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Metabolic syndrome in antipsychotic naive African patients with severe mental illness in usual care:

Metabolic syndrome prevalence and incidence

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Abstract

Aim—To determine the prevalence and incidence of metabolic syndrome in individuals with a first episode of severe mental illness from South Africa.

Methods—Antipsychotic naïve study subjects with a first episode of severe mental illness and control subjects were recruited at baseline for a prospective study. Individuals without metabolic syndrome at baseline were followed up for 12 months after antipsychotic medication was initiated. Metabolic syndrome was determined at baseline and at the 12 month follow – up using the Joint Interim Statement criteria.

Results—At baseline, the 67 study (M:F; 48:19) and 67 control subjects (M:F; 48:19) had a mean age of 22.8 ($\pm$ 3.7) and 23.3 ($\pm$ 2.6) years ($p=0.4$) respectively. The majority were of black African ethnicity (97 %) and 82 % were diagnosed with schizophrenia. There was no difference in the prevalence of metabolic syndrome (4.5 %) or any of the individual components between the study and control group prior to the initiation of antipsychotics. Of the 64 study subjects without metabolic syndrome at baseline, only 36 (M:F; 25: 11) completed the 12 month follow - up (response rate 56.3%) and 2 subjects developed metabolic syndrome. The incidence of metabolic syndrome was 5.5 % with a significant increase in the elevated waist circumference criterion after one year of antipsychotic treatment ($p = 0.02$).

Conclusions—There was a low prevalence and incidence of metabolic syndrome in this group of patients with a first episode of severe mental illness.

Keywords

antipsychotic agents; metabolic syndrome X; South Africa

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Introduction

Antipsychotic medication is often the only treatment for severe mental illness (SMI) in South Africa (S.A) because of the challenges and feasibility of implementing psychosocial interventions (Brooke-Sumner et al., 2015). All antipsychotic medications are reported to have metabolic side effects (Leucht et al., 2013) and the prevalence of metabolic syndrome (MetS) is three times higher (Mitchell, Vancampfort, De Herdt, Yu, & De Hert, 2013), with a significantly higher risk (Vancampfort et al., 2013) in medicated patients compared to unmedicated patients with schizophrenia. However, there are reports of diabetes mellitus in patients with schizophrenia decades before the discovery of antipsychotic medication (Kohen, 2004) and a higher prevalence of diabetes mellitus in first degree relatives of individuals with schizophrenia has been reported (Van Welie et al., 2013). This suggests that the metabolic risk attributable to antipsychotic medication is neither simple nor straight forward because some people with schizophrenia may have an inherent predisposition to MetS (Enez Darcin, Yalcin Cavus, Dilbaz, Kaya, & Dogan, 2015).

There is mixed evidence for the increased prevalence of MetS in antipsychotic naïve individuals or those with a brief exposure to antipsychotics compared to controls, with the prevalence ranging from 3.3 – 26 % (Chadda, Ramshankar, Deb, & Sood, 2013). Mitchell *et al* (Mitchell et al., 2013) and Vancampfort *et al* (Vancampfort et al., 2013) in meta - analyses found a similar international average MetS prevalence of 9.8 % and 10% respectively in drug naïve first episode patients. In the only study from S.A, Chiliza *et al* (Chiliza et al., 2015) recently reported a high prevalence of MetS (16%) in first episode antipsychotic naïve patients treated with flupenthixol decanoate.

Several studies have investigated the prevalence of the individual components of MetS rather than the full blown syndrome (Chadda et al., 2013; Garcia-Rizo, Kirkpatrick, Fernandez-Egea, Oliveira, & Bernardo, 2016; Perez-Iglesias et al., 2009; Ryan, Collins, & Thakore, 2003). There has historically been an interest in glucose homeostasis and mental illness (Kohen, 2004) with reports of an increased prevalence of fasting plasma glucose (Yang et al., 2015), impaired glucose tolerance (Fernandez-Egea et al., 2009; Ryan et al., 2003) and even frank diabetes mellitus (Verma, Subramaniam, Liew, & Poon, 2009) in antipsychotic naïve patients. However, as is the case with the overall prevalence of MetS, there is conflicting evidence with reports of no glucose and lipid abnormalities at the start of the illness (Arranz et al., 2004; Perez-Iglesias et al., 2009; Sengupta et al., 2008).

