Beta-cell Function and Metabolic Clearance Rate of Glucose in Patients with Major Mental Health Disorders on Antipsychotic Drug Treatment

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Authors' contribution: KSA designed the study, VOL made the diagnosis, SKR did the laboratory analysis, all authors recruited the patients, SKR wrote the draft of the manuscript while all authors edited and approved of the final draft of manuscript, KSA supervised the entire research.

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Abstract: Background: Insulin resistance and metabolic alteration continue to be essential features of major mental health disorders (MMHD) with poorly understood and multifaceted mechanisms. This study was carried out to provide information on insulin resistance, beta-cell function, metabolic clearance rate of glucose and their possible interplay with duration of antipsychotic use in patients with major mental health disorders.

Methodology: Plasma levels of glucose and insulin were determined in 124 patients with MMHD after an overnight fast and at 30 and 120 min of standard Oral Glucose Tolerance Test. Thereafter, indices of insulin resistance, beta-cell function and estimated metabolic clearance rate of glucose (eMCR) were calculated appropriately. Statistical analysis was done using ANOVA, Kruskal Wallis, independent Student's t-test and Mann-Whitney *U*. *P*-values less than 0.05 were considered as statistically significant.

Results: Metabolic factors (fasting and postprandial glucose and insulin), indices of insulin sensitivity and β-cell function were not significantly different when patients with schizophrenia, bipolar and depression were compared with one another. Postprandial insulin level at 30 min (30 min PPI), estimated First and Second Phases of Insulin Release (eFPIR, eSPIR) were significantly lower in patients on atypical antipsychotic drugs [18.15 (3.57-40.35) μIU/ml), 617.63 (320.06-911.31) pmol/l, 180.30 (114.82–249.39) pmol/l] compared with patients on typical antipsychotic drugs [27.48 (13.33–47.68) μIU/ml, 767.69 (530.58-1198.35) pmol/l, 209.89 (154.01-310.97) pmol/l]. Furthermore, the mean waist circumference and body mass index were significantly higher in patients who have been on anti-psychotic drug for more than 10 years compared with patients with less than 5 years history of anti-psychotic use. eMCR of glucose progressively declined with increasing duration of antipsychotic use and it was significantly lower in patients who have been on antipsychotic drugs for more than 10 years [8.09 (5.90-9.44) ml.kg^{-1}.min^{-1}] compared with patients who have been on the drugs for less than 5 years [9.03 (7.47-10.04) ml.kg^{-1}.min^{-1}].

Conclusion: Patients on atypical antipsychotics seem to have insulin secretion phases consistent with β-cell dysfunction. Also, chronicity of antipsychotic treatment predisposes patients with major mental health disorders to central adiposity and low metabolic clearance rate of glucose, a forerunner of glucose intolerance.

Keywords: Beta-cell dysfunction■Chronic antipsychotic treatment■Insulin resistance■Major mental health disorders■Metabolic clearance rate of glucose

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INTRODUCTION

Insulin, secreted by the beta-cell of the pancreas, is an anabolic hormone with pleiotropic effects on the liver, skeletal muscle, adipose tissue and brain cells among others.[1] The association between insulin and psychosis was reported decades ago when deep insulin coma therapy was used to treat schizophrenia.[2]

Impairment in insulin action and/or secretion is associated with metabolic disorders such as diabetes, and cardiovascular diseases.[3] It is suggested that physiologic stress, such as mental illness could trigger insulin resistance (IR) peripherally in order to ensure steady supply of insulin and glucose to the brain to prevent neuronal death.[4–6] Shiloah et al.[7] reported that individuals with psychosis have concomitant insulin resistance and β-cell dysfunction, which reverse as the psychosis resolves. Recently, Akinlade et al.[8] also reported a strong association between major mental illnesses and metabolic disorders.

