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Metabolic profile of antipsychotic-naive individuals with non-affective psychosis

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Background
Some studies suggest individuals with schizophrenia have an increased risk of diabetes prior to antipsychotic use. Small sample sizes and the potential for confounding by hypercortisolaemia have decreased confidence in those results.

Aims
To examine diabetes-related factors in newly diagnosed, antipsychotic-naive people with non-affective psychosis.

Method
Participants with psychosis (the psychosis group; $n = 50$) and matched controls (the control group; $n = 50$) were given a 2 h oral glucose tolerance test. Fasting concentrations were also determined for adiponectin, interleukin-6 and C-reactive protein.

Results
Compared with the control group, the psychosis group had significant increases in 2 h glucose and interleukin-6 concentrations, and in the prevalence of abnormal glucose tolerance (16% of psychosis group *v.* 0% of control group). Adiponectin and C-reactive protein concentrations did not differ significantly between the two groups. These findings could not be attributed to differences in cortisol concentrations, smoking, gender, neighbourhood of residence, body mass index, aerobic conditioning, ethnicity, socioeconomic status or age.

Conclusions
Individuals with non-affective psychosis appear to have an increased prevalence of abnormal glucose tolerance prior to antipsychotic treatment, as well as abnormalities in a related inflammatory molecule. These underlying problems may contribute to the metabolic side-effects of antipsychotic medications.

Declaration of interest
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Schizophrenia is associated with a marked increase in mortality.[1] An increased suicide rate, poor healthcare, poor health habits and medication side-effects all contribute to this problem. Cardiovascular disease accounts for the greatest number of early deaths.[2] Consistent with this picture, cardiovascular risk factors such as type 2 diabetes, dyslipidaemia, hypertension, smoking and obesity have a much higher prevalence in people with schizophrenia than in the general population.[3,4]

In recent years, the metabolic side-effects of antipsychotic medications have received a great deal of attention, as they increase the risk of diabetes, and perhaps hyperlipidaemia as well.[5] These problems in turn increase the mortality rate among people who take antipsychotic medications. However, individuals with schizophrenia may have an increased risk of diabetes independently of antipsychotic medications. Studies that antedate the use of modern antipsychotics found glucose abnormalities had an increased prevalence in people with schizophrenia,[6] although poor matching to controls and lack of clear diagnostic criteria weakened those studies. More recent studies of antipsychotic-naive individuals with non-affective psychosis also showed a higher prevalence of diabetes or impaired glucose tolerance (glucose blood levels $\geqslant 7.8$ mmol/l (140 mg/dl) 2 h after ingesting 75 g of glucose) in a glucose tolerance test. These studies were limited by a small sample size;[7] a relative hypercortisolaemia in the individuals with psychosis, which may contribute to glucose intolerance;[8] or a lack of matching for the potentially confounding factors of smoking and body mass index (BMI).[9] A study with a larger sample size[10] did not find a difference in glucose metabolism indices between participants with psychosis and controls, but the groups in that study were not well matched for age, smoking or BMI; moreover, in the same study, only fasting glucose values were assessed, rather than the results of a glucose tolerance test, which is more sensitive to glucose abnormalities.[11]

Given the limitations of the previous studies, the evidence is not conclusive that people with schizophrenia have an increased risk of diabetes independently of antipsychotic use. In addition, it is not known whether other abnormalities that are associated with diabetes are also present. These include increased inflammatory markers[12] and abnormalities in hormones associated with glucose metabolism, fat metabolism and inflammation.[13]

We hypothesised that antipsychotic-naive people with non-affective psychosis would have an increase in the prevalence of impaired glucose tolerance or diabetes when newly diagnosed, as well as abnormalities in other markers associated with an increased risk of diabetes: increases in interleukin-6 and C-reactive protein, and a decrease in adiponectin. We compared individuals with non-affective psychosis – that is, schizophrenia and related disorders – to healthy controls, as these disorders share clinical and genetic factors with schizophrenia, and most newly diagnosed individuals with these disorders receive a diagnosis of schizophrenia within the first year after first clinical contact.[14]

Method

Participants

People with psychosis (the psychosis group) were recruited at the time of their first clinical contact for psychotic symptoms at a general academic hospital (the Hospital Clinic of Barcelona). As part of the Spanish national health system, the hospital offers psychiatric services for all who live in the surrounding catchment area, Esquerra Eixample, in the city of Barcelona. Esquerra Eixample is a relatively homogeneous middle/upper-middle class neighbourhood in the centre of the city. Although it is also possible to seek private care outside of the assigned catchment area, the Hospital Clinic is a regional referral center for psychosis, and in a survey of 2968 admissions to the emergency department of a large general hospital in an adjoining catchment area, there were no individuals with psychosis from Esquerra Eixample.

