Abnormal glycemic homeostasis at the onset of serious mental illnesses: a common pathway

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Abstract

OBJECTIVE—Patients with serious mental illnesses exhibit a reduced lifespan compared with the general population, a finding that can not solely rely on high suicide risk, low access to medical care and unhealthy lifestyle. The main causes of death are medical related pathologies such as type 2 diabetes mellitus and cardiovascular disease; however pharmacological treatment might play a role.

MATERIAL AND METHODS—We compared a two hour glucose load in naïve patients at the onset of a serious mental illness (N=102) (84 patients with a first episode of schizophrenia and related disorders, 6 with a first episode of bipolar I disorder and 12 with a first episode of major depression disorder) with another psychiatric diagnose, adjustment disorder (N=17) and matched controls (N=98).

RESULTS—Young patients with serious mental illness showed an increased two hour glucose load compared with adjustment disorder and the control group. Mean two hour glucose values

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[±Standard Deviation] were: for schizophrenia and related disorders 106.51 mg/dL [±32.0], for bipolar disorder 118.33 mg/dL [±34.3], for major depressive disorder 107.42 mg/dL [±34.5], for adjustment disorder 79.06 mg/dL[±24.4] and for the control group 82.11 mg/dL [±23.3] (p<0.001).

CONCLUSIONS—Our results reflect an abnormal metabolic pathway at the onset of the disease before any pharmacological treatment or other confounding factors might have taken place. Our results suggest a similar glycemic pathway in serious mental illnesses and the subsequent need of primary and secondary prevention strategies.

1. INTRODUCTION

Patients diagnosed with a serious mental illness (SMI) exhibit a reduced life expectancy compared with the general population (Druss et al., 2011). An increased suicide risk (Gomez-Duran et al., 2014), unhealthy lifestyle (Brown et al., 1999), low access to medical care or poor health care (Folsom et al., 2005) contribute to the excess risk. However the leading cause of morbidity and subsequent mortality is medical related pathologies (Nordentoft et al., 2013).

Most studies focus on a specific diagnosis of SMI (Laursen et al., 2013), while only few compare results taking SMI as a group (Druss et al., 2011; Laursen et al., 2007; Nordentoft et al., 2013). In those studies, patients with a diagnosis of schizophrenia had higher mortality risk ratios from natural causes (cancer, endocrine or cardiovascular diseases) than patients diagnosed with affective disorders (which suffered from higher risk ratios of unnatural deaths, such as suicide). Recent studies in North American cohorts reveal a pattern of increased disability and costs (Eaton et al., 2008) and reduced life expectancy (Druss et al., 2011) not only in SMI but also in the general mental health population.

Among the diverse associated pathologies increased in SMI, type 2 diabetes mellitus (T2DM) has historically been a subject of interest. Studies in the pre-antipsychotic era described an altered glycemic homeostasis in mental health patients (McIntyre et al., 2005). Research dates back as far as 1674, when the British physician Thomas Willis discovered (by tasting) that glycosuria was a sign of diabetes and proposed that this disease was caused by "sadness or long sorrow and other depressions"(Willis, 1971). In 1880, the British psychiatrist Henry Maudsley wrote that "diabetes is a disease that often shows itself in families where insanity prevails" (Maudsley, 1880). In his seminal study in 1919, Kooy evaluated psychiatric patients after regular meals, and using plasma glucose levels was able to detect hyperglycemia in melancholia and catatonia.

Pharmacological treatment confounded subsequent studies, as many psychotropic drugs alter biochemical parameters (Charatan and Bartlett, 1955) and increase weight (Allison and Casey, 2001), leading to a high prevalence of metabolic abnormalities (abdominal obesity,

blood pressure, lipid and glucose metabolism alterations). Later epidemiological studies reflected a high prevalence of T2DM in schizophrenia (Mitchell et al., 2013), bipolar disorder (Calkin et al., 2013) or major depressive disorder (Roy and Lloyd, 2012) although those results might have been confounded by treatment. However, research in treatment-naïve patients found metabolic abnormalities at the onset of mental disorder, in non-affective psychosis (Fernandez-Egea et al., 2009a; Ryan et al., 2003; Saddichha et al., 2008; Spelman et al., 2007) as well as bipolar (Garcia-Rizo et al., 2014b) or major depression disorder (Garcia-Rizo et al., 2013).