The first year after initiation of antipsychotic medication is generally regarded as a “critical” period for the development of MetS (Srihari et al., 2013). However, it is not clear at what point the metabolic abnormalities develop, because although the differential risk of individual antipsychotics for MetS is well established (Rummel-Kluge et al., 2010), the mechanisms underlying antipsychotic induced MetS are not fully understood (Ballon, Pajvani, Freyberg, Leibel, & Lieberman, 2014). Studies conducted to determine the trajectory of antipsychotic induced MetS have reported that metabolic abnormalities can occur as early as 47 days after treatment is initiated (Correll et al., 2014); but increases in MetS ranging from less than two fold (Chiliza et al., 2015) after one year of treatment to five - fold after 6 weeks (Saddichha, Manjunatha, Ameen, & Akhtar, 2008) have been reported.

Furthermore, non - pharmacological factors such as low levels of aerobic exercise (Nyboe, Vestergaard, Moeller, Lund, & Videbech, 2015), an unhealthy high fat, low fibre diet (Dipasquale et al., 2013), cigarette smoking (Lasser et al., 2000), genetic factors (Malan-Müller et al., 2016) and hypothalamic pituitary axis hyperactivity (Borges, Gayer-Anderson, & Mondelli, 2013) also contribute to the incidence of MetS after the initiation of antipsychotics.

There is significant variability regarding the incidence and trajectory of MetS in antipsychotic naive patients globally with limited information in usual care settings (Correll et al., 2014). Moreover, not many studies included matched control groups (Mitchell et al., 2013; Vancampfort et al., 2013). We therefore conducted a study to compare the prevalence of MetS at baseline, in antipsychotic naive patients with a first episode of SMI and a matched control group from S.A. Further, the incidence of MetS was determined in patients who were followed up for 12 months after initiation of antipsychotic medication.

Research design and Methods

Research design and participants

This was an, observational, longitudinal cohort study conducted in usual care at King Edward VIII Hospital (KEH) in Durban, South Africa. The psychiatric unit has been described previously (Saloojee, Burns, & Motala, 2016). In and out patients between the ages of 18 and 65 years with a first episode of schizophrenia, bipolar 1 mood disorder or schizoaffective disorder diagnosed using the Diagnostic and Statistical Manual of Mental Disorders (American Psychiatric Association. (2000). *Diagnostic and statistical manual of mental disorders: DSM-IV-TR*. Washington, DC: Author., n.d.) and who could provide written informed consent were recruited from January 2012 to December 2015.

Baseline and follow - up

At baseline, all study group participants were reported to have no lifetime exposure (antipsychotic naive) or minimal exposure to antipsychotic medication. Minimal exposure was defined as lifetime exposure not exceeding four days and categorized as antipsychotic naïve. Participants with co morbid substance use disorders were not excluded. Control subjects for this study included hospital staff, health science students and members of the public who were recruited by placing posters explaining the study purpose and procedures on hospital notice boards. Control subjects were generally physically healthy, had no lifetime diagnosis of a mental illness and were matched for age, gender and ethnicity with study subjects. Exclusion criteria for participants and controls included pregnancy and HIV.

All antipsychotic naive study subjects were commenced on antipsychotic medication at baseline. Study subjects without MetS at baseline who completed the 12 month follow up formed the follow - up group for this analysis. Study subjects were assessed at baseline and at the 12 month follow – up visit. Subjects' clinical records were examined for psychotropic medication. There were no study restrictions regarding the choice of antipsychotic prescribed, dose range, switching of antipsychotics or use of other psychotropic medication during the follow up period.. However, prescription practices were restricted by the

availability of antipsychotics on the provincial formulary. There are no early intervention services in this province. Control subjects were not followed up.