The psychosis group had a maximum cumulative (lifetime) antipsychotic exposure of 1 week, and no antipsychotic use in the 30 days prior to the study. Participants with psychosis were allowed to receive anti-anxiety medication (lorazepam) the night before blood was drawn, to a maximum of 3 mg, but not on the day of assessment.

The healthy control group (the control group) were recruited using advertisements. We attempted to match the control group to the psychosis group on BMI, age, gender, smoking habit (average number of cigarettes per day), and residence in the catchment area (yes/no) of the Hospital Clinic. All of the participants were White residents of Spain except for one Asian and one North African person in each of the groups. The control group had no current or prior diagnosis of any Axis I DSM–IV[15] psychiatric disorder, after being assessed with the structured clinical interview for Axis I DSM–IV psychiatric disorders (SCID–I).[16]

Additional inclusion and exclusion criteria for all participants were: age from 18 to 64 years; no history of diabetes or other serious medical or neurological condition associated with glucose intolerance or insulin resistance (e.g. Cushing's disease); not taking a medication associated with insulin resistance (hydrochlorothiazide, furosemide, ethacrynic acid (available in the USA), metolazone, chlortalidone, beta blockers, glucocorticoids, phenytoin, nicotinic acid, ciclosporine, pentamidine or narcotics); no history of cocaine use in the previous 30 days; and have not previously received an antipsychotic or antidepressant medication. Additional exclusion criteria for the control group were no lifetime diagnosis of schizophrenia or major depressive disorder and no current diagnosis of adjustment disorder. All participants gave informed consent for participation in the study, which was conducted under the supervision of the institutional review boards of the authors' institutions.

Masked to glucose measures, individuals from the two groups that had been recruited were chosen in such a way to assure good matching as a group on gender, age, BMI and smoking habit, and to have an equal number of people in each group. This entailed omitting 6 people from the psychosis group, primarily because of a lower BMI, as well as 22 people in the control group, for purposes of matching.

A secondary, confirmatory analysis was also conducted in which all of the participants who had been recruited were included, and the matching variables were used as covariates.

Metabolic and psychiatric assessment

All participants were given a 2 h, 75 g oral glucose tolerance test, which began between 08.00 and 09.00 after an overnight fast. Fasting insulin, glycosylated haemoglobin (HbA_{1c}), C-reactive protein, interleukin-6, adiponectin, and cortisol blood concentrations were also recorded. Adiponectin was recorded for 38 participants in the psychosis group and 48 in the control group, as it was included after the study began. Height, weight, and waist and hip circumference, when wearing underwear and without shoes, were recorded between the baseline and two blood samples.

Serum insulin concentrations were measured in duplicate by monoclonal immunoradiometric assay (Medgenix Diagnostics, Fleunes, Belgium). No cross-reaction with proinsulin was detected. Glycosylated haemoglobin (HbA_{1c}) was determined by high-performance liquid chromatography (HA 8121, Menarini Diagnostici, Firenze, Italy; normal range 3.4–5.5%). Cortisol was measured using a radioimmunoassay (Immuchem, Ivoz-Ramet, Belgium). Body mass index was calculated using the formula (weight (kg)/height (m^2)). Homoeostatic model assessments (HOMA) of steady state beta-cell function, insulin sensitivity and insulin resistance were calculated as percentages of a normal reference population of young people without diabetes. The HOMA calculator version 2.2 (www.dtu.ox.ac.uk) was used to calculate the HOMA indices.

Glucose tolerance was categorised according to American Diabetes Association guidelines:

(a) normal tolerance was defined by a fasting plasma glucose concentration at baseline <5.6 mmol/l (100 mg/dl) and a 2 h concentration <7.8 mmol/l (140 mg/dl);

(b) impaired fasting glucose was defined as glucose levels of 5.6–7.0 mmol/l (100–125 mg/dl) in fasting individuals;

(c) impaired glucose tolerance was defined as 2 h glucose levels of 7.8–11.1 mmol/l (140–199 mg/dl) on the 75 g oral glucose tolerance test; and

(d) a diagnosis of diabetes was defined by a fasting plasma glucose $\geqslant 7.0$ mmol/l (126 mg/dl) or a 2 h glucose equal or greater to 11.1 mmol/l (200 mg/dl).

