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Meta-analysis of glucose tolerance, insulin, and insulin resistance in antipsychotic-naïve patients with nonaffective psychosis

Anne Marie Greenhalgh [a], Leticia Gonzalez-Blanco [b,c], Clemente Garcia-Rizo [c,d,e], Emilio Fernandez-Egea [f,g], Brian Miller [h], Miguel Bernardo Arroyo [c,d,e], Brian Kirkpatrick [a,*]

[a] Department of Psychiatry & Behavioral Sciences, University of Nevada School of Medicine, Reno, NV, United States
[b] Department of Psychiatry, University of Oviedo, & Servicio de Salud del Principado de Asturias, Oviedo, Spain
[c] Centro de Investigación Biomédica en Red de Salud Mental (CIBERSAM), Spain
[d] Schizophrenia Program, Department of Psychiatry, Neuroscience Institute, Hospital Clinic, University of Barcelona, Barcelona, Spain
[e] Institut d'Investigacions Biomèdiques August Pi i Sunyer (IDIBAPS), Spain
[f] Department of Psychiatry, University of Cambridge, Cambridge, UK
[g] Cambridgeshire and Peterborough NHS Foundation Trust, Huntingdon, UK
[h] Department of Psychiatry and Health Behavior, Medical College of Georgia, Augusta University, Augusta, GA, United States

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ABSTRACT

Background: Some studies have suggested that antipsychotic-naïve patients with nonaffective psychosis (NAP) have glucose intolerance.
Aims: To conduct a systematic review and meta-analysis of fasting glucose (FG), two hour values in the oral glucose tolerance test (2HG), fasting insulin concentration (INS), and insulin resistance (IR).
Method: We identified possibly relevant studies, then selected studies, following usual guidelines, with two authors reviewing the manuscripts. We required studies to include subjects with nonaffective psychosis and control subjects.
Results: There were 911 patients and 870 control subjects in the analysis of FG; their average ages were respectively 28.7 and 29.5 years. Significant differences were found for all four variables, with effect size estimates ranging from 0.21 to 0.58.
Conclusions: As a group, at the time of first clinical contact for psychosis, people with NAP have a slight increase in FG, which most of them maintain in the normal range despite a small increase in IR by secreting additional INS. When faced with a physiological challenge such as a glucose tolerance test or antipsychotics, they are no longer able to maintain a normal glucose concentration.

1. Introduction

Most research on nonaffective psychosis (NAP) understandably focuses on brain function and biology, but people with this group of disorders have a number of physiological and anatomical abnormalities in the periphery as well (Kirkpatrick et al., 2014). These include increased systemic inflammation (Miller et al., 2011, 2014), low birth weight (Abel et al., 2010; Cannon et al., 2002), a low body mass index prior to antipsychotic use (Wahlbeck et al., 2001), and an increased prevalence of minor physical anomalies from head to toe (Weinberg et al., 2007; Xu et al., 2011).

Family studies have found an increased risk of type 2 diabetes or abnormal glucose in the first degree relatives of people with NAP (Fernandez-Egea et al., 2008a, 2008b; Mukherjee et al., 1989; Van Welie et al., 2013), suggesting that patients with psychosis may have an increased risk of diabetes that exists prior to exposure to antipsychotics, many of which increase the risk of diabetes (American Diabetes Association and American Psychiatric Association, 2004). Some studies of antipsychotic-naïve patients with NAP have also found increased fasting glucose (Ryan et al., 2003) or abnormal glucose tolerance on a glucose tolerance test (Fernandez-Egea et al., 2009), but the results have been inconsistent. Confirmation that the increased risk of diabetes in this group is present independently of antipsychotics would imply that glucose monitoring should not be confined to those who gain weight with these medications, or even confined to patients taking antipsychotics.

We performed a systematic review and a meta-analysis to assess glucose intolerance in people with NAP prior to antipsychotic use. We

* Corresponding author at: Department of Psychiatry and Behavioral Sciences, University of Nevada School of Medicine, 5190 Neil Road, Suite 215, Reno, NV 89502, United States.
E-mail address: bkirkpatrick2@aol.com (B. Kirkpatrick).

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assessed fasting glucose (FG), two hour values in the oral glucose tolerance test (2HG), fasting insulin (INS), and insulin resistance (IR).

2. Materials and methods

2.1. Search strategy

We followed PRISMA guidelines but we began our project before registering, so our study was not registered. A preliminary search was done for systematic reviews to avoid publishing a duplicate review. Studies were identified by systematic searches from 1950 to 2016 in Medline, PsycINFO and Web of Science in independent searches by two authors (AG and LGB). Search terms included: schizophrenia, psychosis, naïve, untreated, antipsychotic naïve, and antipsychotic free, fasting glucose, diabetes, glucose tolerance test, insulin or insulin resistance. The titles and abstracts were screened for eligibility by two reviewers (AG and either LGB or BK). The search covered articles through February 2016. The search was supplemented by reference lists from relevant review articles and the articles included in the study. These articles were examined by two of these same reviewers to determine which met the inclusion and exclusion criteria.

2.2. Inclusion/exclusion criteria

In order to include a study the following criteria had to be met: patients with NAP with maximum cumulative (lifetime) antipsychotic exposure of 1 week and no antipsychotic use in the 30 days prior to the study; a matched control group of subjects without psychosis; participants were at least 16 years of age; FG was measured, or a 2HG conducted, after an overnight fast; the paper was published in English; and the data had to be either in the article or accessible from the author upon request. We defined NAP to include schizophrenia, schizophreniform disorder, delusional disorder, brief psychosis, and psychotic disorder not otherwise specified. A diagnosis of schizoaffective disorder was an exclusion criterion, unless separate data for NAP only was available. We chose to study NAP rather than schizophrenia and not including schizoaffective disorder because of evidence from studies of newly diagnosed patients that there is substantial diagnostic stability within this group of disorders, with patients often shifting to a diagnosis of schizophrenia on ten-year follow-up (Bromet et al., 2011; Castro-Fornieles et al., 2011; Schwartz et al., 2000).