Anthropometric and laboratory assessments

Weight in kilograms (kg) and height in centimetres (cm) were measured for calculation of the body mass index (BMI). Waist circumference was measured using a soft tape measure at the mid-point between the upper border of the iliac crest and the inferior margin of the last rib. Blood pressure was measured with the subject in the sitting position after a ten minute rest; two readings were taken with a minimum interval of ten minutes and the mean of the two readings was used to record the blood pressure. Venous blood sampling was performed after an overnight fast for plasma glucose and serum lipids (total cholesterol, total triglycerides, high density lipoprotein [HDL] cholesterol, low density lipoprotein [LDL] cholesterol). MetS was defined using the 2009 Joint Interim Statement (JIS) definition (Alberti et al., 2009). Waist circumference cut off points used in this study: whites, blacks and coloureds (mixed ethnicity): men 94 cm, women 80 cm.

Statistical analysis

Data was analysed using the Statistical Package for Social Sciences (SPSS) version 21. In the baseline and follow – up study, data was analysed using means $\pm$ standard deviation (SD) for continuous data and frequency tables for categorical data. Significant associations in contingency tables (cross tabulations) were assessed using the standard Pearson's chi-square (χ^2) test. If an expected cell count in the cross tabulation was less than 5, then the Fishers exact test was used. An independent samples t-test was used for comparing differences in continuous variables, and a *p*-value less than 0.05 was considered to be statistically significant.

This study was approved by the Biomedical Research Ethics Committee of the University of KwaZulu - Natal. Written informed consent was obtained from all study and control subjects in English or Isizulu

Results

Baseline

Figure 1 shows the enrolment flow diagram for the baseline and follow - up study.. At baseline, there were 67 study (M:F 48:19) and 67 control subjects (M:F 48:19). The mean age was 22.8 and 23.3 years ($p=0.4$) in the study and control groups, respectively, and 97 % were of black African ethnicity. The most common diagnosis was schizophrenia (82 %), followed by schizoaffective disorder (11.9%) and bipolar disorder (6%). About half of the study subjects smoked cigarettes (50.7 %) and used cannabis (49.3%). Except for mean waist circumference which was higher in the study group ($p= 0.02$), there was no significant difference in the clinical and demographic characteristics between the study and control subjects (Table 1).

Table 2 shows that the overall prevalence of MetS was 4.5 % in both the study and control groups prior to the initiation of antipsychotic medication. There was no significant

difference for any of the individual components between the study and control groups. Despite the low overall prevalence of MetS there was a high prevalence of the elevated waist circumference (23.9 % and 20.9%) and low HDL cholesterol criterion (38.8% and 31.3 %) in the study and control subjects, respectively

Follow up

Study subjects with MetS at baseline (n = 3) were excluded from the follow up analysis. Of the 64 study subjects without MetS at baseline, only 36 subjects (M: F 25:11) completed the 12 month follow up, with a response rate of 56.3 % (Figure 1). The mean fasting plasma glucose was higher in the group that completed the follow up (4.89 mmol/l) compared to those that did not (4.46 mmol/l) ($p = 0.007$); but both values were within the normal range. There were no other statistically significant differences in the clinical and demographic characteristics of participants who completed followed up compared to those who did not complete follow up.

Table 3 shows that at the 12 month follow – up, all study subjects were on antipsychotic medication (n= 36) with 41.7% (15) on more than one psychotropic agent. Of the 21 subjects (58.3%) on antipsychotic monotherapy, 3 (8.3%) were on a FGA and 18 (50%) on a SGA. The most commonly prescribed antipsychotic alone or in combination with other drugs was risperidone (55.6 %). Only 2 subjects were taking clozapine (5.5%). There was a statistically significant increase in the mean BMI and waist circumference at follow up ($p = 0.03$).

By the end of the follow - up, only 2 subjects developed MetS with an incidence of 5.5 % and, except for the elevated waist circumference criterion ($p=0.02$), there was no statistically significant difference in any of the other MetS components from baseline (Table 4). No further analyses were conducted, including comparisons across antipsychotic medication because of the small number of incident cases.

Discussion

In this study, in a group of antipsychotic naïve individuals with a first episode of SMI, there was a low prevalence (4.5%) and incidence (5.5 %) of MetS using JIS criteria. At baseline, there was no difference in the prevalence of MetS and individual components in the study and control groups. After one year of antipsychotic treatment, there was a significant increase in the elevated waist circumference criterion of MetS from baseline.