Although the aetiology of IR in major mental illnesses is poorly understood, there is an avalanche of reports suggesting that it is multifactorial.[9] For example, hypothalamic-pituitary-adrenal (HPA) axis activation, hypo-functioning in the central serotonin system, sympathomedullary system, immunological system and the use of depressants are some of the factors associated with insulin resistance in patients with depression.[9–11] Peripheral insulin resistance which usually manifests as hyperinsulinaemia with its associated low glucose utilization, is suggested to be responsible for decreased appetite and

weight loss in patients with depression.[9,12] Similarly, glucoregulatory disturbances have been noticed in patients with schizophrenia even before the advent of antipsychosis.[13,14] However, this disturbances became prominent after the introduction of antipsychotics.[15]

Hyperinsulinaemia and higher insulin resistance are reported to be higher in schizophrenics on antipsychotics compared with schizophrenics not receiving antipsychotic. Interestingly, there was no significant difference in their fasting glucose levels.[14] In contrast to depression and schizophrenia, manic state was associated with increased insulin sensitivity, which was not related to lithium.[16] It however remains unclear if this sensitivity is related to increased physical activity usually associated with mania.[9] In patients with bipolar, fasting and postprandial hyperinsulinaemia as well as elevated HOMA-IR value have been reported. These partly explain the high prevalence of IR and T2DM risk reported in them.[17,18] Furthermore, current use of antipsychotics has been shown to be significantly related to IR which is considered an important factor in resistance to antipsychotic treatment in bipolar disorder.[19]

It is becoming apparent that antipsychotic-induced IR evolves through mechanisms that are somewhat different from the normal mechanisms in diabetes.[20] Johnson et al.[21] showed that antipsychotics cause $\alpha 2$ antagonism and inactivate muscarinic receptors thereby causing reduction in insulin release induced by acetycholine (ACh) which subsequently cause hyperglycaemia. Other reports also showed that certain atypical antipsychotics such as olanzapine and clozapine have high affinity for histaminergic, muscarinic, orexigenic and adrenergic receptors which causes increased expression of orexigenic peptides, reduction in lipolytic activity in white adipose tissue, reduction in uncoupling protein-1 (UCP-1) expression and loss of leptin signaling resulting in hyperphagic behavior, fat accumulation, reduced thermogenesis (due to reduction of orexin) and consequently, weight gain which plays an important role in the development of diabetes and cardiovascular diseases.[22–26]

In this environment, there is the dearth of information on IR, beta-cell function, metabolic clearance rate of glucose and their possible interplay with the use and chronicity of antipsychotic treatment in patients with major mental health disorders. This thus, serves as the basis for this study.

MATERIALS AND METHODS

Study centre

The study was carried out between January and April 2015 at the New World Psychiatric Hospital, a 60 bedded mental health facility located in South-West Local Government area of Ibadan, Oyo state, Nigeria.

Study participants and recruitment technique

We recruited consecutive patients who utilized the study centre during the study period that met the inclusion criteria. The first participant was randomly selected, and subsequent ones, consecutively until they were all interviewed. Information on the study participants and their characteristics are already reported.[8] Briefly, 135 adult patients with mental illness were enrolled into the study after which 124 of them with either schizophrenia, depression or bipolar were carefully selected for this study.

Diagnosis of major mental disorders

The diagnosis of either schizophrenia, depression or bipolar disorder was made using the Structured Clinical Interview for DSM IV Axis I Disorder (SCID) version 2.0[27] to confirm all the initial diagnoses made before the commencement of the study. The diagnosis was allocated by one of us (VOL), a trained psychiatrist.

Exclusion criteria

We excluded patients who were less than 18 years of age and all those with severe and unstable general medial conditions.

Ethical approval

The study was approved by the University of Ibadan/University College Hospital (UI/UCH) Joint Ethics Review Committee while written informed consent/assent was obtained from the participants or their guardians as appropriate.

Sample collection

Venous blood was collected after an overnight fast (0 min) and at 30 and 120 min post standard 75-g oral glucose tolerance test (OGTT) to determine the plasma levels of glucose and insulin.

Laboratory analyses

Plasma level of glucose was determined using glucose oxidase method while insulin level was determined using ELISA (Genway Biotechnology, USA) following the manufacturers' instructions.

Calculation of indices of insulin resistance/sensitivity

a. Computer-based homeostatic model assessment (HOMA) index of insulin sensitivity (HOMA2-S%), computer-based homeostatic model assessment (HOMA) index of beta-cell function (HOMA2-B%), and computer-based homeostatic model assessment

Table 1. Characteristics of the study participants.

