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Altered metabolic parameters in association with antipsychotic medication use in diabetes: A population based case-control study

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ABSTRACT

Aims: This study assess differences in clinical variables in diabetes patients prescribed antipsychotic medication and determines relative schizophrenia prevalence in the diabetes population.
Methods: This population-based case-control study utilizing Scotland's national diabetes registry (SCI-diabetes) and linked psychiatric hospital discharge data (SMR04) established diabetes phenotypes in a patient cohort prescribed long term antipsychotic medication ($n = 2362$) (cases). Cases were matched 1:10 to diabetes patients not prescribed antipsychotic medication (controls) for BMI, gender; diabetes type; birth year; diagnosis date; smoking status. Sub-groups with defined schizophrenia ($n = 196$) or bipolar disorder ($n = 190$) were further examined. Schizophrenia prevalence in the diabetes versus general population was compared.
Results: During follow up, antipsychotic prescription was associated with lower HbA1c (55.1 (95% CI 54.5–55.8) or 7.2 (95% CI 7.1–7.3)% vs 58.2 (58.0–58.4) mmol or 7.5 (95% CI 7.5–7.5)% $p < 0.001$) lower serum total cholesterol, 4.2 (4.1–4.2) vs 4.3 (4.2–4.3) mmol/l, $p < 0.001$, lower blood pressure (systolic 130 (130.17–131.29) vs 134 (134.3–134.7) mmHg, $p < 0.001$), higher prescription of oral hypoglycaemic medication (42% (40–45) vs 38% (37–39) $p < 0.001$), similar statin prescriptions (85% (81–89) vs 85% (84–86), $p = 0.55$), and lower retinopathy rates (28% (25.6–30.5) vs 32% (31.5–33.1), $p < 0.001$). HbA1c at diagnosis was similar ($p = 0.27$). Schizophrenia prevalence was higher in the diabetes versus general population with differences across age groups (Scottish population versus diabetic population rate of 522.2 (522.1–522.3) versus 717.4 (703.4–731.9) per 100,000).
Conclusions: We confirm higher diabetes rates in schizophrenia up to age 70, similar attendance rates and clinical measurements that are not worse in a large well-matched population-based Scottish sample prescribed antipsychotic medication versus matched general diabetes patients.

1. Introduction

Diabetes is around 2–4 times more prevalent in patients with Schizophrenia (Fernandez-Egea et al., 2009; Kirkpatrick et al., 2012), which may be due to shared susceptibility genes (Lin and Shuldiner, 2010), stress (and related hormones, i.e., raised cortisol levels) (Dinan, 2004), demographic characteristics (age, gender, ethnicity, geographic location) (Holt et al., 2005; Lin and Shuldiner, 2010; Melkersson and Dahl, 2004), or comorbid illness (Holt et al., 2005).

Weight gain and other lifestyle factors (such as smoking, sedentary lifestyle, poor diet, etc.) that are common in patients with schizophrenia can influence diabetes development irrespective of medication (De Hert et al., 2009; Haddad, 2004; Holt et al., 2005; Rouillon and Sorbara, 2005). However schizophrenia may be an independent risk factor, as glycaemic abnormalities have been observed in patients irrespective of other factors (Bushe and Leonard, 2004). Diabetes conversely may increase the risk of schizophrenia (Haddad, 2004; Lin and Shuldiner, 2010; Rouillon and Sorbara, 2005).

Much of the literature however focuses on the gluco-toxic effects of anti-psychotic (atypical drugs in particular, e.g., clozapine) suggesting medication induced weight gain drives the association with diabetes (Jafari et al., 2012; Lin and Shuldiner, 2010; Melkersson and Dahl, 2004; Rouillon and Sorbara, 2005).

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Emerging evidence suggests that antipsychotic medication may alter gut microbiota which may precipitate weight gain and predispose patients to diabetes (Bahr et al., 2015; Morgan et al., 2015). Others suggest diabetes development is independent of weight gain (Bushe and Leonard, 2004). The type of anti-psychotic drug or illness itself might increase the risk of developing diabetes (Bushe and Leonard, 2004; Melkersson and Dahl, 2004; Rummel-Kluge et al., 2010) and secondary hormonal changes may influence the metabolic changes (Bushe and Leonard, 2004; Melkersson and Dahl, 2004; Rummel-Kluge et al., 2010).

Most studies to date have evaluated the risk of diabetes development in this population, but not on the metabolic changes, attendance behavior and outcomes of those with established diabetes, which is the focus of this study.

