndrome and its components,[42,43]

but, on the other hand, antipsychotics have been shown to be correlated with better cognitive functioning in schizophrenia.[44] Future studies are needed to clarify the direct and indirect effects of antipsychotics, through metabolic components, on cognition.

This study had a number of limitations. First, the sample size was relatively small. Second, the sample may not have been representative of the entire population of patients with schizophrenia (eg, the patients were mostly middle-aged). Third, this study was limited by being cross-sectional rather than prospective in design. Fourth, a number of important data were not available, such as the duration of hyperglycemia or hypertension, the duration of treatment with antipsychotics, and other moderating factors, such as the duration of smoking and use of medications that may affect cognition (eg, opioids, benzodiazepines, anticholinergics, renin-angiotensin system blockers).

In conclusion, our findings suggest that certain components of the metabolic syndrome, namely, hypertension and hyperglycemia, may be linked to cognitive functioning in patients with schizophrenia. These results have some clinical implications. Several studies have found that treatment of hypertension in other populations is associated with cognitive improvement.[39,45] After replication with longitudinal approaches, these findings may support complementary therapeutic approaches.

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