Besides these three major psychiatric illnesses, several other psychiatric diagnoses have been associated with medical pathologies and glycemic abnormalities. Anxiety disorders have received some attention although results have been contradictory (Herva et al., 2006; Hildrum et al., 2009). In a meta-analysis published in 2013 based on 6 studies, post traumatic stress disorder was associated with an increased prevalence of coronary heart disease and cardiovascular mortality (Edmondson et al., 2013). Nevertheless it is important to note that the age of those patients ranged from 36 to 52 years old and so the natural process of ageing might have increased the risk of developing T2DM. Another study reported an association between post traumatic stress disorder and patients who sought help for T2DM (Miller-Archie et al., 2014) even after co-varying by potential confounding factors, such as age and body mass index (BMI). However, in these groups as well, antidepressant or antipsychotic treatments might have confounded these associations. Another potentially confounding factor is stress, which is associated with increased inflammatory and cortisol responses (Carvalho et al., 2015). These are risk factors for glucose intolerance (Kempf et al., 2008).

In the current study, we tested the hypothesis that abnormal glycemic homeostasis is associated with serious mental illness prior to psychopharmacological treatment compared with controls. We also examined adjustment disorder, defined as the development of emotional or behavioral symptoms in response to an identifiable stressor(s) occurring within 3 months of the onset of the stressor(s). Examination of this disorder allowed us to consider the stress response as a confounding factor.

2. MATERIAL AND METHODS

2.1. Participants

Patients with a first episode of non-affective psychosis, major depressive disorder or adjustment disorder were recruited at the time of their first lifetime contact with psychiatric services in a general academic hospital (Hospital Clinic of Barcelona). The catchment area for the hospital, Example Esquerre, is a relatively homogeneous middle/upper middle class neighborhood in the center of Barcelona. 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. The major depression and adjustment disorder subjects were enrolled if they had never previously received antidepressant, antipsychotic or mood stabilizing pharmacological treatment. Patients 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 the blood sampling and the oral glucose tolerance test (oGTT). Healthy control subjects were recruited using

advertisements. All subjects come from a larger study of diabetes in neuropsychiatric disorders (Fernandez-Egea et al., 2009b) where additional inclusion and exclusion criteria are reported.

Two-hour glucose data has previously been published on 64 patients with psychosis (Kirkpatrick et al., 2012) so 20 additional subjects are now presented. We have published data on 15 patients with depression (Garcia-Rizo et al., 2013), and because of matching, now present data from 12 of those patients. We have previously published a statement of the percentage of 7 patients with bipolar disorder had impaired glucose tolerance (Garcia-Rizo et al., 2014); here we present two hour glucose values instead. We have not published data on adjustment disorder, so all of those patients are new to publication. As for control subjects 84 were described previously (Kirkpatrick et al., 2012).

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 and conducted in accordance with the Declaration of Helsinki. Seven patients in the non-affective psychosis group ended subsequently received a diagnosis of type I bipolar disorder, consistent with results in the literature (Salvatore et al., 2009), and were considered separately.

2.2 Metabolic and psychiatric assessments

All participants underwent an oGTT which began between 08.00 and 09.00 after an overnight fast. Participants had a fasting blood sample drawn, then were given a 75mg glucose solution. They rested for 120 minutes at which point a second blood sample was obtained for measurement of glucose, the two hour glucose load value (2HG). All participants were assessed with the structured clinical interview for Axis I DSM–IV psychiatric disorders (SCID–I; First and Spitzer, 1999).

