**ORIGINAL ARTICLE**

# Screening for Metabolic Syndrome in Patients on Antipsychotic Medication - A Cross-Sectional Study in a Pakistani Sample

RAHEEL AZIZ[1], AHSAN UL HAQ[2], BUSHRA MUBARIKA BUTT[3]

## ABSTRACT

Metabolic syndrome includes a number of cardiovascular risk factors that increase morbidity and mortality. Studies have identified increase in incidence of metabolic syndrome in patients with severe mental illness. Atypical antipsychotic medications have been linked with increased risk of metabolic syndrome.

**Method:** 50 consecutive patients who were on antipsychotic medication for 3 months or more were screened for metabolic syndrome using a brief questionnaire, measurement of waist circumference or Body Mass Index and blood pressure and a subsequent blood test for fasting glucose and lipid profile. The anonymised data was analysed and presence of metabolic syndrome was identified using the consensus criteria by WHO, International Diabetic Federation and US National Cholesterol Education Program Adult Treatment Panel III.

**Results:** 96% of the study population were taking second generation antipsychotic medication and for more than 12 months. 30% of the patients were obese and had BMI above 30Kg/m$^2$. 18% of the total sample had elevated BP at or above 135/85 mmHg. 16 % of the patients had elevated Fasting Plasma Glucose Levels above 100mg/dl. 62% of the patients had dyslipidemia. Although 62% of the study sample had at least one individual cardiovascular risk factor (elevated triglyceride level) and 30% had two risk factors (obesity and dyslipidemia), applying the consensus criteria for presence of metabolic syndrome and using cut-off of 3 out of 5 criteria, only 14% of the sample were categorised as having metabolic syndrome.

**Conclusion:** Patients taking antipsychotic medication long-term are at significant risk of metabolic syndrome. A careful risk–benefit analysis should inform the initial choice of antipsychotic medication. Psychiatrists should educate patients about the illness as well as medication related side effects and promote healthy lifestyle practices. Patients should be screened at baseline and monitored at regular intervals throughout the treatment.

**Keywords:** Metabolic, antipsychotic, psychiatric, Pakistani

## INTRODUCTION

Metabolic syndrome is a major public health problem and a global epidemic according to the World Health Organisation (WHO). [1,2] It is a combination of cardiovascular risk factors comprising of clinical signs and less than optimal laboratory investigations. It has four main components: Central Obesity, that can be measured by ethnicity specific reference values or assumed if Body Mass Index (BMI) is above 30 Kg/m$^2$, Hypertension, Insulin Resistance or elevated Fasting Plasma Glucose levels and Dyslipidemia that is raised fasting triglyceride or low levels of HDL (high density lipoprotein) cholesterol.

Various international organisations such as WHO[1], International Diabetes Federation[3] (IDF), European Group for the Study of Insulin Resistance[4] (EUGR) as well as US National Cholesterol Education Program Adult Treatment Panel III[5] (NCEP ATP III) have suggested slightly different combinations of above factors to identify metabolic syndrome though focussing mainly on insulin resistance and central obesity. According to the IDF definition[3], criteria for metabolic syndrome include central obesity plus any 2 of the following 4 factors: elevated fasting plasma glucose or prior diagnosis of type-2 diabetes, elevated fasting triglycerides, reduced fasting HDL cholesterol and elevated blood pressure. According to NCEP ATP III definition[5] any three of the 5 factors including central obesity are sufficient to identify metabolic syndrome. There has been a consensus that any three of the above individual components indicate presence of metabolic syndrome[6,7,8].

According to the estimates by IDF[3], around 20-25% population worldwide are affected by metabolic syndrome and it is linked to increase in the risk of heart attack or stroke by threefold and a twofold high likelihood of death. Metabolic syndrome in

[1]*Consultant Psychiatrist, Guided Discovery Limited, UK*
[2]*Visiting Consultant Psychiatrist, Dr A.Q. Khan Hospital, Lahore, Pakistan*
[3]*Consultant Psychiatrist, Nottinghamshire Healthcare Foundation NHS Trust, UK*
*Correspondence to Dr Raheel Aziz,*
*Email: draheelaz@doctors.org.uk*

Schizophrenia patients varies widely from 8.9% to 68% but is estimated to be around 5 times higher than that in the general population[9]. Prevalence of metabolic syndrome in bipolar disorder[10] has been estimated to be between 25 and 27%.