Parameters	Mean ± Standard deviation	Median (Interquartile range)
Anthropometric & clinical indices		
WC (cm)	86.93 ± 13.95	85.00 (77.00-96.00)
BMI (kg/m^2)	25.28 ± 5.37	24.40 (21.23-28.08)
SBP (mmHg)	113.01 ± 14.59	110.00 (100.00-120.00)
DBP (mmHg)	74.91 ± 10.70	70.00 (70.00-80.00)
Metabolic factors		
FPG (mg/dl)	91.39 ± 15.67	89.60 (82.58-98.93)
30 min PPG (mg/dl)	136.04 ± 28.38	132.10 (115.70-151.80)
2 h PPG (mg/dl)	123.67 ± 31.07	117.00 (103.10-138.60)
FPI (μIU/ml)	8.86 ± 23.88	1.76 (0.68-4.05)
30 min PPI (μIU/ml)	38.85 ± 42.67	28.05 (8.90-50.32)
2 h PPI (μIU/ml)	50.57 ± 50.06	32.48 (18.11-60.61)
Indices of insulin sensitivity/resistance		
HOMA-IR	2.12 ± 5.84	0.38 (0.17-0.92)
HOMA2-IR	1.05 ± 2.64	0.23 (0.09-0.52)
FIRI	34.36 ± 94.56	6.10 (2.83-14.96)
1/FI	1.80 ± 5.22	0.57 (0.25-1.47)
QUICKI	0.52 ± 0.35	0.46 (0.39-0.54)
HOMA2-S%	1385.98 ± 4037.80	440.55 (191.60-1072.60)
eMCR (ml.kg^{-1}.min^{-1})	8.12 ± 2.26	8.50 (6.74-9.82)
Modified Matsuda	2.21 ± 8.59	0.48 (0.21-1.25)
Indices of β-cell function		
HOMA2-β%	72.67 ± 118.95	33.20 (23.23-59.98)
eFPIR(pmol/l)	935.52 ± 901.73	683.97 (464.82-1084.16)
eSPIR(pmol/l)	253.28 ± 211.07	195.26 (144.96-277.21)

WC = waist circumference, BMI = body mass index, SBP = systolic blood pressure, DBP = diastolic blood pressure, FPG = fasting plasma glucose, 30 min PPG = 30 min postprandial glucose, 2 h PPG = 2 h postprandial glucose, FPI = fasting plasma insulin, 30 min PPI = 30 min postprandial insulin, 2 h PPI = 2 h postprandial insulin, HOMA = homeostasis model assessment, HOMA-S% = HOMA of insulin sensitivity, HOMA-B% = HOMA of β-cell function, IR = insulin resistance, FIRI = fasting insulin resistance index, FI = fasting insulin, QUICKI = quantitative insulin sensitivity check index, eMCR = estimated metabolic clearance rate of glucose, eFPIS = estimated first phase of insulin release, eSPIS = estimated second phase of insulin release.

(HOMA) index of insulin resistance (HOMA2-IR) were calculated using homeostasis model assessment-2 (HOMA-2) calculator (www.dtu.ox.ac.uk/homa).

b. Homeostasis model assessment-estimated insulin resistance (HOMA-IR) was calculated as the product of fasting insulin (μU/ml) and fasting glucose (mmol/l) divided by 22.5
c. Quantitative Insulin Sensitivity Check Index (QUICKI) was calculated as 1/[log fasting insulin (μU/ml) + log fasting glucose (mg/dl)]
d. 1/FI was calculated as the reciprocal of fasting insulin
e. Fasting insulin resistance index (FIRI) was calculated as (fasting glucose × fasting insulin)/25.
f. Modified Matsuda index ($ISI_{Matsuda}$) was calculated as $10{,}000/\sqrt{[(G_{fasting} \times I_{fasting}) \times (G_{OGTT} \times I_{OGTT})]}$, where fasting glucose and insulin data are taken from time 0 of the OGTT and at 30 min during the OGTT. The square root is used to correct for nonlinear distribution of insulin, and 10,000 is a scaling factor in the equation.[3]

Table 2. Metabolic factors, indices of insulin sensitivity and β-cell function in patients with schizophrenia, bipolar disorder and depression.

