Journal of Psychiatry

Japir and Osman, J Psychiatry 2020, 23:1

Research Article Open Access

Olanzapine-Induced Metabolic Syndrome What Can We Learn from Africa, Sudan

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Abstract

It is still unclear whether ethnic and cultural differences of individuals living in Africa continent would affect the emergence of the well-established findings of olanzapine related metabolic syndrome in the international literature, in ways that can be attributed to idiosyncratic, biological, cultural or otherwise. Therefore, we carried out a cross-sectional study involving 100 candidates enrolled, consecutively from two national psychiatric clinics in Khartoum, Sudan. All participants were taking Olanzapine monotherapy for a period of nine month or more. This article describes findings related to presence or absence of Metabolic Syndrome (MetS), and any medical and sociodemographic factors associated with the condition. We also, worked out the 10 year Framingham risk score for the likelihood of developing coronary heart disease for all candidates. Metabolic syndrome was found in 45% of all subjects. Moreover, candidates that presented with metabolic syndrome did so, regardless of the dose size of olanzapine, the diagnosis prescribed for or their gender. However, greater vulnerability for developing MetS, was detected in subjects with family history of diabetes. Consequently, these patients were found to have a higher 10 year Framingham risk score for coronary disease.

Keywords: Metabolic syndrome; Olanzapine; Weight gain

Introduction

Significant variation exists in the prevalence of Metabolic Syndrome (MetS), depending on the defining diagnostic criteria for the condition; the population studied and associated correlates. Regardless, the obesity epidemic is increasing the prevalence of MetS in all western countries [1]. Around 34% of people met the criteria for metabolic syndrome set by the National Cholesterol Education Program Adult Treatment Panel III (NCEP ATPIII), National Health and Nutrition Examination Survey (NHANES, 2003-2006) [2,3]. Its estimated that there has been a 5% increase in the prevalence of MetS in the last 15 years, according to the National Health and Nutrition Examination Survey (NHANES) [4,5]. Similar results were obtained by the WHO with respect to their estimates of MetS [6,7]. A high prevalence has been estimated based on the definition of the International Diabetes Federation (IDF) [8,9]. IDF definition adopted a lower cut off values for waist circumference, thus, estimated higher prevalence [10]. Despite the variation in estimating the prevalence of MetS, it is still estimated that a large majority of the population is at an increased risk of developing Diabetes Mellitus Type 2 (DMT2) and Coronary Heart Disease (CHD) [11].

The prevalence of MetS is also increasing in developing countries, with an estimated figure of 9.8% in Indian urban dwellers and 42% in urban Iranian females [12]. The increased prevalence of MetS in developing countries is associated with a shift from a traditional lifestyle to a more western lifestyle [13,14].

Multiple factors contribute to the rise in obesity and MetS in developing countries, namely epidemiological and demographic transition (demographic transition refers to the shift to low fertility, low mortality and high life expectancy; epidemiological transition means shifting from infectious diseases to diseases related to lifestyle). This shift in metabolism and body composition then increases the BMI, resulting in generalized obesity and an increase in both DMT2 and dyslipidaemia [15].

Earlier studies have found a link between some mental illnesses and MetS [16-18]. Reasons given for this connections were genetic in case of schizophrenia, beside negative psychopathology, unhealthy diet and sedentary lifestyle [19,20]. This link, however was later disputed by findings that patients developed weight gain and MetS regardless of their diagnosis [21].

An increasing body of research suggests that weight gain and obesity due to Second Generation Antipsychotics (SGA), occurs at an early phase of treatment in patients with psychosis [22-24].

Moreover, use of atypical antipsychotics produced about four times greater likelihood for developing MS. This is of concern because atypical antipsychotics are the first- choice medications for schizophrenia [24,25].

However, little is known of MetS prevalence in Africa, and particularly in vulnerable psychiatric patients on olanzapine treatment, Therefore, this study aimed to examine whether these earlier findings regarding MetS in relation to SGA, namely olanzapine, applies equally in the cultural and geographical setting of Sudan, in Africa.

Methodology

Study design

This was a cross-sectional hospital-based study, conducted in the period from 25th January 2014 to 25th April 2014. The study was carried out at outpatient clinics of two national psychiatric hospitals in capital of Sudan (Khartoum), i.e. Eltigani Elmahi Teaching Hospital and Baashar Teaching Hospital. The former is the biggest psychiatric hospital in Sudan. Both hospitals cater for a population of 6 million, besides receiving referrals from surrounding provinces. Patients,were screened by a senior psychiatrists for confirmation of eligibility for

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Received: May 10, 2019; **Accepted:** December 28, 2019; **Published:** January 03, 2020

Citation: Japir AMA, Osman AH (2020) Olanzapine-Induced Metabolic Syndrome What Can We Learn from Africa, Sudan. J Psychiatry 23: 470.

this study, using the International Classification of Disease (ICD10), criteria for confirmation of functional psychosis, as, entry criteria, beside must have been taking Olanzepine monotherapy (not combined with any other psychotropic medication) for a period of nine Month or more. We excluded from the study, pregnant women, patients with serious physical organic illness affecting their weight such as, neoplasm, anorexia nervosa and patients with interrupted adherence to treatment.