Patients with severe mental illness or Schizophrenia are at higher risk of chronic diseases including cardiovascular disease, non-insulin dependent diabetes[11] and respiratory disease and as a result have reduced life expectancy and die 10-20 years younger compared to the general population[12,13]. Schizophrenia is associated two- to three fold high prevalence of diabetes in comparison with the general population[11].

Antipsychotics are the mainstay of treatment in all forms of psychotic disorders, are widely used in Bipolar Affective Disorder and are prescribed off-label in other psychiatric conditions. The use of second generation or atypical antipsychotics has been increasing in the last couple of decades. Compared with the first-generation antipsychotics, atypical antipsychotics cause fewer extra-pyramidal side-effects however induce more weight gain and are associated with metabolic side-effects. People receiving long-term antipsychotic medication are at high risk of metabolic syndrome however are not routinely monitored for such risk.[14,15,16,17]

This cross-sectional study was carried out to evaluate presence of metabolic syndrome in a sample of Pakistani psychiatric population on long-term antipsychotic medication, with the aim to promote awareness about regular physical health checks and screening for and management of metabolic effects of antipsychotic medication.

## PATIENTS AND METHODS

The study population was identified from the psychiatry outpatient department of Dr A.Q. Khan Hospital Lahore. After seeking approval from the relevant hospital authority, patients who were taking antipsychotic medication for 3 months or longer were invited to take part in the screening study. 50 consecutive patients who consented to take part were included and given a brief questionnaire, a physical examination and a subsequent blood test. The questionnaire included enquiry into basic demographics, given psychiatric diagnosis, current antipsychotic medication dose and duration of treatment, smoking status and any current substance misuse, and personal as well as family history (in first degree relatives) of Hypertension, Diabetes and Ischaemic Heart Disease. A physical examination was carried out to measure Blood Pressure and waist circumference, and height and weight to calculate Body Mass Index. A fasting blood sample was arranged for Glucose and Lipid Profile and results were later incorporated in the respective data sheet. The cost of the investigations was funded through a charitable grant from non-pharmaceutical sources to ensure there was no conflict of interest. The patient identifiable information was treated confidentially. Anonymised data was analysed and presence of metabolic syndrome was confirmed using the cut-off of any 3 of the five criteria. The patients who screened positive for metabolic syndrome or any individual criteria were given health advice and offered review of treatment.

## RESULTS

Out of the total sample of 50 patients, 76% were male and 24% were female. 40% of the patients were overweight with their BMI above 25Kg/m$^2$. The mean BMI in this patient group was 33.9±5.5 Kg/m$^2$. Three quarters (75%) of the overweight patients and 30% of the total sample were obese and had BMI above 30Kg/m$^2$. 18% of the total sample had elevated BP at or above 135/85 mmHg. 16 % of the patients had elevated Fasting Plasma Glucose Levels above 100mg/dl. 62% of the patients had dyslipidemia with Fasting Triglyceride levels of more than 150mg/dl whilst a smaller proportion of these and 16% of the total sample had low HDL Cholesterol (Table-1).

Table 1: Markers of metabolic syndrome (n=50)

| | |
|---|---|
| **Age** | 35±10.9 |
| **Male** | 38(76%) |
| **Female** | 12(24%) |
| **Body Mass Index (Kg/m²)** | |
| <25 | 30(60%) |
| 25-30 | 5(10%) |
| >30 | 15(30%) |
| **Systolic Blood Pressure (mmHg)** | |
| <135/85 | 41(82%) |
| >135/85 | 9(18%) |
| **Fasting Plasma Glucose (mg/dl)** | |
| <100 | 42(84%) |
| >100 | 8(16%) |
| **Dyslipidemia** | |
| HDL Cholestrol<50mg/dl | |
| | 8(16%) |
| Triglycerides >150mg/dl | |
| | 31(62%) |

Majority of the patients (96%) were on second-generation or atypical antipsychotic medications. 47 patients (94%) were on current antipsychotic medication for more than 12 months. 35 patients (70%) had a diagnosis of Schizophrenia whilst 15(30%) had been diagnosed with Bipolar Affective Disorder. More than half (56%) had been unwell for

less than 5 years and the duration of illness was more than 5 years in 22 patients (44%). 2 patients (4%) had a prior diagnosis of Type 2 Diabetes and 8 patients( 16%) were known to have Hypertension. 23 patients (46%) reported a family history of Diabetes and 20 patients (40%) reported a family history of Hypertension in their first degree relatives. 10 patients (20%) were current smokers whilst 40 patients (80%) either didn't smoke or were ex-smokers and had given up smoking more than 12 months ago. Substance misuse was reported by only 2 patients (4%).