Parameters	Schizophrenia (n = 81)	Bipolar (n = 27)	Depression (n = 14)	*P*-value
Metabolic factors				
FPG (mg/dl)	92.81 ± 16.31	89.24 ± 15.19	87.36 ± 12.18	0.349
30 min PPG (mg/dl)	136.69 ± 30.56	137.95 ± 24.66	128.75 ± 22.18	0.584
2 h PPG (mg/dl)	121.32 ± 28.49	128.12 ± 33.63	128.81 ± 40.47	0.499
FPI (μIU/ml)	1.60 (0.62-3.45)	1.54 (0.64-3.03)	2.73 (1.13-14.20)	0.303
30 min PPI (μIU/ml)	27.10 (5.84-51.86)	32.20 (13.66-43.18)	21.51 (6.59-49.60)	0.774
2 h PPI (μIU/ml)	32.38 (18.59-62.57)	29.40 (12.80-51.42)	27.67 (12.16-125.24)	0.824
Indices of insulin sensitivity/resistance				
HOMA-IR	0.35 (0.16-0.75)	0.33 (0.13-0.62)	0.52 (0.28-2.90)	0.381
HOMA2-IR	0.21 (0.09-0.44)	0.21 (0.08-0.38)	0.34 (0.15-1.78)	0.332
FIRI	0.56 (2.54-12.16)	5.36 (2.05-10.03)	8.44 (4.60-46.95)	0.381
1/FI	0.63 (0.29-1.62)	0.66 (0.33-1.58)	0.37 (0.07-1.08)	0.303
QUICKI	0.47 (0.40-0.56)	0.47 (0.42-0.59)	0.43 (0.33-0.50)	0.381
HOMA2-S%	474.20 (225.65-1156.85)	489.90 (263.30-1234.58)	293.70 (57.25-783.65)	0.332
eMCR ($ml.kg^{-1}.min^{-1}$)	8.54 (7.30-10.01)	8.38 (5.99-9.58)	8.52 (4.17-9.85)	0.597
Modified Matsuda	0.48 (0.21-1.38)	0.39 (0.23-1.02)	0.44 (0.08-0.76)	0.807
Indices of β-cell function				
HOMA2-β%	31.50 (22.85-52.25)	28.40 (22.30-45.53)	56.70 (28.20-169.80)	0.285
eFPIR(pmol/l)	674.94 (418.06-1031.20)	701.05 (541.53-1015.58)	913.29 (513.51-1528.68)	0.915
eSPIR(pmol/l)	187.61 (136.18-266.84)	200.06 (152.75-258.61)	237.34 (151.67-392.47)	0.904

WC = waist circumference, BMI = body mass index, SBP = systolic blood pressure, DBP = diastolic blood pressure, FPG = fasting plasma glucose, 30 min PPG = 30 min postprandial glucose, 2 h PPG = 2 h postprandial glucose, FPI = fasting plasma insulin, 30 min PPI = 30 min postprandial insulin, 2 h PPI = 2 h postprandial insulin, HOMA = homeostasis model assessment, HOMA-S% = HOMA of insulin sensitivity, HOMA-B% = HOMA of β-cell function, IR = insulin resistance, FIRI = fasting insulin resistance index, FI = fasting insulin, QUICKI = quantitative insulin sensitivity check index, eMCR = estimated metabolic clearance rate of glucose, eFPIS = estimated first phase of insulin release, eSPIS = estimated second phase of insulin release.

g. Estimated metabolic clearance rate of glucose ($ml.kg^{-1}.min^{-1}$) was calculated as $19.240 - 0.281 \times BMI - 0.00498 \times I_{120} - 0.333 \times G_{120}$.[28]
h. Estimated first phase insulin release (pmol/l) was calculated as $1283 + 1.829 \times I_{30} - 138.7 \times G_{30} + 3.772 \times I_0$.[28]
i. Estimated second phase insulin release (pmol/l) was calculated as $286 + 0.416 \times I_{30} - 25.94 \times G_{30} + 0.926 \times I_0$.[28]

Statistical analysis

Statistical analysis was done using SPSS version 20.0. The distribution of the data was assessed using histogram with normal curve. Results are presented as mean ± standard deviation or as median (interquartile range) for Gaussian and non-Gaussian distributed data respectively. Statistical analysis was done using ANOVA, Kruskal Wallis, independent Student's t-test and Mann-Whitney *U*. *P*-values less than 0.05 were considered as statistically significant.