2.3. Data analysis

One author (AG) recorded the data from the studies, which was independently verified by a second (LGB). The statistical analyses were performed in the Stata 13.1 software program. Effect size (ES) estimates (Hedges' g) were calculated for the outcome variables concentration. Random effects, pooled ES estimates and 95% confidence intervals were calculated using the method of DerSimonian and Laird (1986); p-Values were considered statistically significant at the $p < 0.05$ level.

We examined heterogeneity in the ES estimates using chi-square (Cochran, 1950). We also performed sensitivity analyses of FG, INS, 2HG and IR by removing one study at a time and repeating the meta-analysis for each parameter to examine the impact on the ES estimate (Higgins and Green, 2011). Forest plots and funnel plots were examined for FG, INS, 2HG, and IR.

Meta-regression was conducted for the categorical variables of body mass index and smoking, that is, whether or not the groups were matched on these variables; FG, the variable with the most data, was the dependent variable. We also entered family history exclusions as a categorical variable in meta-regression, as in some studies the patient and control groups were matched on the presence/absence of a family history of diabetes. Meta-regression was also conducted for body mass index, using the effect estimate for these in each study as the independent variable and ES for FG as the dependent variable.

3. Results

Of the 334 publications originally found with the search strategy, 19 met the inclusion criteria and presented data on FG (Fig. 1). These nineteen studies (see Fig. 2 for references) had 911 patients with NAP and 870 control subjects; the age of the control subjects was 0.8 years greater than that of patients, which with the large sample sizes was statistically significant (respective ages (SD) for patients and control subjects were 28.7 (7.3) and 29.5 (6.0) years; $t = -2.63$, $p < 0.01$). There were 10 studies with data on INS (see Fig. 4 for references), 9 for IR (see Fig. 5 for references), and 4 for 2HG (see Fig. 3 for references).

Significant differences between patients and control subjects were found for all four variables, with ES estimates of 0.21 [95% CI 0.11, 0.31; $p < 0.001$; Fig. 2] for FG, 0.28 [95% CI 0.15, 0.42; $p < 0.001$; Fig. 3] for INS, 0.30 [95% CI 0.17, 0.44; $p < 0.001$; Fig. 4] for IR, and 0.58 [95% CI 0.38, 0.78; $p < 0.001$; Fig. 5] for 2HG.

Heterogeneity was significant with all studies included in the meta-analysis for FG [I-squared = 55.1%, $p = 0.002$]. After removal of the most divergent study (Zhang et al., 2015), the heterogeneity was no longer significant for FG [I-squared = 36.5%, $p = 0.062$] and the ES remained significant [ES = 0.16; $p = 0.002$]. Heterogeneity was also significant with all studies included in the meta-analysis for 2HG [I-squared = 83.2%, $p < 0.001$]. In a sensitivity analysis, heterogeneity remained significant after removal of each individual study.

Heterogeneity was significant with all studies included in the meta-analysis for INS [I-squared = 76.5%, $p < 0.001$]. After removal of the most divergent study (Arranz et al., 2004), heterogeneity was no longer significant [I-squared = 39.6%, $p = 0.103$] and the ES remained significant [ES = 0.46; $p < 0.001$].

Heterogeneity was significant with all studies included in the meta-analysis for IR [I-squared = 63.5%, $p = 0.005$]. After removal of the most divergent study (Arranz et al., 2004), the heterogeneity was no longer significant for INS [I-squared = 9.1%, $p = 0.359$] and the ES remained significant [ES = 0.44; $p < 0.001$].

In meta-regression, age was not a significant predictor of ES ($p < 0.5$). No other independent variable we examined (body mass index, cortisol, family history exclusions, and smoking) was a significant predictor of FG in meta-regression (data not shown). There did not appear to be a significant publication bias on funnel plots (Figs. 6-9 in supplementary materials).

4. Discussion

In a meta-analysis, we found significant differences between antipsychotic-naïve patients with NAP and control subjects in FG, INS, and IR. These ES estimates were small, ranging from 0.21 to 0.30. However, when given an oral glucose tolerance test, patients exhibited abnormal glucose tolerance with an ES of 0.58, which is a "medium" effect size. In meta-regression, age was not a significant predictor of ES although patients were on average 0.83 years younger than control subjects. As a consequence, the greater glucose-related abnormalities cannot be attributed to confounding by greater age in the patients. Body mass index, cortisol, family history exclusions, and smoking were also not significant predictors of ES in meta-regression. There did not appear to be a significant publication bias on funnel plots.

There are limitations to our analysis. The number of studies for IR and 2HG was small, nine and four, respectively, although the number of patients and that of control subjects were 525 and 406, and 237 and 189, respectively. Many of the studies also had limited matching. It would be desirable for any future studies to match on age, sex, body mass index or waist-hip ratio, smoking, and other substance use. The FG studies included patients of Western European, Indian, and East Asian ethnicity, suggesting that this is a generalizable effect, but the 2HG studies did not include examination of East Asian patients, raising the question of generalizability of this effect. Only one paper provided information on glucose for schizophrenia and other diagnoses within