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Differences in glucose tolerance between deficit and nondeficit schizophrenia

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Abstract

Some studies suggest that schizophrenia is associated with an increased risk of diabetes independently of antipsychotic use. People with deficit schizophrenia, which is characterized by primary (or idiopathic), enduring negative symptoms, differ from those with nondeficit schizophrenia on course of illness, treatment response, risk factors, and biological correlates. We hypothesized that deficit and nondeficit subjects would also differ with regard to glucose tolerance. Newly diagnosed, antipsychotic-naïve subjects with nonaffective psychosis and matched control subjects were administered a 75 g oral glucose tolerance test (GTT). Two-hour glucose concentrations were significantly higher in the nondeficit patients (*N*=23; mean [SD] of 121.6 [42.0]) than in deficit (*N*=23; 100.2 [23.1]) and control subjects (*N*=59; 83.8 [21.9]); the deficit subjects also had significantly higher two-hour glucose concentrations than did the control subjects. These results provide further support that the deficit group has a distinctive etiopathophysiology.

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Contributors

Drs. Kirkpatrick, Fernandez-Egea, and Bernardo designed the study and contributed to analyses and manuscript preparation. Dr. Garcia-Rizo was involved in data collection, interpretation, and manuscript preparation.

Conflict of interest

Dr. Fernandez-Egea received consulting fees and honoraria from Pfizer.

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Dr. Bernardo received consultant fees from Bristol-Meyer-Squibb and Wyeth. He also received honoraria from Janssen-Cilag, Eli Lilly Company, Pfizer, Synthelabo, Glaxo SmithKline, and AstraZeneca.

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Keywords

Diabetes; Schizophrenia; Negative symptoms; Deficit syndrome

1. Introduction

Comparisons of subtypes have long been an aspect of schizophrenia research. Subtypes based on the related concepts of apathy, anhedonia, and negative symptoms have been examined for many years (Andreasen and Olsen, 1982; Crow, 1985). A proposed negative symptom subtype is deficit schizophrenia (Carpenter et al., 1988), which is characterized by negative symptoms that are enduring or trait features. The criteria for deficit schizophrenia (Kirkpatrick et al., 1989) also require that these negative symptoms be considered primary (or idiopathic), that is, they are not due to depression, overwhelming hallucinations or delusions, medication side effects, etc. This group comprises about 20% of patients with schizophrenia (Kirkpatrick et al., 1993, 2000b).

In addition to good interrater reliability (Amador et al., 1999; Fenton and McGlashan, 1992; Kirkpatrick et al., 1993), the deficit subtype has been shown to differ from other, nondeficit patients with schizophrenia on a variety of measures. Differences in course of illness, signs and symptoms other than negative symptoms, risk factors, biological correlates, and treatment response have all been found (Kirkpatrick et al., 2001). We have previously presented the hypothesis that deficit schizophrenia is a disease that is separate from other forms of schizophrenia, and outlined methods to test that hypothesis (Kirkpatrick et al., 2001). The alternative explanation for the deficit/nondeficit differences is that the deficit group has a more severe form of the same pathophysiology found in other forms of schizophrenia. The greater cognitive impairment (Cohen et al., 2007) and poorer level of function (Kirkpatrick et al., 1996b; Tek et al., 2001a,b) found in deficit schizophrenia, and the presence of significant negative symptoms in addition to positive symptoms, are all consistent with this “more of the same” interpretation. However, in some studies, the deficit group did not have a more severe form of the same abnormality found in nondeficit schizophrenia. Instead, with regard to some variables, the deficit group was either more normal than nondeficit subjects, or neither group was more normal, but both differed from control subjects (e.g., excess winter birth in nondeficit schizophrenia vs. excess summer births in deficit schizophrenia; Messias et al., 2004).

