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Original Article

Metabolic abnormalities in an early psychosis service: a retrospective, naturalistic cross-sectional study

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Abstract

Aim: There is an increasing recognition of the impact of weight gain on the development of metabolic abnormalities in young people receiving atypical antipsychotic drugs for first-episode psychosis. This study examined the prevalence of such abnormalities in a specialist early-intervention community mental health team.

Methods: A retrospective case record audit of 85 patients 16–27 years old attending the Early Psychosis Service between October 2006 and June 2008, who had at least one metabolic measure defined as: weight, body mass index (BMI), waist circumference, blood pressure, and fasting blood glucose and lipids. Metabolic syndrome identified by the International Diabetes Federation (IDF) criteria.

Results: Fifty-five percent of males and 42% of females were overweight or obese at a median treatment duration of 8 months. Duration of antipsychotic therapy was associated with higher BMI ($r = 0.28$, $P < 0.01$). More than 40% of the total sample had high waist circumference. Of the 64 subjects with complete metabolic data, eight (12.5%) met full IDF criteria for metabolic syndrome, and another 21 (32.8%) had either increased waist with one metabolic abnormality or normal waist and two metabolic abnormalities.

Conclusions: Over a third of young patients being treated for their first episode of psychosis either had metabolic syndrome or showed metabolic abnormalities. Treatment duration related to higher BMI and greater prevalence of metabolic syndrome. Detection of metabolic complications after treatment instigation in patients with first-episode psychosis will permit early intervention with lifestyle or drug interventions in those at risk of significant physical health morbidity.

Key words: antipsychotic-monitoring, first-episode psychosis, metabolic syndrome.

INTRODUCTION

Obesity, dyslipidaemia and hyperglycaemia are epidemic public health problems[1] that particularly effect patients receiving treatment with antipsychotic medications.[2–4] Australian consensus guidelines and screening algorithms have been developed with recommendations for identification of diabetes and cardiometabolic monitoring in patients with psychotic disorders.[5,6] However, significant barriers exist to implementation of routine cardiometabolic monitoring and intervention in this patient group.[7,8] Weight gain[9–15] and metabolic abnormalities[16–21] frequently complicate the management of first-episode psychosis (FEP). Clinically significant weight gain has been estimated to occur

in 23–61% of FEP patients prescribed antipsychotic medications for 10–16 weeks, with rates increasing to 58–100% after 1–2 years of treatment.[11] Lipid abnormalities have been reported to emerge in the first 12 weeks of treatment[22] and insulin resistance can occur in the first year.[18]

Glucose dysregulation in drug-naive FEP patients has been documented in some[23–26] but not in all studies;[20,27] if confirmed, a unique susceptibility to the development of diabetes and metabolic syndrome (MetS) exists in this population. In addition, although some of the cardiometabolic risk factors may reflect poor diet and sedentariness, antipsychotic agents may contribute to increased morbidity via other mechanisms.

MetS was defined by the International Diabetic Federation (IDF) in 2005[28] as an increased waist circumference, combined with at least two other abnormalities (hypertension, low high-density lipoprotein (HDL), raised fasting blood glucose or triglycerides). Presence of MetS confers an increased risk of morbidity and mortality, usually cardiovascular, which is estimated to reduce life expectancy by 20%.[29] In a recent Australian study of patients with severe mental illness, more than 50% met criteria for MetS.[30]

De Hert and colleagues[16] studied 230 drug naive FEP patients (mean age 22 years). They reported significantly greater incidence of MetS following a 3-year treatment with second-generation antipsychotics (30%) than was observed in a historical comparison group who received treatment with first generation antipsychotics (13%). A recent study that examined a child and adolescent cohort found that significant weight gain (e.g. 4.4–8.5 kg) and metabolic abnormalities occurred rapidly, over a 10–12-week period, in drug naive patients receiving second-generation antipsychotic treatment.[31]

The Early Psychosis Programme (EPP), in Sydney, is a small multidisciplinary team targeting young people between the ages of 15–25 years experiencing first onset of psychosis and are within 2 years of symptom onset. EPP is integrated across both community and inpatient services, and draws from a suburban Sydney catchment of 280 000 people. Patients receive comprehensive medical and psychosocial interventions for up to 2 years including a recovery-focused group programme 'Recovery and Discovery in Community and Lifestyle' ('RaDiCaL').