The concept of SMI is by definition related with psychotic symptomatology (bipolar disorder, schizoaffective disorder or schizophrenia). However the chronicity and the disability related with major depression disorder, besides the specific characteristics associated with ageing or mortality; allow us to include the diagnosis in between SMI. Sometimes the definition is mixed in research articles so we do include the current paragraph to highlight the concept and the reasons for the inclusion. The US Department of Health and Human Sciences definition of SMI, "a long lasting and severe condition that seriously interferes with a person's ability to take part in major life activities", supports our concept.

Initially two hundred thirty three patients were included in the study. Eighty-eight had a diagnosis of first episode of non affective psychosis, seven of type I bipolar disorder, fifteen of major depressive disorder, nineteen of adjustment disorder, and one hundred four were healthy subjects.

In order to be able to match the samples and to focus on the typical ages of onset of psychosis and bipolar disorder, only patients aged between 18 and 40 years were included in our primary analysis. This sample (N=217) consisted 84 with a diagnosis of non-affective

psychosis, 6 with I bipolar disorder, 12 with major depressive disorder, 17 with adjustment disorder, and 98 matched control subjects. The non-affective psychosis group included 49 patients with paranoid schizophrenia, 1 with disorganized schizophrenia, 1 with catatonic schizophrenia, 5 with undifferentiated schizophrenia, 11 patients with brief psychotic disorder, 10 with schizophreniform disorder, 6 with psychotic disorder not otherwise specified and 1 with schizoaffective disorder.

2.3 Statistical Analysis

The matched groups by age, gender and BMI were compared using ANOVA test, or the chi-square test for comparisons of proportions. Significance was defined as $p < 0.05$ for all statistical tests, and these were performed using SPSS version 19.0 for Windows.

Two general linear model (GLM) analyses were performed. In the first, all the 233 subjects were included. In the second, 215 subjects were included (2 of the 217 subjects in the matched group were missing the BMI value): 82 patients diagnosed with first episode psychosis, 6 patients diagnosed with bipolar disorder, 12 patients diagnosed with major depression, 17 patients diagnosed with adjustment disorder and 98 controls. In both analyses the dependent variable was 2 hour glucose value; diagnosis and gender were fixed factors, while age and BMI were covariates.

3. RESULTS

Patients and controls were similar regarding the matched variables, age, gender and BMI. Mean fasting glucose and fasting insulin values are also displayed (TABLE). Values are presented as mean with standard deviation [±].

Mean two hour glucose load (2HG) was 106.51 mg/dL[±32.0] for psychosis, 118.33 mg/dL[±34.3] for bipolar disorder, 107.42 mg/dL[±34.5] for major depression disorder, 79.06 mg/dL[±24.4] for adjustment disorder, and 82.11 mg/dL[±23.3] for healthy controls ($p < 0.001$) (FIGURE).

Bonferroni post-hoc comparisons were performed for 2HG between controls and psychosis subjects ($p < 0.001$), controls and depressive subjects ($p = 0.035$), and controls and bipolar ($p = 0.024$); there was no significant difference found between controls and adjustment disorder patients ($p > 0.999$).

Mean two hour insulin values were only available for some subjects in the psychosis group: (N=34) 34.76 mU/L [±28.8] and in the control group: (N=45) 22.28 mU/L [±20.3] ($p = 0.028$). Values were log-transformed due to non-normal distribution.

In the initial GLM analysis with all 233 subjects there were significant relationships for age ($p < 0.001$), BMI ($p = 0.047$) and diagnosis ($p < 0.001$) but not for gender ($p = 0.803$).

The same analysis (GLM) in the homogenized sample (ages between 18 and 40 years; N=215) was performed. Significant association was found for diagnosis ($p < 0.001$) while age ($p = 0.059$), BMI ($p = 0.083$) and gender ($p = 0.585$) did not reflect statistically significant differences.

4. DISCUSSION

Our results confirm an increase 2HG value in patients diagnosed with SMI, non-affective psychosis, bipolar I disorder, and major depressive disorder, compared to both adjustment disorder and matched controls. Although glucose levels in major depressive disorder and bipolar disorder were higher than in psychosis subjects, the number of patients in those affective groups was relatively small and that might have reflected a non-significant difference. Two hour insulin values were only presented in psychosis and controls subjects. They do reflect an increased insulin production in order to balance glucose levels, a finding consistent with insulin resistance.