Prior to the introduction of the first modern antipsychotics in the 1950's, several studies suggested that schizophrenia was associated with an increased risk of diabetes (Braceland et al., 1945; Freeman, 1946; Langfeldt, 1952; Lorenz, 1922, Meduna et al. 1942; Robinson and Shelton, 1940). Unfortunately, those studies did not use explicit diagnostic criteria for schizophrenia, and potentially confounding factors such as body mass index (BMI) and smoking were not considered. Some recent studies of newly diagnosed, antipsychotic-naïve patients with schizophrenia or nonaffective psychosis have had stronger methods, although problems with potential confounding by hypercortisolemia in the psychosis group, and incomplete matching for key demographic variables, have weakened some of the studies (Ryan et al., 2003; Spelman et al., 2007; Arranz et al., 2004). In a study of 50 newly diagnosed, antipsychotic-naïve patients with nonaffective psychosis and matched control subjects, we found increased glucose concentrations at two hours in a glucose tolerance test (GTT), but not at baseline (Fernandez-Egea et al., submitted). The GTT difference we found in these antipsychotic-naïve patients could not be attributed to differences in age, smoking, ethnicity, gender, BMI, neighborhood of residence, socioeconomic status, antipsychotic medications, or an increased cortisol concentration in the psychotic subjects.

The possibility raised by these studies that schizophrenia may be associated with diabetes independently of poor health habits and medication side effects has received indirect support from family studies. Mukherjee et al. (1989) found an increased prevalence of type 2 diabetes mellitus among first degree relatives of schizophrenia patients, although that study used norms from population data, rather than a comparison of patients with matched controls. We have recently replicated the finding of an increased prevalence of type 2 diabetes in the relatives of schizophrenia probands, using antipsychotic-naïve, newly diagnosed patients and matched controls (Fernandez-Egea et al., 2008b). Another study (Spelman et al., 2007) also found an increased prevalence of impaired glucose tolerance in an oral glucose tolerance test (GTT) in both newly diagnosed, antipsychoticnaïve patients with schizophrenia (10.8%) and their first degree relatives (18%) compared to healthy controls (0%). However, in that study, the relatives and healthy controls were not well matched for age, BMI, and smoking habit, which are known risk factors for developing diabetes. In a study with closer matching and without confounding by hypercortisolemia in the relatives group, we also found increased two-hour glucose concentrations in first degree relatives (Fernandez-Egea et al., 2008a).

Because, as noted above, deficit and nondeficit schizophrenia differ with regard to many variables, including those related to etiopathophysiology, we tested the hypothesis that they would also differ in the results of a GTT. The evidence that diabetes has an increased prevalence in the relatives of people with schizophrenia, and that deficit and nondeficit schizophrenia differ with regard to family history (Hong et al., 2003; Kirkpatrick et al., 2000a,b; Ross et al., 2000) provided support for this hypothesis. Consistent with other studies, we hypothesized that the two groups would not differ at baseline, but would differ on two-hour glucose concentrations.

2. Materials and methods

2.1. Subjects and procedure

Newly diagnosed, antipsychotic-naïve patients with non-affective psychosis were assessed at the time of their first contact with psychiatric services. The patients met criteria for schizophrenia, schizophreniform disorder, brief psychotic disorder, delusional disorder, or psychotic disorder not otherwise specified. Subjects with schizoaffective disorder were not included. The patients had a maximum cumulative lifetime exposure to antipsychotics of one week, and no antipsychotic use in the 30 days prior to study entry. Exclusion criteria for the control subjects included a history of a psychotic disorder or major depression, or a current diagnosis of adjustment disorder.

The setting was an academic medical center in Barcelona that provides health services for residents of the surrounding catchment area as part of the Spanish national health care system. The catchment area is a relatively homogeneous, middle class/upper middle class neighborhood in the middle of Barcelona. Spain also permits private care outside of the assigned catchment area. However, the hospital is also a regional referral center for psychosis, and in a survey of admissions to the emergency department of a large general hospital in an adjoining catchment area, there were no patients with psychosis from the catchment area.

Control subjects were recruited using advertisements, and were matched to the psychosis subjects on BMI, age, gender, ethnicity, socioeconomic status (SES), and smoking habit (average number of cigarettes per day). They did not have a lifetime diagnosis of schizophrenia or major depressive disorder, or a current diagnosis of adjustment disorder, and had not previously received an antipsychotic or antidepressant medication.

All subjects were interviewed using the Spanish translation of the Structured Clinical Interview for DSM-IV Axis I Disorders, clinician version (SCID-I). They were also administered the

Dartmouth Assessment of Lifestyle Inventory (Rosenberg et al., 1998) to quantify substance abuse. SES was assessed using the Hollingshead–Redlich scale (Hollingshead and Redlich, 1958).