In October 2006, routine metabolic monitoring was implemented for all EPP patients as a quality improvement project. The present report describes the metabolic abnormalities found in a group of patients who were being treated in the programme over an 18-month time period beginning in October 2006.

METHODS

One hundred thirty-six patients were evaluated in this retrospective file audit. This included all patients who were currently in the programme in October 2006 and new referrals made between October 2006 and June 2008. Two groups of patients were excluded from the study. The first group comprised those who did not undergo an initial assessment, did not meet patient intake criteria or whose contact with the programme was limited to less than 1 month (No or minimal engagement, $n = 19$ patients). The second group comprised patients who were engaged with the programme, but for whom no metabolic monitoring was obtained (engagement without any metabolic measurements, $n = 32$). This comprised patients who were approaching discharge at the time routine monitoring was initiated in the programme or else were minimally engaged with the programme.

Sociodemographic variables and current medications were collected and recorded in the patient file following patient interview on the Metabolic Monitoring Chart by the medical or nursing staff. Patient weight was measured using calibrated electronic scales, and height was measured utilizing a wall-mounted stadiometer with the patient barefoot. Waist circumference was measured at the mid point between the iliac crest and the lower rib using a tape measure. Blood pressure was recorded manually using a calibrated sphygmomanometer with the patient seated. Fasting pathology tests were conducted at a local private pathology laboratory. Psychiatric diagnoses were confirmed utilizing a retrospective Structured Clinical Interview for Diagnostic Statistical Manual for Mental Disorders, Fourth Edition (SCID) chart review by a senior clinician (JC) and experienced clinical research scientist (PBW).

Body mass index (BMI) cut-offs to define overweight and obesity were derived from World Health Organization (WHO) international standards. There is considerable controversy regarding appropriate BMI cut-offs for different Asian populations.[32] This expert consensus statement recommended that WHO BMI cut-off points should be retained as international classifications. We utilized the criteria for abnormal waist circumference defined by IDF guidelines which takes into account ethnicity.[28]

Statistical analyses were performed using Predictive Analytics Software Statistics 18.0 (SPSS Inc., Chicago, IL, USA). *T*-test and chi-squared analyses of relevant demographic variables were conducted comparing male and female subjects. Chi-squared statistics were also used to examine which MetS parameters were significantly different between males and females. Regression analyses were conducted to identify factors associated with higher BMI. As the data were obtained as part of routine clinical care, the study was conducted as a quality improvement project under the auspices of the Mental Health Programme, South Eastern Sydney Illawarra Area Health Service.

Analyses were performed on 85 patients who had a metabolic monitoring chart that contained data from at least one time-point. Where there was data available at more than one time-point, those obtained at the longest interval since entry to the service were selected, to enable the clearest 'snapshot' of the effects of antipsychotic medications on cardiometabolic abnormalities.

RESULTS

Descriptive statistics: Demographic and risk factor variables (Table 1)

Diagnoses (retrospective SCID)

The sample consisted of 55 patients with schizophrenia, 15 with bipolar affective disorder, 7 with schizoaffective disorder, 3 with major depressive disorder, 2 schizophreniform disorder, 1 dysthymia, 1 delusional disorder and 1 substance-induced anxiety disorder. Patients were grouped into those with schizophrenia spectrum disorders (schizophreniform disorder, schizophrenia, schizoaffective disorder and delusional disorder), bipolar affective disorder and other (patients with other diagnoses).