Our results highlight the inherent risk of patients with SMI for developing glycemic abnormalities and the subsequent increase in the risk of future medical co-morbidities such as T2DM and cardiovascular disease.

Increased 2HG levels in first episode patients with non-affective psychosis, bipolar disorder and major depressive disorder have been separately described (Fernandez-Egea et al., 2009b; Garcia-Rizo et al., 2014b, 2012). However, the normal values found in adjustment disorder patients are contradictory with what expected from studies in post traumatic stress disorder. An important issue that complicates interpretation of our results is that adjustment disorder is by definition not a chronic problem, while these other disorders typically are.

The increased 2HG value in SMI compared with controls and adjustment disorder patients has diverse important implications for mental health providers and policy makers, as it raises the urgent need for developing prevention strategies at the early stages of the disease. A 2HG value between 140 and 200 mg/dl, impaired glucose tolerance, is a predictor of T2DM, suggesting a pre-diabetic state. An increased albeit normal 2HG is associated with peripheral insulin resistance and impaired early and late phase insulin response (Meyer et al., 2006). Indeed 2HG is an excellent predictor of coronary heart diseases and ischemic stroke both in already hyperglycemic and normo-glycemic fasting subjects (Ning et al., 2012). Also 2HG has been associated with atherosclerosis through an increased carotid intima-media thickness (Kato et al., 2014). As we have previously stated, SMI is associated with increased morbidity and mortality, mainly due to cardiovascular related pathologies (Laursen et al., 2007).

The idea of a continuum in major psychiatric diagnosis has been studied from a clinical (Leigh, 2009) and an immunological point of view (Altamura et al., 2013). Several of those ideas rely on the allostatic load (AL) concept. Briefly, allostasis refers to the adaptive processes to stress that lead to the activation of diverse biological systems through the body to maintain equilibrium and cope with challenges. AL relates to the situation where under repeated or chronic stress, the physiological homeostasis systems through the entire body become unbalanced and prone to developing diverse diseases. The concept of AL has been examined in bipolar disorder (Grande et al., 2012), major depressive disorder (Wilkinson and Goodyer, 2011) and schizophrenia (Nugent et al., 2015).

Another concept widely used with regard to morbidity and mortality in SMI is the accelerated ageing concept. It represents a syndrome in which diverse pathologies appear in

a similar pattern as in the regular population however at early stages of life, conducting to an increased morbidity and early mortality. The concept has been applied to schizophrenia (Kirkpatrick et al., 2008), bipolar disorder (Rizzo et al., 2014) and major depressive disorder (Wolkowitz et al., 2011) suggesting an early life programming pathway; the developmental origins of health and disease model (Gluckman and Hanson, 2006).

This early programming pathway has been already presented in major psychiatric illnesses (Garcia-Rizo et al., 2014a). Briefly, naïve patients with SMI might represent, from a metabolic point of view, a selection bias of an already described human adaptive physiological pathway, the early programming. As described in literature, patients with SMI exhibit an increased prevalence of obstetric complications (Brown et al., 1995) and stressful events during childhood and early adulthood (Harley et al., 2010) that might increase the risk of mental health diseases, while conferring an increased risk of developing diverse other pathologies, mainly type 2 diabetes and cardiovascular diseases (Reynolds et al., 2013). This seminal concept, the thrifty phenotype hypothesis (Hales and Barker, 1992), was initially referred to prenatal events, although further research highlighted the importance of childhood and early adulthood events (Gluckman and Hanson, 2006).