Additional inclusion and exclusion criteria for all subjects were: 1) age from 18 to 64 years, 2) no history of diabetes or other serious medical or neurological condition associated with glucose intolerance or insulin resistance (e.g. Cushing's disease), 3) not taking a medication associated with insulin resistance (hydrochlorothiazide, furosemide, ethacrynic acid, metolazone, chlorthalidone, beta blockers, glucocorticoids, phenytoin, nicotinic acid, cyclosporine, pentamidine, or narcotics), and 4) no history of cocaine use in the previous 30 days.

All subjects underwent a two-hour, two-sample, 75 g oral glucose tolerance test between 8 and 9 AM after an overnight fast. Cortisol blood levels were also recorded at baseline. BMI was calculated using the formula [weight (kg)/height (m)2].

All subjects gave informed consent for participation in the study, which was conducted under the supervision of the institutional review boards of the Hospital Clinic of Barcelona, the University of Maryland Baltimore, and the Medical College of Georgia.

2.2. Deficit/nondeficit categorization

To make the deficit/nondeficit categorization, we used the PANSS to implement the Proxy for the Deficit Syndrome (PDS; Chemerinski et al., 2006; Dickerson et al., 2006; Kirkpatrick et al., 1993, 1996a,b,c, 1998, 2000a,b, 2001, 2002a,b; Messias et al., 2003, 2004). The validity of the PDS is supported by demonstration of deficit/nondeficit relationships that replicate those found in other populations. The PDS has previously been used in a newly diagnosed sample (Kirkpatrick et al., 1996c); in that study, the deficit/nondeficit categorizations that were made were shown to be highly stable over the first two years of illness.

Consistent with previous usage (Chemerinski et al., 2006; Dickerson et al., 2006; Kirkpatrick et al., 1993, 1996a,b,c, 1998, 2000a, 2001, 2002a,b; Messias et al., 2003, 2004), our PDS categorizations had three steps. In the first step, patients (*N*=56) were assigned a PDS score consisting of PANSS item scores; the PANSS ratings were completed on the day of the GTT, before any of the glucose measures were available to the investigators. A continuous PDS score was defined by PANSS item scores: PDS=blunted affect+lack of spontaneity and flow of conversation−(hostility+guilt+anxiety+depressive mood). This score quantified the combination of prominent negative symptoms and a lack of distress that is characteristic of deficit compared to nondeficit patients (Kirkpatrick et al., 1993, 1994), with high scores reflecting deficit-like features (high negative symptom scores and an absence of dysphoria), and low scores reflecting their absence. In the second step, patients with high PDS scores were assigned to the putative deficit group (*N*=23), while the other patients were designated nondeficit (*N*=33). Although in some previous studies an ambiguous middle group was not categorized and was not included in analyses, the results of the third, validation step (see below) showed that doing so was not necessary in this sample. The distribution of scores also resulted in a higher percentage of patients assigned to the deficit group than usual, but as noted, the validation results were reassuring in this regard.

In the third step, the validity of the categorization was tested by comparing the features of the two groups to those found in deficit and nondeficit groups in other studies, including especially studies based on administration of the Schedule for the Deficit Syndrome (SDS), which is the standard for diagnosis of these two groups (Kirkpatrick et al., 1989). A good categorization would yield a deficit group that, in addition to high negative symptoms and an absence of dysphoria (present in that group by definition, because of use of the PDS), would not have a

greater length of illness or more severe psychotic symptoms. The sum of the delusions and hallucinatory behavior items on the PANSS was analyzed separately from the conceptual disorganization item (Kirkpatrick and Ryan, 2000).

The deficit and nondeficit groups differed significantly on the smoking measure. In addition, although the average BMI of the two groups was not significantly different (p=.39), a better match for that variable was also desirable. As a consequence, and because of missing data for socioeconomic status, we dropped 10 subjects from the nondeficit group so that that group was better matched to the deficit group with regard to smoking and BMI, leaving 23 putative deficit subjects and 23 nondeficit subjects. Control subjects were also dropped—again, blind to glucose measures—to assure a good match of both patient groups to the control group on BMI, age, gender, ethnicity, SES, and smoking habit (average number of cigarettes per day). There were 59 control subjects included.

The principal outcome variable was two-hour glucose concentration, which is more sensitive to abnormalities in glucose tolerance than are fasting measures. Statistical tests were performed using version 14.0 for Windows of SPSS (Statistical Package for Social Sciences). We also conducted a multiple regression with the deficit and nondeficit groups with less desirable matching in which deficit/nondeficit categorization, smoking, SES, and BMI were the independent variables, and two-hour glucose concentration was the dependent variable.