The low prevalence of MetS in antipsychotic naïve individuals in this study confirms the findings of Fleischhacker *et al* (5.6%) (Fleischhacker et al., 2013), Patel *et al* (4.3%), (Patel et al., 2009) De Hert *et al* (5.6%) (De Hert et al., 2008) and Srihari *et al* (1.31%) (Srihari et al., 2013) and the meta- analyses of Mitchell *et al* (Mitchell et al., 2013) and Vancampfort *et al* (Vancampfort et al., 2013); but is in contrast to the findings of Enez Darcin *et al* (29.3 %) (Enez Darcin et al., 2015), Correll *et al* (13.2%) (Correll et al., 2014) and Chiliza *et al* (16%) (Chiliza et al., 2015).

Possible explanations for our finding of a low prevalence of MetS in antipsychotic naïve individuals with SMI include a high proportion of black African participants (97%) and an increased prevalence of cannabis abuse (49.3%).

Ethnic differences in the prevalence of MetS and the individual components have been reported previously in patients with a first and multiple episodes of mental illness (Tek et al., 2015) (McEvoy et al., 2005). Patel *et al* (Patel et al., 2009) reported a significantly lower prevalence in African American patients with minimal antipsychotic exposure compared to patients of other ethnicities (2.9 % vs. 5.3 %). There is a suggestion that current MetS definitions may underestimate the risk of MetS in blacks because the distribution of body fat and thresholds for insulin resistance are higher in black compared to white people (De Lucia Rolfe, Ong, Sleight, Dunger, & Norris, 2015). In the only other study from S.A, Chiliza *et al* (Chiliza et al., 2015), reported a higher prevalence of MetS (16 %) in antipsychotic naïve individuals with a first episode of schizophrenia. However, the proportion of black African participants was much lower in that study (14%) than in the current study (97 %). Taken together, our results and that of Chiliza *et al* (Chiliza et al., 2015) suggest that ethnic differences may contribute to the variable findings regarding the prevalence of MetS at the onset of the mental illness. A recent meta – analysis found that Asian patients were less susceptible to antipsychotic associated weight gain than patients from Western countries with a first episode of psychosis (Tek et al., 2015)

The metabolic effects of cannabis in the general population has been reported previously; and a recent study has shown that the risk of MetS was significantly lower in frequent cannabis users compared to occasional and non – users (Waterreus et al., 2016).

Despite the low overall prevalence of MetS in antipsychotic naïve individuals in this study, the picture was different for the individual MetS components: 23.9% patients had an elevated waist circumference, 9% had an elevated fasting plasma glucose and 39% had a low HDL cholesterol level. There was a low prevalence of raised triglyceride levels in both the study (1.5%) and control groups (1.5%); this is in keeping with a population study from rural KwaZulu – Natal (Motala, Esterhuizen, Pirie, & Omar, 2011) but different from that observed in large European (14%) (Fleischhacker et al., 2013) and North American (21.7 %) (Correll et al., 2014) studies of individuals with first episode schizophrenia. Similarly, the high prevalence of low HDL cholesterol levels (39%) among individuals with a first episode of SMI in this study was almost double that compared to first episode SMI patients in an international meta – analysis (20.4 %)(Mitchell et al., 2013) and a recent study from Europe (19.2 %) (Nyboe et al., 2015); but similar to that in the control group and is probably a reflection of the lipid profile of individuals from SSA (Motala et al., 2011; Sumner et al., 2010)

The incidence of MetS in this study (5.5 %) is lower than that reported by Attux *et al* (6.8 %) (Attux, Quintana, & Chav, 2007), Patel *et al* (13.4 %) (Patel et al., 2009) and De hert *et al* (SGA 27.8 %, FGA 9.8 %) (De Hert et al., 2008) after 6, 12 and 36 months of treatment respectively. Although not directly comparable. Srihari *et al* (Srihari et al., 2013), Patel *et al* (Patel et al., 2009), Chiliza *et al* (Chiliza et al., 2015) and Nyboe *et al* (Nyboe et al., 2015)

reported that the prevalence of MetS increased from 1.31% to 5.26%, 4.3 % to 13.4 %, 16% to 25% and from 10.2 % to 25% respectively after 1 year of treatment.