TABLE 1. Descriptive statistics: demographic and risk factor variables

	Total (n = 85)	Male (n = 50)	Female (n = 35)	Statistical test
Age (years) (mean)	22.2	21.83	22.85	t = 1.87, P = 0.06
Age (years) (range)	16.8–27.6	16.8–27.6	18.1–27.2	
Ethnicity (%)				
Asian	10 (12)	5 (10)	5 (14)	
Indigenous	9 (10)	3 (6)	6 (17)	
Caucasian	64 (78)	42 (84)	24 (69)	
Time in EPP (months)				Mann–Whitney U = 779, P = 0.39, ns
Mean (range)	14.47 (0–56)	13.86	15.34	
Median	8.19	11.01	9.27	
Smokers (%)	56/85 (66)	35 (70)	21 (60)	
FH Diabetes (%)	28/68 (41)	13/38 (34)	15/30 (50)	
FH CVD (%)	33/65 (51)	22/36 (61)	11/29 (38)	
BMI mean (range)	26.10 (16.5–44.9)	25.87 (19.5–44.9)	26.43 (16.5–43.2)	t = 0.65, ns

BMI, body mass index; EPP, Early Psychosis Program; FH, family history; CVD, cardiovascular disease.

TABLE 2. Diagnostic group demographic and risk factor variables

	Schizophrenia spectrum (n = 65)	Bipolar affective disorder (n = 15)	Statistical test
Age (years) (mean)	22.16	23.46	t = 1.85, P = 0.07
Range	16.84–27.61	21.24–26.15	
Sex			χ^2 = 3.32, ns
Male	40	9	
Female	25	6	
Time in EPP (months)			t = 2.16, P < 0.04
Mean	15.9	9.67	
Range	0–55.9	0.7–26	
BMI mean	25.98	26.09	t = 0.08, ns

BMI, body mass index; EPP, Early Psychosis Program; ns, not significant.

Patients with schizophrenia spectrum disorders and bipolar disorders were compared across a range of demographic and risk factor variables (see Table 2). The two groups did not differ significantly on any of these variables.

Patients with schizophrenia spectrum diagnoses and bipolar affective disorder had similar demographic variables or BMI. Therefore, subsequent analyses were conducted across the whole sample.

Medications

The majority of the sample were prescribed one or more second-generation antipsychotics (SGA) at the time of the review ($n = 75$ (88%)). Risperidone, olanzapine and quetiapine were prescribed more frequently (≥10 patients) while other SGAs were less frequently prescribed (amisulpiride, aripiprazole, paliperidone and ziprasidone (≤7 patients). Over a quarter were receiving mood stabilizer (lithium or valproate) (24 (28%)) almost all of whom were concurrently prescribed an SGA (22 (25%)). A similar percentage were receiving an antidepressant (24 (28%)), with 21 prescribed a selective serotonin re-uptake inhibitor (SSRI) whilst three were prescribed a non-SSRI antidepressant. Five subjects were not prescribed psychotropic medications at the time of review and five were prescribed clozapine.

BMI

The majority of males (55%) had a weight disorder: 40% were overweight and 15% were obese. In females, 42% had a weight disorder: 12% were overweight and 30% were obese. The prevalence of obesity or morbid obesity affected twice as many females were males (Table 3).

Regression analyses were conducted to identify factors associated with higher BMI. Length of time in the EPP programme was associated with higher BMI ($r = 0.28$, $P = 0.008$). There was a trend for those receiving mood stabilizers to have higher BMI, not reaching statistical significance. ($r = 0.20$, $P = 0.08$). There were no other significant predictors of BMI. Antipsychotic polypharmacy was not a significant predictor of increased BMI (probably reflecting concomitant use of mood stabilizers in those on a single SGA and those who were prescribed more than one SGA in this cross-sectional evaluation of medication status).

MetS

Using the IDF criteria to define MetS, Table 4 describes the proportion of the sample with abnormalities on key parameters. Over 40% of the total sample had an increased waist circumference, placing them at risk for MetS. There was evidence of hypertension, raised triglycerides or low HDL in approximately one-quarter of the total sample. Blood glucose abnormalities were comparatively infrequent in this young sample.

Waist circumference was the only significant gender difference with females more likely to have abnormal waist circumference according to IDF criteria. There was a trend for hypertension to be more frequent among males compared with females, but this was not statistically significant. The remaining IDF parameters did not show gender differences.