Data describing the three matched groups are presented in Table 1.

3. Results

By definition, the deficit group had more severe negative symptoms but less dysphoria. However, the deficit and nondeficit groups were also very similar with regard to age, gender composition, duration of untreated psychosis, smoking, BMI, the severity of hallucinations +delusions or disorganization (as measured by PANSS items), SES, aerobic conditioning (as measured by resting heart rate), and ethnicity. Both groups were also similar to the control group with respect to these variables (see Table 1). None of the patients were receiving antidepressant or mood-stabilizing drugs.

The physiological data are presented in Table 2. All three groups were very similar with regard to baseline glucose concentration: the respective means (SD) were 83.5 (8.9), 84.1 (14.6), and 83.8 (7.2; F=.017; df=2, 108; p=.98). Nor was there a difference in hemoglobin A1C or fasting insulin concentrations (F=1.57; df=2, 105; p=.21].

However, as hypothesized, there was a significant difference among the groups in glucose concentration at two hours; the respective means (SD) for the deficit, nondeficit, and control groups were 100.2 (23.1), 121.6 (42.0), and 83.8 (21.9) (F=.017; df=2, 108; p<.001). Post hoc analyses showed that the deficit and nondeficit groups differed significantly from each other (p=.009, using LSD), and both differed significantly from the control subjects (p=.014 for deficit, and p<.001 for nondeficit). The difference between the nondeficit group and the other two groups was not due to one or two outliers; the percentage of subjects with impaired glucose tolerance (2HG concentrations ≥140 and <200 mg/dl) or diabetes (2HG≥200 mg/dl; Nathan et al., 2007) were 8%, 22%, and 3% in the deficit, nondeficit, and control groups, respectively. Use of nonparametric statistical tests led to the same pattern of results for 2HG, providing further confirmation that outliers were not the cause of the group differences.

Cortisol differed significantly among the three groups in an analysis of variance; the means for the deficit, nondeficit, and controls groups were 18.7 (5.6), 17.9 (5.2), and 21.2 (5.9), respectively (p<04). In a post hoc analysis, there was a significant difference between the nondeficit and control groups only. However, the importance of this difference was doubtful,

as in the three groups combined (deficit, nondeficit, and control subjects), in a multiple regression analysis that included age, gender, BMI, smoking, SES, and cortisol as predictor variables, and two-hour glucose concentration as the dependent variable, cortisol was not significantly related to glucose concentration (data not shown). In a simple bivariate analysis that included all of the subjects, two-hour glucose concentration and cortisol were not significantly correlated (p=.47). In addition, when the DALI score for alcohol, or the DALI score for other drug abuse, was included, deficit/nondeficit categorization remained a significant predictor of two-hour glucose concentration.

4. Discussion

In this study, newly diagnosed, antipsychotic-naïve patients with nonaffective psychosis and features of deficit schizophrenia were found to differ from other patients without deficit features on the GTT. The nondeficit group had significantly higher two-hour glucose concentration than did the deficit group, and both the deficit and nondeficit groups had higher two-hour glucose concentrations than did matched control subjects. These findings could not be attributed to confounding by age, gender, ethnicity, duration or severity of psychosis, antipsychotic use (as the subjects were antipsychotic-naïve), antidepressant or mood-stabilizing drugs, socioeconomic status of the family of origin, aerobic conditioning, body mass index, smoking, or blood cortisol concentration.

We used the PDS rather than the Schedule for the Deficit Syndrome (Kirkpatrick et al., 1989), which is the standard method for making the deficit/nondeficit categorization. The general validity of the PDS approach has been demonstrated in a number of other studies, in which patients categorized using the PDS had a number of correlates found in groups diagnosed using the Schedule for the Deficit Syndrome (Chemerinski et al., 2006; Dickerson et al., 2006; Kirkpatrick et al., 1993, 1996a,b,c, 1998, 2000a,b, 2001, 2002a,b; Messias et al., 2004). In the present study, we further validated the categorization by showing that the deficit group had more severe negative symptoms (Kirkpatrick et al., 1989) and less dysphoria (Kirkpatrick et al., 1993, 1994), but did not have greater psychotic symptoms. We have previously applied the PDS to another newly diagnosed sample (Kirkpatrick et al., 1996c); the validity of this approach in such a population was supported by demonstration of deficit/nondeficit relationships that replicate those found in other populations, and by the high stability of the deficit/nondeficit categorizations over the first two years of illness. To the extent that there are miscategorizations with the PDS, compared to categorizations made using the SDS, these should have biased our study toward a false-negative result, rather than to false-positive. For this reason, the size of the deficit/nondeficit difference we report here may be an underestimate. Replication, ideally using the SDS, would be desirable.