Discordant findings regarding the prevalence and incidence of MetS in antipsychotic naïve individuals are likely to be due to measured and unmeasured confounding variables arising from differences in methodology such as the variable cumulative duration of antipsychotic exposure (Chiliza et al., 2015; Wu et al., 2013), sample sizes ranging from 40 to 300 participants (Enez Darcin et al., 2015) gender and age distribution of the sample (Chadda et al., 2013), genetic factors (Malan-Müller et al., 2016), high rates of switching and discontinuation of antipsychotics in the first year of treatment (Whale et al., 2016) and follow up periods ranging from 22 days (Zhai et al., 2016) to one year (Chiliza et al., 2015; Nyboe et al., 2015).

There are several important limitations of this study. No conclusions can be drawn regarding risk of MetS and individual antipsychotics because the naturalistic design resulted in the non – randomization of participants to specific antipsychotic medication. It is also possible that the incidence of MetS in this study is unrelated to antipsychotic medication because adherence was not assured and the control group was not followed up. it.

Furthermore, there was a high rate of attrition in this study and it is possible that patients who experienced a higher rate of weight gain may have been lost to follow up as non – compliance has been associated with weight gain (Weiden, Mackell, & McDonnell, 2004). Lastly, the incidence of MetS may be biased because of the lack of information on lifestyle factors, high attrition rate, few incident cases and small sample size which could have resulted in a lack of power.

Despite these limitations the findings of this study in a black African population extends the work of others globally in trying to establish the role of ethnicity in the pre - treatment prevalence of MetS. This study also draws attention to the reality of treating patients with a first episode of SMI in usual care in Africa, with a study from Nigeria reporting a higher attrition rate (76%) than ours after the initiation of antipsychotics (Esan, 2014). Although antipsychotic discontinuation rates are high in first episode psychosis globally, disengagement from services is not (Whale et al., 2016). The negative findings of this study strengthen the need for the development of early intervention services in the developing world, given that there exists a window of opportunity for the prevention of MetS in the early phases of SMI..

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Figure 1.
Flow diagram for enrolment of baseline and follow – up subjects

Table 1

Demographic and clinical characteristics of the study group (n=67) (antipsychotic naive) and control group (n= 67) at baseline

Characteristic	Study group (n=67)	Control group (n=67)	p
Gender			
Male	71.6(48)	71.6(48)	1
Female	28.4 (19)	28.4(19)	1
Age (years) age $\pm$ SD	22.8 $\pm$ 3.7	23.3 $\pm$ 2.6	0.4
Age group (years)			
18–24	73.1(49)	73.1(49)	1
25–34	26.9(18)	26.9(18)	1
Ethnicity			
African	97(65)	97(65)	1
White	1.5(1)	1.5(1)	1
Coloured (mixed race)	1.5(1)	1.5(1)	1
Diagnosis			
Schizophrenia	82.1(55)	-	
Schizoaffective disorder	11.9(8)	-	
Bipolar mood disorder	6.0(4)	-	
Cigarette Smoking	50.7(34)	35.8(24)	0.08
Cannabis use	49.3 (33)		
Body Mass Index (BMI) (kg/m ²)	24.4 $\pm$ 3.5	24.6 $\pm$ 5.3	0.4
BMI category:			
Normal: < 25	62.7(42)	65.7(44)	
Overweight: 25 – 29.9	29.8(20)	20.9(14)	
Obese: > 30	7.5(5)	13.4(9)	
Waist circumference (cm)	83.6 $\pm$ 8.9	80 $\pm$ 10	0.02
Blood pressure (mmHg):			
Systolic	112.9 $\pm$ 11.2	113.7 $\pm$ 13.5	0.7
Diastolic	72.1 $\pm$ 8.2	70.7 $\pm$ 12.2	0.4
Fasting plasma glucose (mmol/l)	4.7 $\pm$ 0.7	4.8 $\pm$ 0.4	0.8
Serum lipids (mmol/l):			
Total cholesterol	3.7 $\pm$ 0.8	3.8 $\pm$ 0.7	0.6
Total triglycerides	0.7 $\pm$ 0.3	0.7 $\pm$ 0.4	0.9
High density lipoprotein cholesterol	1.2 $\pm$ 0.3	1.2 $\pm$ 0.3	0.8
Low density lipoprotein cholesterol	2.3 $\pm$ 1.2	2.2 $\pm$ 0.7	0.5