Eight subjects (5 females and 3 males) met the IDF criteria for MetS. Three subjects of this group were on clozapine and the majority (2 females, 3 males) were on concurrent mood stabilizers. Therefore, of the total sample, 9.4% fulfilled IDF criteria for MetS. However, complete data was only available in 64 of the 85 subjects, giving a prevalence estimate of 12.5%. In addition to those who already met the full criteria for MetS, a large number were at high risk of MetS because of either an increased waist circumference (WC) with one abnormality ($n = 13$), or a WC in the normal range with abnormalities on at least 2 IDF parameters ($n = 8$).

In those subjects meeting criteria for MetS ($n = 8$), BMI ranged from overweight (28.1 kg m^{-2}) to morbidly obese (43.1 kg m^{-2}). The majority were hypertensive (75%) and had abnormal lipids (either low HDL (75%) and/or high triglycerides (87%). There

TABLE 3. Body Mass Index (BMI)

BMI (kg m^{-2})	Males ($n = 49$)	Females ($n = 34$)	Total ($n = 83$)
Underweight (<19.9)	2 (4%)	4 (11%)	6 (7%)
Normal (20–24.9)	21 (42%)	16 (46%)	37 (44%)
Overweight (25–29.9)	19 (40%)	4 (12%)	23 (28%)
Obese (30–34.9)	6 (13%)	6 (18%)	12 (14%)
Morbidly obese (≥35)	1 (2%)	4 (12%)	5 (6%)

TABLE 4. Rates of abnormalities on IDF MetS criteria

IDF MetS criterion	Males *n* (%)	Females *n* (%)	Total *n* (%)
Waist circumference (female ≥ 80, male ≥ 90† or 94 cm††)	16/48 (33)	19/33 (58)	35/81 (43) $\chi^2 = 4.68$, $P = 0.03$
Blood pressure§	13/42 (31)	5/34 (15)	18/76 (24) $\chi^2 = 2.74$, $P = 0.1$, ns
Fasting blood glucose‡	3/40 (8)	1/29 (3)	4/69 (6) $\chi^2 = 0.51$, $P = 0.48$, ns
Triglyceride¶	12/40 (30)	10/31 (32)	22/71 (31) $\chi^2 = 0.04$, $P = 0.84$, ns
HDL‡‡	10/38 (26)	10/31 (32)	20/69 (29) $\chi^2 = 0.29$, $P = 0.59$, ns

†SE Asian, Japanese, Central or South American males.
‡≥5.6 mmol L^{-1}.
§Systolic ≥ 130 mm Hg or diastolic ≥ 85 mm Hg.
¶≥1.7 mmol L^{-1}.
††Europid males.
‡‡m <1.03 mmol L^{-1}; f < 1.29 mmol L^{-1}.
Denominator varied across different measures as not all were available for each subject.
HDL, high-density lipoprotein; IDF MetS, International Diabetic Federation metabolic syndrome; ns, not significant.

were no fasting glucose abnormalities detected in this group. The majority of patients with MetS (75%) had a diagnosis of schizophrenia or schizoaffective disorder. Time spent in the EPP programme was longer (mean 29.4 months standard deviation (SD) 16.2) for those subjects with MetS versus those subjects without MetS (mean 12.9 months, SD 13.3). Statistical analysis of this relationship with time in treatment was not conducted, as many of the non-MetS group had significant metabolic abnormalities that placed them at risk for subsequently meeting MetS criteria.

DISCUSSION

This naturalistic study of a cohort of FEP patients treated by a community-based specialist service found that 34% patients after a median of 8.19 months of treatment met full criteria, or were at significant risk, for the development of MetS. In those with complete data, one in eight (12.5%) met criteria for MetS. These findings were comparable with treatment-emergent rates of MetS (at 1 year) reported by Patel *et al.*[17] in the CAFÉ study (13.4%). Even higher rates were reported by De Hert *et al.*[16] (30.6%) who examined patients after 3 years of treatment with SGAs. Remarkably, Saddicha *et al.*[33] also reported a five-fold increase (18%) in MetS among FEP patients treated with SGAs for 6 weeks compared with matched healthy controls. Thus the prevalence of MetS in FEP is high and has significant implications for a wide range of subsequent morbidity and mortality.