RESULTS

Table 1 contains the general [anthropometric (waist circumference and body mass index), clinical (blood pressure) and metabolic (fasting and postprandial glucose and insulin as well as indices of insulin sensitivity and beta-cell function)] characteristics of the study participants. In Table 2, the median values of indices of insulin sensitivity, β-cell function and the mean levels of selected metabolic factors were not significantly different when patients with schizophrenia, bipolar and depression were compared with one another.

Table 3. Changes in metabolic factors, indices of insulin sensitivity and β-cell function in patients on typical and atypical anti-psychotics.

Parameters	Typical	Atypical	*P*-value
Anthropometric & clinical indices			
WC (cm)	84.99 ± 13.38	88.55 ± 14.42	0.177
BMI (kg/m^2)	24.72 ± 4.97	25.49 ± 5.69	0.449
SBP (mmHg)	112.24 ± 12.37	114.12 ± 16.66	0.496
DBP (mmHg)	74.58 ± 11.73	75.41 ± 9.82	0.693
Metabolic factors			
FPG (mg/dl)	91.69 ± 14.49	90.01 ± 13.02	0.525
30 min PPG (mg/dl)	132.20 ± 23.72	139.85 ± 30.69	0.147
2 h PPG (mg/dl)	123.92 ± 26.60	120.14 ± 35.03	0.522
FPI (μIU/ml)	1.60 (0.80-3.40)	1.60 (0.59-3.34)	0.769
30 min PPI (μIU/ml)	27.48 (13.33-47.68)	18.15 (3.57-40.35)	0.028*
2 h PPI (μIU/ml)	35.90 (17.70-59.65)	31.73 (16.63-61.74)	0.516
Indices of insulin sensitivity/resistance			
HOMA-IR	0.35 (0.19-0.73)	0.36 (0.12-0.74)	0.748
HOMA2-IR	0.21 (0.10-0.44)	0.21 (0.07-0.43)	0.757
FIRI	5.62 (3.07-11.75)	5.91 (1.93-11.97)	0.748
1/FI	0.63 (0.30-1.26)	0.63 (0.30-1.69)	0.769
QUICKI	0.47 (0.41-0.53)	0.46 (0.40-0.59)	0.748
HOMA2-S%	472.35 (228.43-972.08)	475.55 (231.13-1335.13)	0.757
eMCR (ml.kg^{-1}.min^{-1})	8.81 (7.34-9.79)	8.56 (6.42-10.07)	0.976
Modified Matsuda	0.45 (0.17-0.97)	0.75 (0.27-2.24)	0.069
Indices of β-cell function			
HOMA2-β%	33.2 (23.00-58.80)	30.45 (22.10-55.05)	0.662
eFPIR(pmol/l)	767.69 (530.58-1198.35)	617.63 (320.06-911.31)	0.023*
eSPIR(pmol/l)	209.89 (154.01-310.97)	180.30 (114.82-249.39)	0.026*

**Significant at P < 0.05, WC = waist circumference, BMI = body mass index, SBP = systolic blood pressure, DBP = diastolic blood pressure, FPG = fasting plasma glucose, 30 min PPG = 30 min postprandial glucose, 2 h PPG = 2 h postprandial glucose, FPI = fasting plasma insulin, 30 min PPI = 30 min postprandial insulin, 2 h PPI = 2 h postprandial insulin, HOMA = homeostasis model assessment, HOMA-S % = HOMA of insulin sensitivity, HOMA-B% = HOMA of β-cell function, IR = insulin resistance, FIRI = fasting insulin resistance index, FI = fasting insulin, QUICKI = quantitative insulin sensitivity check index, eMCR = estimated metabolic clearance rate of glucose, eFPIS = estimated first phase of insulin release, eSPIS = estimated second phase of insulin release.*

The possible effect of using typical and atypical anti-psychotic drugs on the metabolic factors, insulin sensitivity and β-cell function is shown in Table 3. The median levels of 30 min PPI, eFPIR and eSPIR were significantly lower in patients on atypical drugs compared with patients on typical drugs. Similarly, the possible effect of duration of both typical and atypical anti-psychotic use on the metabolic factors, insulin sensitivity and β-cell function was determined. As shown in Table 4, the mean WC and BMI were significantly higher in patients who have been on any form of anti-psychotic drug for more than 10 years compared with the patients with less than 5 years history of anti-psychotic use. Furthermore, the median eMCR of glucose progressively declined from the less than 5 years group through more than 10 years group and it was significantly lower in patients who have been on antipsychotic drugs for more than 10 years compared with patients who have been on the drugs for less than 5 years (Table 4).