All participants were interviewed using the Spanish translation of the Structured Clinical Interview for DSM–IV Axis I disorders, clinician version (SCID–I).[16] They were also administered the Dartmouth Assessment of Lifestyle Inventory,[17] which quantifies substance misuse. Socioeconomic status of the family of origin was assessed with the Hollingshead–Rendlich scale.[18]

Statistical analysis

The two matched groups were compared using the non-paired Student's *t*-test, or the χ^2 test for comparisons of proportions. Significance was defined as $P<0.05$ for all statistical tests, and these were performed using SPSS version 12.0 for Windows.

Two multiple regression analyses were performed. In the first, the two matched groups (n=50 in each group) were included, whereas in the second analysis, all of the individuals who had been recruited (i.e. not only those in the two matched groups; n=56 people with psychosis and n=72 controls) were included. The dependent variable was glucose concentration at 2 h; the independent variables were diagnosis (individuals with psychosis *v.* controls as a 0/1 variable), age, gender, BMI, smoking (average number of cigarettes per day), residence in the catchment area (as a 0/1 variable), cortisol blood levels and socioeconomic status.

As interleukin-6 values were not normally distributed, we evaluated this variable as a category, with high or abnormal values defined as interleukin-6 >5 μ/ml and low or normal values <5 μ/ml.[19]

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Results

The psychosis group ($n=50$) included 35 people with schizophrenia, 8 with schizophreniform disorder, 4 with brief psychotic disorder, 2 with delusional disorder and 1 with psychosis not otherwise specified; there were 50 people in the control group. The two groups were very similar with regard to demographics, BMI, smoking (which in our sample population was correlated with measures of misuse of other drugs, including alcohol; data not shown) and percentage living in the catchment area (Table 1). Socioeconomic status differed between the two groups, being lower for the psychosis group (mean 37.4 (s.d. = 15.5) *v.* mean 44.1 (s.d. = 14.2); $P=0.042$).

Glucose metabolism

Fasting measures of glucose metabolism were very similar for the two groups. Baseline glucose concentration were 4.55 mmol/l (s.d. = 0.66) (83 mg/dl (s.d. = 12.1)) for the psychosis group and 4.65 mmol/l (s.d. = 0.38) (84 mg/dl (s.d. = 6.9)) for the control group ($P=0.313$). One individual with psychosis (fasting plasma glucose = 7.48 mmol/l (136 mg/dl)) and one person in the control group (fasting plasma glucose = 5.55 mmol/l (101 mg/dl)) did not have a normal fasting glucose. The values for fasting insulin were 10.3 mU/l (s.d. = 7.3) *v.* 9.6 mU/l (s.d. = 3.8) ($P=0.576$), and the values for HbA_{1c} were 4.4% (s.d. = 0.38) *v.* 4.5% (s.d. = 0.29) ($P=0.197$). The homoeostasis model measures of insulin sensitivity, insulin release and insulin resistance were also not significantly different ($P>0.26$ for all three variables; Table 2).

In contrast, 2 h glucose differed significantly ($P<0.001$) between the two groups: the psychosis group had a mean concentration of 6.10 mmol/l (s.d. = 1.93) (111 mg/dl (s.d. = 35.2)) whereas the control group had a mean of 4.49 mmol/l (s.d. = 1.06) (82 mg/dl (s.d. = 19.3)). Eight people with psychosis had impaired glucose tolerance ($n=7$) or type 2 diabetes ($n=1$), whereas none of the control group did (combined percentages, 16% *v.* 0% for the psychosis and control groups, respectively; $P=0.003$).

In a multiple regression analysis, with 2 h glucose as the dependent variable and age, gender, smoking habit (average number of cigarettes per day), diagnosis, BMI, cortisol and socioeconomic status as the independent variables, diagnosis was significantly associated with 2 h glucose concentration (Table 3). Body mass index, and waist and hip ratio were correlated ($r=0.287$, $P=0.004$), and substituting waist:hip ratio for BMI gave the same pattern of results.

The multiple regression analysis that included the whole sample showed similar results: diagnosis ($P<0.0001$) remained significant, as did smoking ($P=0.005$), BMI ($P=0.004$) and catchment area ($P=0.008$); however, cortisol concentration, age, gender and socioeconomic status were not significant.