Data are % (n) and mean $\pm$ SD

Table 2

Prevalence of metabolic syndrome in the study group vs. control group at baseline

	Study group (n=67)	Control group (n=67)	p
Metabolic Syndrome (MetS)	4.5(3)	4.5(3)	1
Individual components of MetS:			
Increased waist circumference (cm)	23.9(16)	20.9(14)	0.68
Elevated blood pressure (mmHg):			
Systolic	4.5(3)	11.9(8)	0.11
Diastolic	9.0(6)	11.9(8)	0.57
Elevated fasting plasma glucose (mmol/l)	9.0(6)	11.9(8)	0.57
Elevated serum triglycerides (mmol/l)	1.5(1)	1.5(1)	1
Low high density lipoprotein cholesterol (mmol/l)	38.8(26)	31.3(21)	0.36
Number of MetS criteria met:			
0	29	30	0.86
1	24	23	0.86
2	11	11	1
3	3	3	1
4	0	0	0
5	0	0	0

Data are % (n)

Table 3

Demographic and clinical characteristics of antipsychotic naïve subjects with severe mental illness at baseline (n= 36) and after one year of treatment (n= 36)

Variable	Baseline (n=36)	Follow - up (n=36)	p
Gender			
Male	69.4(25)	69.4(25)	
Female	30.6(11)	30.6(11)	
Diagnosis			
Schizophrenia	80.6(29)	72.2(26)	
Schizoaffective disorder	2.8(1)	11.1(4)	
Bipolar mood disorder	16.7(6)	16.7(6)	
Cannabis use			
Negative	52.8(19)	47.2(17)	
Positive	47.2 (17)	52.8(19)	
Antipsychotic medication			
FGA monotherapy	-	8.3(3)	
SGA monotherapy	-	50 (18)	
Combined FGA and SGA	-	16.7(6)	
Zuclopenthixol decanoate	-	22.2(8)	
Sodium valproate	-	25(9)	
Polytherapy	-	41.7(15)	
Body Mass Index (BMI) (kg/m ²)	23.7 ± 3	25.5 ± 3.8	0.03
BMI category:			
Normal: < 25	72.2 (26)	47.2(17)	0.03
Overweight: 25 – 29.9	22.2(8)	41.7(15)	0.08
Obese: > 30	5.6 (2)	11.1(4)	0.4
Waist circumference (cm)	82.3 ± 9	87.6 ± 11.1	0.03
Blood pressure (mmHg):			
Systolic	113 ± 9	113.6 ± 9.2	0.79
Diastolic	71.2. ± 7.9	73.1 ± 7	0.30
Fasting plasma glucose (mmol/l)	4.9 ± 0.5	4.9 ± 0.5	0.72
Serum lipids (mmol/l):			
Total cholesterol	3.6 ± 0.74	3.8 ± 0.8	0.27
Total triglycerides	0.7 ± 0.3	0.7 ± 0.3	0.83
High density lipoprotein cholesterol	1.2 ± 0.3	1.3 ± 0.3	0.3
Low density lipoprotein cholesterol	2.1 ± 0.5	2.2 ± 0.7	0.46

Data are % (n) and mean ± SD

Table 4

Prevalence of metabolic syndrome and individual components at baseline and follow – up in subjects who completed one year of antipsychotic treatment (n=36)

Variable	Baseline (n=36)	Follow – up (n=36)	p
Metabolic Syndrome (MetS)	0 (0)	5.5 (2)	0.2
Individual components of MetS:			
Increased waist circumference (cm)	16.7(6)	41.7 (15)	0.02
Elevated blood pressure (mmHg):			
Systolic	2.8 (1)	8.3 (3)	0.3
Diastolic	5.6 (2)	0 (0)	0.2
Elevated fasting plasma glucose (mmol/l)	5.6 (2)	11.1 (4)	0.4
Elevated serum triglycerides (mmol/l)	2.8 (1)	2.8 (1)	1
Low high density lipoprotein –cholesterol (mmol/l)	44.4 (16)	33.3 (12)	0.3
Number of MetS criteria met:			
0	16	14	
1	12	12	
2	8	8	
3	0	2	
4	0	0	
5	0	0	

Data are %(n)