Although a greater proportion of patients (62%) had at least one individual cardiovascular risk factor (elevated triglyceride level) and 30% had two risk factors (obesity and dyslipidemia), applying the consensus criteria for presence of metabolic syndrome and using cut-off of 3 out of 5 criteria, only 7 patients (14%) were categorised as having metabolic syndrome. They were exclusively male and majority of them had a diagnosis of Schizophrenia. The duration of mental illness was 5 years or longer and all of them were on current antipsychotic medication for longer than 12 months. All of these patients were on second generation/atypical antipsychotic medications (Table-2). None of these patients were previously known to have Diabetes or Hypertension. Only 2 of the 7 patients (28%) had a known family history of Diabetes whilst 5 patients (62%) had a known family history of Hypertension in their first degree relatives. Only 2(28%) were current smokers (Table-3).

Table 2: Relationship with Illness Duration and Treatment

| | **Metabolic syndrome** | |
|---|---|---|
| | **Positive** | **Negative** |
| Male | 7(100%) | 31(72%) |
| Female | Nil | 12(28%) |
| Age | 34.4±7.6 | 35.0±11.4 |
| **Diagnosis** | | |
| Schizophrenia | 5(71.4%) | 30(69.8%) |
| Bipolar Disorder | 2(28.6%) | 13(30.2%) |
| **Duration of Illness** | | |
| upto 2 years | Nil | 7(16%) |
| 2- 5 years | 6(86%) | 15(35%) |
| 5-10 years | 1(14%) | 15(35%) |
| >10 years | Nil | 6(14%) |
| **Antipsychotics** | | |
| Clozapine | 3(43%) | 6(14%) |
| Olanzapine | Nil | 3(7%) |
| Quetiapine | 1(14%) | 15(35%) |
| Aripirazole | 2(29%) | 5(12%) |
| Risperidone | 1(14%) | 12(28%) |
| Haloperidol | Nil | 1(2%) |
| Flupenthixol depot | Nil | 1(2%) |
| **Treatment Length** | | |
| 3-12 months | Nil | 3(7%) |
| >12 months | 7(100%) | 40(93%) |

Table 3: Relationship with personal and family history

| | **Metabolic Syndrome** | |
|---|---|---|
| | **Positive** | **Negative** |
| **Personal history** | | |
| Cardiovascular | Unknown | Unknown |
| Diabetes | Unknown | 2(4.7%) |
| Hypertension | Unknown | 8(18.6%) |
| Dyslipidemia | Unknown | Unknown |
| **Family history** | | |
| Cardiovascular | Unknown | Unknown |
| Diabetes | 2(28.6%) | 21(48.8%) |
| Hypertension | 4(51.1%) | 16(37.2%) |
| Dyslipidemia | Unknown | Unknown |
| **Smoking status** | | |
| Current Smoker | 2(28.6%) | 8(18.6%) |
| Non/Ex-smoker | 5(71.4%) | 35(81.4%) |
| **Substance misuse** | | |
| | Nil | 2(4.7%) |

## DISCUSSION

Our study sample was small however it highlighted the significant risk of metabolic syndrome in patients on long-term antipsychotic medication irrespective of their diagnosis. Applying the cut-off of at least 3 criteria, only 14% of the study sample was categorized as having metabolic syndrome however, 40% of the sample was either pre-obese or obese and 62% had dyslipidemia in the form of elevated triglyceride levels. 30% of the study population had two cardiovascular risk factors. All these patients would be regarded as being at high risk of developing a full blown metabolic syndrome with potential increase in likelihood of cardiovascular adverse events.

Curiously, no patient who met 3 criteria had a pre-diagnosed Diabetes or Hypertension, although 4% of the total sample had a known personal history of Diabetes and 16% had Hypertension. It is plausible that once diagnosed with Hypertension or Diabetes, they were receiving effective treatment and didn't cumulate other cardiovascular risk factors.