DISCUSSION

Insulin resistance and metabolic alteration continue to be essential features of major mental health disorders.[29]

Table 4. Changes in metabolic factors, indices of insulin sensitivity and β-cell function in patients with major mental health disorders and duration of antipsychotic use.

Parameters	<5 years	5–10 years	>10 years	P1	P2	P3
Anthropometric & clinical indices						
WC (cm)	84.30 ± 12.81	86.84 ± 14.71	92.50 ± 15.01	0.462	0.014*	0.232
BMI (kg/m^2)	24.42 ± 5.19	24.99 ± 5.05	27.09 ± 5.58	0.668	0.042*	0.217
SBP (mmHg)	112.38 ± 12.69	114.11 ± 14.91	113.59 ± 15.82	0.614	0.714	0.916
DBP (mmHg)	74.80 ± 9.96	74.42 ± 13.91	73.91 ± 10.13	0.894	0.718	0.893
Metabolic factors						
FPG (mg/dl)	90.30 ± 14.15	88.08 ± 13.61	95.32 ± 12.82	0.543	0.143	0.088
30 min PPG (mg/dl)	133.77 ± 26.72	137.58 ± 33.95	140.59 ± 29.46	0.607	0.322	0.766
2 h PPG (mg/dl)	118.62 ± 28.31	117.85 ± 24.73	132.92 ± 35.38	0.915	0.060	0.131
FPI (μIU/ml)	1.47 (0.59-2.60)	1.60 (0.65-2.35)	2.98 (0.62-7.79)	0.700	0.100	0.295
30 min PPI (μIU/ml)	29.12 (6.31-52.80)	26.79 (11.52-37.09)	16.61 (3.67-34.96)	0.166	0.074	0.381
2 h PPI (μIU/ml)	31.38 (16.42-54.06)	37.91 (18.94-101.31)	36.40 (17.15-68.80)	0.246	0.522	0.695
Indices of insulin sensitivity/resistance						
HOMA-IR	0.32 (0.15-0.62)	0.35 (0.13-0.56)	0.55 (0.16-1.95)	0.788	0.085	0.191
HOMA2-IR	0.19 (0.09-0.35)	0.21 (0.08-0.31)	0.37 (0.08-1.04)	0.788	0.091	0.250
FIRI	5.11 (2.42-10.09)	5.64 (2.15-9.02)	8.94 (2.58-31.60)	0.788	0.085	0.191
1/FI	0.68 (0.38-1.69)	0.63 (0.43-1.54)	0.34 (0.14-1.62)	0.700	0.100	0.295
QUICKI	0.47 (0.42-0.56)	0.47 (0.42-0.58)	0.43 (0.35-0.55)	0.788	0.085	0.191
HOMA2-S%	517.50 (287.60-1157.80)	478.00 (319.60-1195.70)	269.20 (99.85-1190.10)	0.788	0.091	0.250
eMCR (ml.kg^{-1}.min^{-1})	9.03 (7.47-10.04)	8.23 (6.32-9.61)	8.09 (5.90-9.44)	0.163	0.033*	0.448
Modified Matsuda	0.49 (0.24-1.47)	0.73 (0.26-1.81)	0.48 (0.13-1.19)	0.621	0.728	0.424
Indices of β-cell function						
HOMA2-β%	30.90 (22.40-51.70)	34.10 (24.80-53.70)	38.20 (16.80-78.45)	0.471	0.312	0.695
eFPIR(pmol/l)	726.45 (423.49-1151.09)	581.01 (408.93-832.02)	639.85 (319.07-1057.52)	0.162	0.419	0.636
eSPIR(pmol/l)	204.22 (144.96-288.87)	178.91 (125.48-232.97)	184.13 (116.00-286.69)	0.146	0.466	0.636