We had previously hypothesized that deficit schizophrenia was a separate disease within the syndrome of schizophrenia, based on studies that had shown that deficit and nondeficit schizophrenia differed with regard to signs and symptoms, risk factors, course of illness, biological correlates, and treatment response (Kirkpatrick et al., 2001). The alternative interpretation of the many deficit/nondeficit differences is that the deficit group simply has a more severe form of the same etiopathophysiology found in the nondeficit group. The greater severity interpretation was based on poorer function and outcome, poorer treatment response, and poorer cognitive function, as well as the presence of two forms of serious pathophysiology (positive psychotic symptoms and primary negative symptoms) in the deficit group, compared to one (psychotic symptoms) in the nondeficit group. In our review, it was noted that some studies were not consistent with the greater severity interpretation (Kirkpatrick et al., 2001). Since the time of that review, other studies have supported the separate disease hypothesis: Mucci et al. (2007) found a double dissociation in evoked potential variables; and more normal

regional brain volume has been found in deficit compared to nondeficit patients by separate groups (Gur et al., 1994; Quarantelli et al., 2002; Galderisi et al., 2008).

Our present finding is also not consistent with an interpretation that the deficit group has a more severe form of the same impairment—abnormal glucose metabolism—that is found in the nondeficit group. Moreover, these findings demonstrate that deficit/nondeficit differences extend beyond psychopathology or measures of mental function, brain pharmacology, or brain structure.

These findings also suggest other testable hypotheses about deficit/nondeficit differences in pulse pressure and telomere content, which we have found to be abnormal in newly diagnosed, antipsychotic-naïve patients with nonaffective psychosis (Fernandez-Egea et al., submitted). In addition, in future research on diabetes in the families of patients with schizophrenia (Fernandez-Egea et al., 2008a,b), it may be useful to separate the probands into deficit and nondeficit groups.

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Table 1

Subject characteristics

	Deficit (*N*=23)	**Nondeficit** (*N*=23)	**Control** (*N*=59)	***p*** **value**
Age	28.8 (9.1)	29.2 (10.2)	28.9 (7.2)	.99
% male	74	70	71	.95
BMI (SD)	23.4 (2.5)	23.2 (4.9)	23.9 (3.1)	.67
Cigarettes/day[a]	5.2 (7.0)	7.9 (8.6)	6.6 (8.1)	.52
SES[b]	36.7 (16.3)	39.8 (16.4)	41.5 (14.6)	.49
PANSS item scores:				
Hallucinations+delusions:	9.0 (2.7)	8.8 (2.3)		.25
Disorganization	4.1 (1.5)	3.6 (1.6)		.60

Values are mean (SD), except for % male.

P values are from ANOVA, except for % male (chi-square).

[a]Percentage of smokers for the three groups were 48%, 65%, and 53% (p=.46).

[b]Because of missing data, respective *N*'s for this variable are 16, 18, and 53.

Table 2

Metabolic measures in deficit, nondeficit, and control subjects

	Deficit (*N*=23)	Nondeficit (*N*=23)	Control (*N*=59)	*p* value
Two-hour glucose	100.2 (23.1)	123.7 (42.2)	85.0 (21.6)	<.001
Fasting glucose	83.5 (8.9)	83.0 (15.0)	83.8 (7.3)	.96
Hemoglobin A1C	4.4 (0.4)	4.4 (0.4)	4.4 (0.3)	.66
Fasting insulin	9.2 (3.4)	11.9 (10.0)	9.6 (3.6)	.19
Heart rate [a]	75.2 (11.3)	78.8 (10.7)	73.6 (12.6)	.24
Cortisol	18.7 (5.6)	18.8 (4.4)	21.2 (5.9)	.09

Values are mean (SD), except for % male.

[a] Because of missing data, respective *N*'s for this variable are 19, 21, and 59.