Given the finding that 96% of the sample were taking second generation antipsychotic medication and for more than 12 months, it can be safely assumed that second generation antipsychotics are being prescribed in preference to older first generation antipsychotic medication. It can be either due to failure of previous treatment trials with other antipsychotics or due to accessible and relatively cheaper newer brands of second generation antipsychotic medication.

Although study numbers were small and definitive conclusions can't be reliably drawn, it appears that in patients taking long term second-generation antipsychotics, a significant proportion had already developed metabolic syndrome and a

much higher proportion was on the course to cumulate multiple cardiovascular risk factors. This finding is in keeping with the known evidence from various studies across the world.[14] In our study sample only 2 patients (4%) were on older or first generation or typical antipsychotics and neither of them had any markers for metabolic syndrome.

Potential causes of metabolic syndrome in psychiatric population include a number of factors.[6] Psychotropic medication including second-generation antipsychotics and mood stabilisers are known risk factors. Prescription of multiple antipsychotics is linked with a higher incidence of metabolic side effects in comparison with antipsychotic monotherapy[18].

Antipsychotic induced weight gain involves multiple mechanisms. These include antagonism at serotonin 5-HT2C receptors that increases insulin resistance and reduces glucose uptake by skeletal muscles and that increases the risk of diabetes, antihistamine effects that cause sedation and reduction in metabolism, and various genetic polymorphisms[19]. A possible common genetic predisposition to both metabolic syndrome and schizophrenia has also been suggested[20].

People with Schizophrenia often have a sedentary lifestyle, have poor dietary habits, smoke excessively and do little physical exercise[21] and these lifestyle factors have significant contribution to causation of metabolic syndrome. Negative symptoms of schizophrenia such as lack of motivation and volition and sedation caused by antipsychotic medication can partly account for such lifestyle.

Studies have also identified inflammation as a major component of metabolic syndrome and psychiatric disorders[22], evidenced by raised C - reactive protein, interleukin IL-6 and TNF-α in both conditions.

It is important that the prescribing clinicians/psychiatrists consider the potential risk of metabolic syndrome whilst making the initial selection of antipsychotic medication. If a patient has pre-existing metabolic syndrome, typical or first generation antipsychotics may offer a better risk-benefit profile. Changing medication later in the course of treatment may prove complicated due to potential risk of relapse.

The monitoring recommendations[23] are best followed using an integrated clinical approach[24]. This includes taking a personal and family history and identifying risk factors at baseline and at intervals after starting treatment; weigh patients track BMI at each follow up; obtain a baseline fasting glucose level and lipid profile for patients with BMI above 27 $kg/m^2$ , then repeat glucose and lipid levels at regular intervals especially if further weight gain occurs; and monitor glucose levels shortly after beginning a new antipsychotic medication and frequently when treating a patient with a prior history of diabetes.

Patients considered for prescription of antipsychotic medication should be screened before and during the treatment for metabolic syndrome. The most cost-effective and convenient way is to measure blood pressure and BMI or waist circumference[25] and these should be repeated for all patients on follow up appointments. Fasting glucose and lipid profile provide objective evidence of progression of metabolic syndrome.

Psychiatrists have a responsibility to educate their patients about their psychiatric illness and prescribed medication and promote healthy lifestyle in particular in patients with metabolic syndrome. A simple advice to eat a balanced diet and take regular exercise may be sufficient and if needed patients should be referred for specialist dietary advice or weight management programmes. Involvement of carers and family may provide additional support for the patients.

Pharmacological treatment of metabolic syndrome involves treatment for individual impaired parameters. Antihypertensive, cholesterol lowering and diabetic medications may be indicated and should be initiated and monitored under the guidance of the appropriate specialists/physicians.

## CONCLUSION

Metabolic syndrome is a significant risk in patients who are prescribed antipsychotic medication. The relationship between metabolic syndrome and psychiatric disorders is complex and can pose challenge in clinical management. A careful risk–benefit analysis should inform the initial choice of antipsychotic medication. Psychiatrists should educate their patients about the illness as well as medication related side effects and promote healthy lifestyle practices. Patients on antipsychotic medication should be screened at baseline and then monitored at regular intervals throughout the treatment. It is imperative to recognise and treat metabolic syndrome early to prevent later complications.

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