Inflammatory markers

Significantly more people in the psychosis group than in the control group had an abnormal interleukin-6 (23% *v.* 8%;

Table 1 Characteristics of the psychosis and control groups

	Psychosis group (*n*=50)	Control group (*n*=50)	Statistics[a]
Age, years: mean (s.d.)	29.4 (8.8)	28.8 (7.7)	t=0.391
Male:female	35:15	35:15	χ^2=1.000
Body mass index, mean (s.d.)	22.9 (3.9)	23.9 (3.1)	t=–1.483
Cigarettes per day, *n*: mean (s.d.)	8.5 (9.6)	7.2 (8.6)	t=0.716
Residing in hospital catchment area, *n* (%)	35 (70.0)	32 (64.0)	χ^2=0.407
Waist:hip ratio, mean (s.d.)	0.87 (0.08)	0.84 (0.06)	t=1.768
Heart rate, mean (s.d.)	77.4 (10.9)	75.1 (11.7)	t=1.011

a. All variables $P>0.10$.

Table 2 Metabolic measures in newly diagnosed, antipsychotic-naïve individuals with non-affective psychosis and the control group

	Psychosis group (*n*=50)	Control group (*n*=50)	Statistics	*P*
Fasting glucose				
mmol/l, mean (s.d.)	4.55 (0.66)	4.65 (0.38)	t=–1.015	0.313
mg/dl, mean (s.d.)	83 (12.1)	84 (6.9)		
Fasting insulin, mU/l: mean (s.d.)	10.3 (7.3)	9.6 (3.8)	t=0.644	0.576
% glycosylated haemoglobin, mean (s.d.)	4.4 (0.38)	4.5 (0.29)	t=–1.298	0.197
HOMA-%B, mean (s.d.)	145.3 (44.5)	136.5 (32.1)	t=1.014	0.262
HOMA-%S, mean (s.d.)	88.9 (45.0)	81.3 (28.7)	t=1.014	0.313
Insulin resistance, mean (s.d.)	1.48 (1.08)	1.40 (0.56)	t=0.509	0.612
2 h glucose				
mmol/l, mean (s.d.)	6.10 (1.93)	4.49 (1.06)	t=5.148	<0.001
mg/dl, mean (s.d.)	111 (35.2)	82 (19.3)		
Impaired glucose tolerance or diabetes, %	16	0	χ^2=8.696	0.003
Cortisol, mg/dl: mean (s.d.)	19.0 (4.98)	20.2 (4.57)	t=–1.269	0.208
Interleukin-6, g/ml: mean (s.d.)	3.63 (6.91)	1.02 (2.10)	t=2.548	0.012
C-reactive protein, mg/l: mean (s.d.)	0.21 (0.28)	0.20 (0.18)	t=0.209	0.835
Adiponectin,[a] mg/dl: mean (s.d.)	12.1 (5.9)	12.9 (5.6)	t=–0.627	0.533

HOMA-%B, homoeostatic model assessments of steady state beta-cell function; HOMA-%S, homoeostatic model assessments of insulin sensitivity.
a. Adiponectin levels were recorded for 39 people in the psychosis group and 48 in the control group.

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Table 3 Association between non-affective psychosis and increased 2 h glucose concentrations: confirmatory multiple regression

	Standardised coefficients	*t*-test	*P*
Diagnosis (psychosis/control)	−0.540	−5.799	<0.001
Average number cigarettes per day	−0.240	−2.601	0.011
Age	0.118	1.228	0.223
Gender	0.011	0.116	0.908
Body mass index	0.266	2.600	0.011
Cortisol concentration	0.087	0.950	0.345
Socioeconomic status	−0.079	−0.865	0.390
Catchment area	−0.210	−2.320	0.023

$P = 0.034$); mean interleukin-6 blood levels were 3.63 (s.d. = 6.91) *v.* 1.02 (s.d. = 2.10) for the psychosis and control groups respectively. C-reactive protein was not significantly different between the groups (0.21 (s.d. = 0.28) *v.* 0.20 (s.d. = 0.18); $P = 0.835$). Cortisol blood levels were slightly lower in the psychosis group (19.0 (s.d. = 4.98) *v.* 20.2 (s.d. = 4.57)). Similar results were obtained using the whole sample (data not shown).

Adiponectin

Adiponectin did not differ significantly between the two groups; the concentrations were 12.1 mg/dl (s.d. = 5.9) in the psychosis group and 12.9 mg/dl (s.d. = 5.6) in the control group ($P = 0.53$). Multiple regression analysis of adiponectin, using gender, age, BMI, diagnosis, smoking habits and socioeconomic status failed to find statistically significant group differences (data not shown).