Although those who met IDF criteria for MetS had been in the EPP programme approximately twice as long as those who did not meet these criteria, it is difficult to interpret the specific factors that might have contributed to the development of MetS given the naturalistic design of the study (i.e. those in treatment for longer were also more likely to have been prescribed clozapine, etc.).

In the present study, those who were receiving clozapine and/or mood stabilizers appeared to be at increased risk for development of MetS and should be a high priority target group for intensive clinical monitoring and early interventions aimed at preventing metabolic morbidity. Any conclusions regarding the direct effects of medication on MetS and metabolic parameters are difficult to draw from this naturalistic study. The current data do not allow conclusions to be drawn regarding the relative prevalence of metabolic abnormalities in patients prescribed different SGAs. The current study is cross-sectional in nature; the patients were prescribed medications according to clinician preference and, in a number of instances, were receiving antipsychotic polypharmacy. Interestingly, De Hert *et al.*[16] noted that the prevalence of MetS in FGA and SGA was the same once clozapine and olanzapine were excluded from the SGA group included in their study. In addition, there is clear evidence that

olanzapine leads to substantial and rapid weight gain when administered to healthy volunteers under rigorous experimental conditions.[34]

LIMITATIONS

One of the limitations of this study was the absence of complete data on relevant metabolic parameters in this cohort (ranging from a low of 79% (HDL) to 95% (WC)). These rates of monitoring are in part because of the decision to exclude from this cohort a number of patients in whom no metabolic data were available ($n = 32$). It is noteworthy, however, that this is a substantial improvement on rates of monitoring noted during a file audit 4 years prior to the present study (WC and lipids were not measured in any of the 14 files audited). Crabb *et al*.[35] recently reported low rates of baseline screening in a specialist first-episode service in Scotland, ranging from 27% (BMI) to 64% (blood pressure). The rates achieved in the EPP programme reflect the priority given to obtaining these measures, and are substantially higher than those reported by Haupt *et al*.[8] in a managed care cohort following the introduction of American Diabetes Association guidelines in 2004 (8.4% baseline lipids pre-guideline vs.10.5% post-guidelines).

Additional limitations include that the study was not prospective in nature, and did not include a non-psychotic comparison group. In addition, change measures could not be obtained because of the cross-sectional design, and the fact that patients were not assessed at identical time-points with respect to their entry to the service. Despite the service adopting a focus on metabolic screening, there was still less than 100% compliance with metabolic monitoring. Equipment required for monitoring, e.g. sphygmomanometers were not readily available and there were difficulties in ensuring patients attended pathology investigations.

Based on this cross-sectional evaluation, we are unable to address the longitudinal progression of metabolic change. Along with an increased focus on monitoring metabolic parameters, the EPP began to implement lifestyle interventions at initial referral to the service, aimed at prevention of weight gain and other metabolic complications. This may have impacted on the rates of metabolic abnormalities detected and the prevalence of MetS in the current study cohort.

CONCLUSIONS

The current naturalistic study has implications for service enhancement for young people with FEP. It confirms recent findings that it is essential to implement monitoring from the very onset of treatment in FEP and to do so across the full range of clinical presentations not just those with obvious evidence of obesity. In the EPP programme, we have consolidated metabolic data on a single form in the patient file to facilitate easy tracking of weight gain and cardiometabolic changes and their relationship to prescription of psychotropic medication. A database has been created where critical metabolic changes are highlighted during routine clinical reviews. Cardiometabolic monitoring occurs has become a cross-disciplinary priority and part of the core business of the programme. In response to the high prevalence of obesity and cardiometabolic complications in this FEP cohort, a physical health stream has been developed as part of the psychosocial recovery programme. This includes lifestyle intervention groups, individual consultations with dieticians and exercise physiologists, and active engagement with general practitioners and endocrinologists.

Standardized assessment of all psychiatric and medical health issues is needed and all psychiatric patients who are on psychotropic medications should be offered similar primary and secondary health care in line with the non-psychiatrically ill population.[2]

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