**Significant at P < 0.05, P1 = less than 5 years compared with 5–10 years, P2 = less than 5 years compared with greater than 10 years, P3 = 5–10 years compared with greater than 10 years, WC = waist circumference, BMI = body mass index, SBP = systolic blood pressure, DBP = diastolic blood pressure, FPG = fasting plasma glucose, 30 min PPG = 30 min postprandial glucose, 2 h PPG = 2 h postprandial glucose, FPI = fasting plasma insulin, 30 min PPI = 30 min postprandial insulin, 2 h PPI = 2 h postprandial insulin, HOMA = homeostasis model assessment, IR = insulin resistance, FIRI = fasting insulin resistance index, FI = fasting insulin, QUICKI = quantitative insulin sensitivity check index, eMCR = estimated metabolic clearance rate of glucose, eFPIS = estimated first phase of insulin release, eSPIS = estimated second phase of insulin release.*

Understanding the pathophysiology of IR in major mental illnesses continues to generate research interest due to its multifactorial nature. Aside that IR can be provoked by mental illness itself, studies have shown that treatment with antipsychotics especially, the atypical types, exert direct IR effects on tissues independent of weight gain, food intake, hunger and the psychiatric disease.[5,20] The observed lower 30 min level of insulin as well as first and second phases of insulin release in patients on atypical drugs compared with those on typical drugs might be suggestive of reduced insulin secretory capacity of β-cells, a manifestation of β-cell dysfunction. Since there were no significant differences in BMI and HOMA-IR between patients on typical antipsychotics and patients on atypical antipsychotics, our observation might suggest that atypical drugs could induce diminished β-cell function which might result in metabolic deterioration. Hegedűs et al.[30] reported that the use of atypical antipsychotics can induce insulin resistance in the absence of apparent obesity. This indicates that the mechanisms via which IR is

induced by antipsychotics are different from the normal mechanisms in diabetes.[20] Therefore, there is the need for Psychiatrists to be aware that patients on antipsychotic treatment have increased risk for metabolic dysregulation even, in the absence of obesity.

It has been shown that there is increased risk of weight gain, new-onset DM, hyperlipidaemia and cardiac dysfunction in patients on antipsychotics.[31] The increased body adiposity is thought to be secondary to central nervous system (CNS)-mediated changes in appetite.[20] Irrespective of the type of anti-psychotics used, our study revealed that the propensity for central adiposity and increased BMI increases with increasing duration of anti-psychotic use. This observation is in line with the reports of Allison et al.,[32] Wirshing et al.[33] and Allison and Casey[34] that showed that both typical and atypical antipsychotics induce weight gain in a dose-dependent manner. The increased adiposity could be attributed to increased adipose tissue glucose and free fatty acid uptake that is associated with chronic antipsychotic treatment which could be further compounded by impaired mobilization of the stored energy.[35]

Metabolic clearance rate (MCR) of glucose, a predictor of insulin sensitivity status,[36] has been shown to be reduced in patients with type 2 diabetes mellitus (T2DM) and it is considered a feature of T2DM.[37,38] Although there is the dearth of information on effect of antipsychotics on MCR of glucose, an experimental study revealed that antipsychotics do not only increase adiposity and decrease insulin sensitivity, they also reduce metabolic clearance rate of insulin[30] which is thought to predict the incidence of T2DM.[39] The observed reduction in eMCR of glucose with increasing duration of anti-psychotic use suggests that patients on chronic treatment with antipsychotics have increased risk of glucose intolerance. Reduction in MCR usually implies lower glucose disposal rate which is an indication of insulin resistance. This assumption is buttressed by the observed progressive increase (though not statistically significant) in the median HOMA-IR values as the duration of antipsychotic use increases. Our observations indicate that metabolic alteration associated with mental illness worsens with chronicity of antipsychotic use and further entrench the call for routine monitoring of body weight and glucose level in patients on antipsychotics as there exists a negative correlation between body mass index (BMI) and MCR.[40,41]

CONCLUSION

It could be concluded from this study that patients on atypical antipsychotics seem to have insulin secretion phases consistent with β-cell dysfunction that is probably, drug induced. Furthermore, chronicity of antipsychotic treatment predisposes patients with major mental health disorders (MMHD) to central adiposity and low metabolic clearance rate of glucose, a forerunner of glucose intolerance. It is therefore necessary that Psychiatrists collaborate with Diabetologists to achieve optimal management of patients with major mental health disorders.

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