Our results have been foretold by animal models of early life stress (Ko and Liu, 2015; Pacheco-Lopez et al., 2011) reflecting the importance of early life stress, not only prenatal but also postnatal in the dual development of mental disability with coronary heart diseases and T2DM (Gluckman et al., 2008). Patients with SMI are medically evaluated due to their psychiatric condition and only after a metabolic challenge, an oral glucose tolerance test [because fasting glucose levels are normal at the onset (Fernandez-Egea et al., 2009b; Garcia-Rizo et al., 2014b, 2012)], an abnormal glycemic state shows up (Fernandez-Egea et al., 2013), in a subset of the population too young to be affected by regular psychiatric lifestyle factors (Kirkpatrick et al., 2012).

Our results cannot inform us of the cause of the co-morbidity between glucose intolerance and neuropsychiatric disorders. It appears unlikely that diabetes induces mental illness, but the possibility that the glucose abnormalities result from mental disorders through hypercortisolemia, which leads to abnormal glucose tolerance, cannot be ruled out. One study (Ryan et al., 2003) found increased cortisol concentration in naïve patients with psychosis who had, as a group, increased fasting glucose.

However, other evidence suggests that the neuropsychiatric symptoms and the glucose tolerance are both caused by a third factor, either shared familial factors (Fernandez-Egea et al., 2008) or problems during gestation, such prenatal malnutrition (Susser and St Clair, 2013) or other causes of low birth weight, which is common to both T2DM (Whincup et al., 2008) and mental health disorders (Boyle et al., 2011).

Several limitations arise from our study. First the bipolar diagnosis, as stated previously is done retrospectively, as around 20% of first episode psychosis patients are later on diagnosed with affective psychosis. In order to maintain the number of subjects and reduce loss to follow-up (patients who are referred to other clinical facilities), we decided to include subjects in their first psychiatric evaluation. Second, and extremely important for matching

purposes, in the initial analysis age and BMI play a significant role in our model, a finding that is minimized by the rational decision of including only patients with ages between 18 and 40 years old, as patients at the onset of SMI. However both variables still range close to the statistical significance, as psychiatric disorders clinically differ at the age of onset and the number of patients included in some groups is quite small.

5. CONCLUSIONS

The results of the study provide further evidence for a specific pathway; an abnormal glucose homeostasis in SMI prior to the use of psychotropic medication, a finding described before such drugs were introduced (McIntyre et al., 2005). The fact that young treatment-naïve patients, at early stages of their psychiatric condition, present already glycemic disturbances reflects a long-lasting, underlying process only detected due to the outbreak of a mental condition.

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HIGHLIGHTS

- Patients with serious mental illnesses present an abnormal glycemic state at onset

- A pre-diabetic state might explain the increased morbidity and mortality over time

- A theoretical explanation relies on the high prevalence of obstetric complications