All 167 eligible patients, who attended the outpatient clinics during the study period, invited to take part in the study; 57 refused to participate, and 10 patients were too ill and lacked the capacity to provide informed consent. In total, 100 patients agreed to take part in the study, and signed a consent form.

Procedure

Participants were given verbal instructions to fast in the ward for 12 hours. Then, blood samples were taken from each participant. A research assistant took a detailed history in a semi-structured interview designed by the research team to assess for risk factors as detailed in the results. Anthropometric measures were taken according to the standardized WHO protocol (the waist was measured at the midpoint between the last palpable rib and the top of the iliac crest and the hip was measured around the widest portion of the buttocks with minimal clothing and minimal tension using a flexible non-stretchable tape). The waist-hip ratio was calculated for each subject. Height and weight were measured and the Body Mass Index (BMI) was calculated. Conventional BMI categories were used (underweight ≤ 20, normal 20-25, overweight 25-30, and obese ≥ 30). Blood samples, were analysed by Sudan National laboratory, for blood sugar, cholesterol, Trigleceride Lipoproteins (TGL), and High Density Lipoproteins (HDL).

We used guidelines recommended by the International Diabetes Federation (IDF), to identify MS, as it gives ethnic specific values for hip and waist circumference that were used as part of the 4 other criteria for diagnosis of this condition; other risk factors, dyslipidaemia (raised triglycerides and lowered high-density lipoprotein cholesterol), elevated TGLs (≥150 mg/dL) or drug treatment for elevated TGL; reduced HDL-C (<40 mg/dL in males, <50 mg/dL in females) or drug treatment for reduced HDL-C; elevated Blood Pressure (BP), (systolic ≥ 130 mmHg and/or diastolic ≥ 85 mmHg) or antihypertensive treatment in a patient with Hypertension (HTN); and elevated FBG (≥ 100 mg/dL) or drug treatment for hyperglycemia.

For every participant, we calculated the Framingham risk score using the modified classic Framingham equation, with 10 year cardiovascular mortality as the endpoint. This is a probabilistic prediction of mortality *via* cardiovascular reason, using the generally known metabolic risks; thus, including the weighted risk factors age, sex, systolic blood pressure, total and high density lipoprotein cholesterol concentrations, smoking, diabetes mellitus, and electrocardiogram based left ventricular hypertrophy.

Compliance with ethical standards

"All procedures performed in studies involving human participants were in accordance with the ethical standards of Sudanese Medical Specialization Board, and, that of the Helsinki declaration 1964, and its later amendments or comparable ethical standards."

Consent: Formal permissions were received from all relevant hospital administerations. Written consents were obtained from all participants, who were provided with an information leaflet explaining the study procedures and confidentiality.

Results

In total, 100 subjects took part in this study; 55 participants were female (55%) and 45 were male (45%). Table 1 shows the prevalence of MetS according to gender; 24 (43.6%) females met the criteria for MetS while 21 (46.6%) males fulfilled criteria for MetS, with a total of 45% of all subject showing evidence of MetS. No significant association was found between MetS and gender (p-value 0.646). Table 2 reveals the distribution of the participants, according to BMI; 45% were within the normal range, 40% were overweight, 12% were obese and 3% were within the underweight category (mean BMI 26.1).

Table 3 shows the distribution of participants according to the dose range of olanzapine; 86 patients were taking 5-10 mg olanzapine, 6 patients were taking 11-15 mg and 8 patients were on a dose of more than 15 mg a day. In this sample, we found that there was no specific association between the dose of olanzapine or the duration of treatment as long as the dose of olanzapine is 5 mg or more for a duration of nine months or more (p-value 0.56 and 0.43, respectively). Table 4 shows the distribution of the study population according to the duration of olanzapine treatment; 13 patients had been taking olanzapine for 9-12 months, 9 patients were on olanzapine for 13-16 months, 1 patient had been on olanzapine for 17-20 months, 4 patients for 21-24 months, and 73 patients had been taking olanzapine for a period of more than 24 months.

Table 5 shows the distribution of participants according to use of alcohol and cigarette smoking, Table 6 shows distribution of participants according to blood high density lipoproteins, and Table 7 shows known family history of chronic vascular disease, diabetes, and hypertension

(No=100)	No.	%
Male	45	45%
Female	55	55%

Table 1: Distribution of the study population according to gender.