1.1. Background

In July–Aug 2012, the authors conducted a small pilot case control study within high risk schizophrenia patients attending a specialized clozapine prescription clinic ($n = 63$) demonstrating a 12.7% prevalence of diabetes with a 7:1 male:female ratio (prevalence of diabetes within the Scottish population for a similar age group is 3.95%). This study suggested that diabetes may be associated with longer duration of schizophrenia ($p = 0.08$), but not with clozapine daily dose ($p = 0.64$). Diabetes patients prescribed clozapine (mean age of 47.9 years (+/−7.6 (SD)), were compared with age and diabetes type matched controls, and demonstrated significantly better glycaemic and cholesterol control (HbA1c (50.8 vs 63.9 mmol/mol, $p < 0.012$), total cholesterol (4.1 vs 4.8 mmol/L, $p = 0.038$) (Perera et al., 2013)). These findings were contrary to expectation and fuelled this more powerful population study.

1.2. Aims

This study aims to (a) explore whether schizophrenia patients are overrepresented in the Scottish diabetes population, and (b) assesses whether patients prescribed regular antipsychotic medication (with presumed underlying mental health conditions) who have developed diabetes have (i) differences in glycaemic control, blood pressure, plasma lipids and complication rates/complications risk compared to those developing diabetes de-novo, and (ii) poorer attendance for clinic or complications screening.

2. Methods

2.1. Background

We performed a population based case control study, using nationwide data linked from psychiatric hospital discharges and Scotland's national diabetes registry (SCI-diabetes). SCI-diabetes contains detailed linked clinical data on all patients in Scotland registered with diabetes. It collates information from multiple sources including medication, screening (retinopathy screening service, foot screening tool), laboratory data and metabolic variables collected during routine care.

2.2. Population data sources

National psychiatric hospital summary discharge data (for Scottish residents 1981–2011 with any diagnosis of schizophrenia who were alive at the end of 2011) were used for prevalence calculations. Data for detailed diabetes phenotype analysis was obtained from SCI-diabetes (see flow chart; Fig. 1). Linkage across healthcare related datasets was facilitated by the unique patient identifier (CHI number). Hospital discharge information for mental health conditions (Scottish Morbidity Record (SMR) 04) was made available through Information Services Division (ISD) using tenth revision of International Classification of Diseases (ICD-10) codes.

2.3. Prevalence calculation

Comparison was made of the prevalence of schizophrenia in the general Scottish population who were alive in 2011 (identified from history of a psychiatric hospital admission with the relevant ICD code) and the prevalence of schizophrenia in the national diabetes population (SCI-diabetes) by age.

2.4. Case selection

From a May 2011 research extract of SCI-diabetes national data, we established cases, namely patients recorded in SCI-diabetes as receiving a prescription for antipsychotic medication. We identified 2386 patients during 2010 prescribed drugs with a BNF code of 4.2.1 (anti-psychotic medication) for at least 12 months in total (including all or part of 2010) regardless of any diagnosis for mental illnesses, referred to as All Antipsychotics (AA) group. Of these 2362 patients were matched and used in further analysis. From within this cohort we identified 196 diabetes patients with a record of psychiatric hospital discharge recording schizophrenia or a related psychosis prior to 2010 (ICD-10 codes F20- F29) (SA group), and 190 patients with a hospital discharge record for bipolar disorder (ICD10 code F31) (BA group). SA and BA groups were established to assess whether effects identified were associated with specific mental health disorders.

2.5. Control selections

For each set of index cases, a comparison group was created by identifying 10 controls for each case from SCI-diabetes matched for gender; diabetes type; birth year (+/−1 year); diagnosis date (+/−1 year); smoking status (the lowest status recorded in 2009 and 2010 was used (in order—current smoker (lowest); ex-smoker; never smoked)); and BMI (mean for 2010) (+/−3 kg/m^2). Patients with a history of any antipsychotic use or any schizophrenia diagnosis (including those excluded from the index cases) were not used as controls. Where there were more than 10 potentially matching records, controls were randomly chosen from those available. Records with fewer than 10 matching records were excluded from analysis.

Of the total available patients using anti-psychotic medication, the percentage matched to 10 controls was 99.0% (AA group), 83.0% (SA group) and 90.5% (BA group). Excluded patients tended to be younger than those matched and with a lower BMI (See Table 1(a) and b)). For all groups smokers and ex-smokers are more likely to be excluded than non-smokers, albeit with small numbers. There was no significant difference in gender.

2.6. Clinical measures and outcomes

Various measures for 2010 (i.e., from Jan 1st 2010 to Dec 31st 2010 inclusive) were extracted to compare the control patients with the cases to test for a difference. These were, (a) the mean value of all HbA1c, systolic and diastolic blood pressure, total cholesterol readings taken in 2010, (b) the HbA1c, systolic and diastolic blood pressure, total cholesterol, foot screening and eye screening record counts (the number of times each was recorded e.g., at a screening visit for each patient in 2010), (c) the foot risk score (worst record of 2010), (d) retinopathy status (worst record of 2010), (e) statin prescription (whether prescribed at any point in 2010), (f) hypoglycaemic medication (whether prescribed at any point in 2010).

Patients with missing data were removed for any comparison where that data was missing, however in the case of data used for