- Early life stressful events would predict metabolic disturbances ongoing at onset
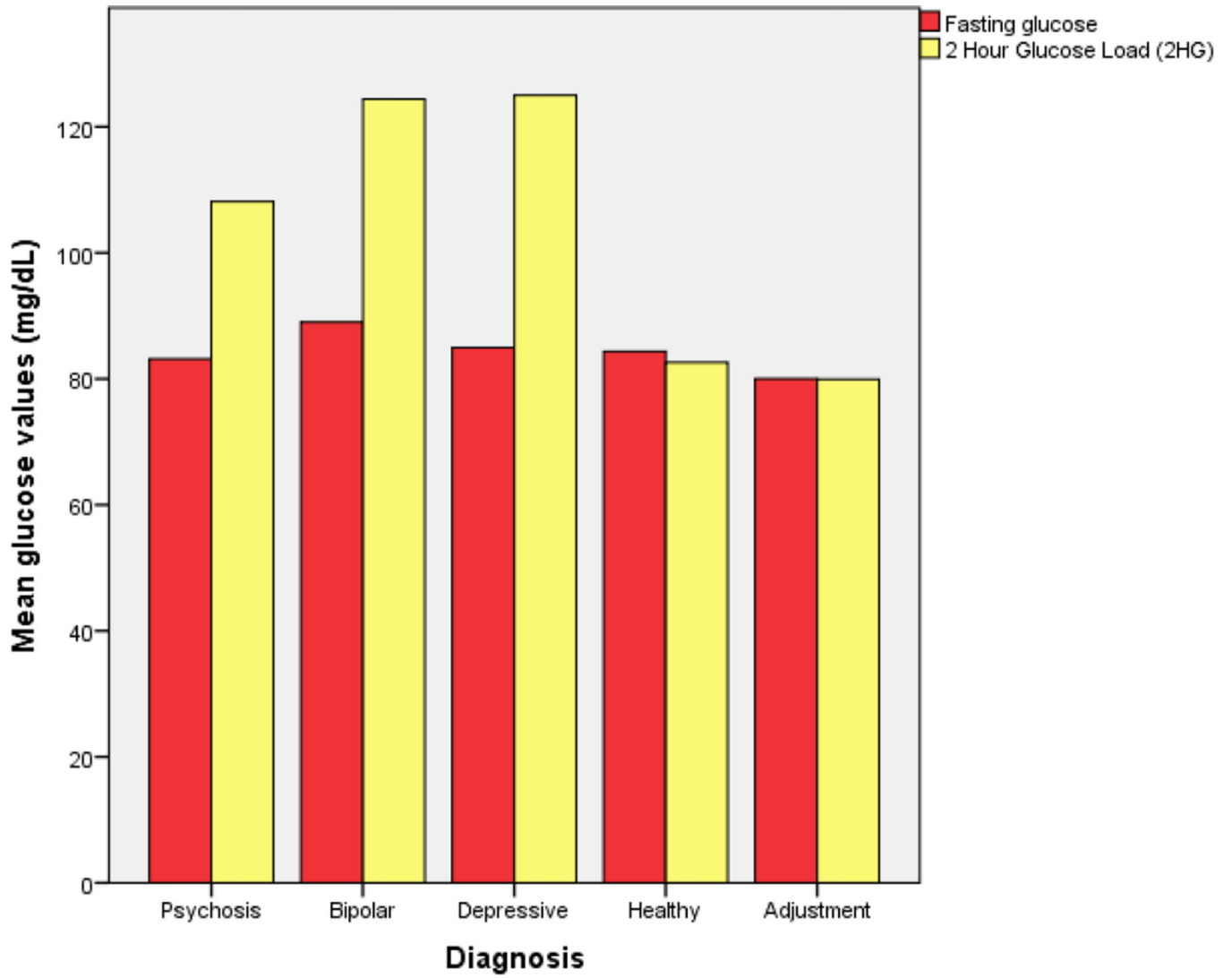
Figure.

Mean fasting and two hour glucose value of the sample (mg/dL)

For interpretation of the references to color in this figure legend, the reader is referred to the web version of the article

TABLE

Sociodemographic and metabolic characteristic of the sample

Mean value [Standard Deviation]	Psychosis (N=84)	Major Depressive Disorder (N=12)	Bipolar Disorder (N=6)	Adjustment Disorder (N=17)	Healthy Controls (N=98)	Statistics
Age (years old)	27.28 [5.5]	26.50 [5.6]	29.70 [4.9]	27.07[4.9]	26.66 [4.3]	p= 0.619
Gender (Male)	64% (N=54)	58% (N=7)	83% (N=5)	41% (N=7)	62% (N=61)	p= 0.339
Body Mass Index (kg/m²) *	22.13 [3.8]	22.62[3.4]	24.73[7.8]	22.65 [2.8]	23.23[2.6]	p= 0.140
Fasting Glucose (mg/dL)	82.24 [8.6]	82.67[9.5]	84.00[10.6]	80.00[7.8]	83.86 [6.80]	p= 0.352
Fasting Insulin (mU/L) **	11.75[14.7]	9.61[3.8]	8.88[4.6]	11.40[7.5]	8.75[3.3]	p=0.336
2 Hour Glucose Load (mg/dL)	106.51[32.0]	107.42[34.5]	118.33[34.3]	79.06[24.4]	82.11 [23.3]	p< 0.001

*
For Body Mass Index N=82 for psychosis

**
For Fasting Insulin N=82 for psychosis and N=96 for controls