Criterion		Olanzapine dose		
		5 to 10 mg	11 to 15 mg	16 to 20 mg
Metabolic syndrome	Yes	40	4	1
	No	46	4	5
Total		86	8	6
p-value 0.349				

Table 2: Distribution of metabolic syndrome according to dose range.

Criterion		Duration of olanzapine treatment in months				
		9 to 12	13 to 16	17 to 20	21 to 24	>24
Metabolic syndrome	Yes	6	4	1	1	33
	No	7	5	0	3	40
p-value 0.595						

Table 3: Distribution of metabolic syndrome according to the duration of olanzapine treatment.

Criterion		Mental illnesses		
		Affective	Schizophrenia	Schizoaffective
Metabolic syndrome	Yes	17	24	4
	No	16	35	4
Total		33	59	8
p-value 0.579				

Table 4: Distribution of metabolic syndrome according to mental illness.

Criterion		Smoke cigarettes			
		Heavy	Moderate	Light	None
Drink alcohol	Yes	0	1	1	1
	No	2	4	18	73
Total		2	5	19	74

Table 5: Distribution of smokers and non-smokers according to alcohol consumption.

Criterion		Number of participants
Triglyceride	High	56
	Normal	44
HDL	Low	53
	Normal	47

Table 6: Distribution of participants according to their triglyceride and HDL values.

First degree diseases	Chronic CVD	DM	DM & HTN	HTN	None	Total
CHD	0	0	0	0	2	2
DM	0	1	1	0	16	18
HTN	0	0	0	1	15	16
DM & HTN	0	0	0	1	6	7
DM & CVD	0	0	0	0	1	1
HTN & CVD	0	0	0	0	5	5
DM, HTN & CVD	0	0	0	1	2	3
DM, HTN & CHD	0	0	0	1	0	1
None	1	0	0	1	45	47
Total	1	1	1	5	92	100
p-value 0.223						
Note: CHD: Coronary Heart Disease; DM: Diabetes Mellitus; HTN: Hypertension; CVD: Cerebrovascular Disease						

Table 7: Association between chronic diseases in the participants and chronic diseases in participant's first-degree relatives.

in nearest relatives. Data from these three tables were used to determine the 10 year Framingham risk score for CHD.

Discussion

MetS has many different diagnostic criteria; in this study, we used the International Diabetic Federation criteria for two reasons: it gives ethnicity-specific reference values for waist circumference and it is an easy and accurate research tool.

Our study showed that the prevalence of MetS in Sudanese patients receiving olanzapine monotherapy for more than nine months was 45% which is in agreement with similar studies in developing countries [26-28].

Our results reveal that 30% of participants (30 patients) were not known to be diabetic but showed an impaired fasting glucose level (more than 100 mg/dL). This may indicate a diabetogenic effect of olanzapine. Similar findings have been obtained by other researchers, that they found association of olanzapine induced MetS and diabetes in individuals that otherwise did not have strong family history of diabetes [22,29,30].

Our findings highlight the important fact that olanzapine-related weight gain and MetS are not gender, age, diagnosis or dose-related side effects, as long as the individual patient has taken olanzapine for a period of more than nine months (p-values 0.595, 0.349, 0.595, respectively).

In contrast to earlier reported findings by some researchers Correl and De Hert et al. showing that MetS is severe and frequent in patients diagnosed with schizophrenia, we did not find this effect specifically linked to a diagnosis [31,32]. In fact, all patients with all forms of psychosis who were receiving olanzapine presented with MetS in equal proportions, with no specific effect to diagnosis as much as to olanzapine intake (p-value 0.579).

The Framingham risk score for the probability of developing CHD in 10 years is generally considered to be sensitive scale for estimating future cardiac risk in MetS patients [33]. The parameters of this scale include smoking, HDL, triglycerides, total cholesterol, age, gender and hypertension. In total, 40% of our subjects (40 patients) were overweight with a mean BMI of 26.1. Therefore, we found that 2 (2%) patients had more than a 16% probability of developing CHD in 10 years, 6 (6%) had a 11-15% probability, 18 (18%) had a 6-10% probability, 21 (21%) had a 1%-5% probability and 53 (53%) had a less than 1% probability. Comparable results have been found in many other studies [34-42].

Conclusion

The prevalence of MetS in Sudanese psychiatric patients receiving olanzapine monotherapy for more than nine months is 45%. The prevalence of MetS after nine months does not appear to be gender, duration, diagnosis or dose dependent. Consequently 47% of participants have had considerably high, Framingham risk score for CHD.

Recommendations

Large longitudinal controlled studies should be conducted to determine the mechanism of how olanzapine induces MetS on the molecular level and the exact associating risk factors, in order to formulate better advice, clinical decisions and patient selection. Moreover, clinical strategies to minimize the incidence of MetS and other metabolic disorders among patients taking olanzapine should be put in place in all countries.

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