Discussion

We found that newly diagnosed antipsychotic-naive people with schizophrenia and related disorders had a higher prevalence of abnormal glucose tolerance or diabetes, and higher interleukin-6 blood concentrations, than did matched controls. These differences could not be attributed to confounding by BMI, gender, age, psychotropic medications, cortisol concentration, socioeconomic status, smoking, aerobic conditioning (as measured by resting heart rate) or drugs that affect glucose tolerance. In our primary analysis, the study sample was chosen from a larger data-set and some people were excluded; however, a multiple regression analysis of the entire sample showed a similar pattern of results.

Limitations

A limitation of this study was that we did not perform a formal evaluation of the diet of the participants, which influences both glucose and adiponectin levels. However, dietary differences seem unlikely to explain the higher glucose levels in the psychosis group, as they were slightly thinner than those in the control group, and glucose intolerance tends to increase with BMI. Moreover, the psychosis group did not appear to have a recent and substantial decrease in weight, an important cause of an increase in adiponectin, as adiponectin blood levels did not differ between the two groups. In addition, all of the participants came from Barcelona, and to the extent that diet was related to socioeconomic status, covarying for that variable did not change the pattern of our results. Socioeconomic status was lower in the psychosis group, but it is unlikely that this variable confounded these differences, as diagnosis was still significantly related to glucose concentration when socioeconomic status was included in the confirmatory multiple regression analysis.

Glucose abnormalities

Other studies have also found an increase in 2 h glucose concentrations in a glucose tolerance test and/or an increase in the prevalence of glucose intolerance defined categorically, in newly diagnosed, antipsychotic-naive people with schizophrenia.[7–9] In some studies, an abnormality was found in the glucose tolerance test[9] but none was found in either fasting glucose or HbA_{1C};[9,10] there were limitations in these studies with regard to matching or hypercortisolaemia, as noted above. Studies in other populations have shown that the glucose tolerance test, which entails a physiological challenge, is a more sensitive measure of abnormalities in glucose metabolism.[11]

Inflammatory markers and adiponectin

Our finding of an increase in interleukin-6, which is associated with diabetes and risk of the subsequent development of diabetes, supports the conclusion that prior to antipsychotic treatment, people with schizophrenia have an increased risk of diabetes.[20] However, the other marker of inflammation that we examined, C-reactive protein, was not significantly greater in the psychosis group than in the control group. A recent meta-analysis by Potvin *et al*[21] that compared more than 2000 people with chronic schizophrenia and controls also found an increase in interleukin-6 without an increase in C-reactive protein. Studies in other populations have also found that interleukin-6 may be a more sensitive marker of the inflammation associated with diabetes than is C-reactive protein.[20]

We found no difference between the psychosis group and the control group in the concentration of adiponectin, which is also involved in glucose and fat metabolism.[13] Two other studies have also failed to find a difference in adiponectin between newly diagnosed, antipsychotic-naive individuals and controls,[8,10] although one preliminary study did find a difference.[7] A study with a larger sample size might find an increase in C-reactive protein and/or other inflammatory markers. It is not known whether baseline measures will predict the metabolic side-effects of antipsychotic medications, nor is it yet clear whether newly diagnosed, antipsychotic-naive people with non-affective psychosis have abnormalities in lipids, as is often found in people with diabetes.

Diabetes and schizophrenia

Should an association between schizophrenia and glucose intolerance be confirmed, this might occur because diabetes and schizophrenia share some common risk factors and/or genetics. An increase in inflammatory markers has been reported in both schizophrenia and diabetes.[20] Some studies have also found an increased prevalence of family history of type 2 diabetes among relatives of people with psychosis[10,22,23] and two recent studies also found abnormal glucose tolerance among the first-degree relatives of schizophrenia probands.[9,24] Birth and gestational

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problems also appear to be risk factors for both schizophrenia and diabetes, low birth weight being the most notable example.[25–28] Exposure to prenatal stress during the second or early third trimester of pregnancy appears to confer on the offspring an increased risk of developing schizophrenia later in life, a finding that is consistent with findings in animals.[29] Prenatal stress and abnormal early development have also become the focus of research in diabetes and other aspects of the metabolic syndrome.[27,30,31]

As a group, people with schizophrenia suffer premature death compared with the general population. No doubt, medication side-effects, an increased suicide rate, poor healthcare and poor health habits all make substantial contributions to this increased mortality. However, the existence of these factors does not exclude the possibility of a pre-existing vulnerability to glucose intolerance that is associated with a pro-inflammatory state. Our results and those of others[7–9,32] suggest that even prior to antipsychotic treatment, schizophrenia is associated with metabolic abnormalities. The interaction of these problems with antipsychotics merits investigation.

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