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Dyslipidaemia in schizophrenic patients on antipsychotic medications in a tertiary hospital in Nigeria

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ABSTRACT

Schizophrenia is a mental disorder characterized by a breakdown of thought processes and by a deficit of typical emotional response accompanied by significant social and/ or occupational dysfunction. This condition plus the administration of antipsychotic medications has been associated with dyslipidaemia in previous studies, some of which presented a conflicting argument. To determine any link, if any, between the development of dyslipidaemia among schizophrenics on medications. Total of 24 schizophrenics on typical antipsychotic medications, 24 schizophrenics not on any medication and 24 healthy controls were recruited for the study. Fasting plasma total cholesterol (CHOL), triglyceride (TG), very low density lipoprotein cholesterol (VLDL), low density lipoprotein cholesterol (LDL) and high density lipoprotein cholesterol (HDL) were estimated. While plasma TG and VLDL concentrations were significantly elevated among medicated schizophrenic patients ($p< 0.01$) compared to the control. Similarly, plasma TG and VLDL concentrations were significantly elevated among medicated schizophrenic patients ($p< 0.01$) compared to the non medicated schizophrenic patients. It is likely that antipsychotic agents promote the elevation of TG and VLDL- Cholesterol profiles; however, these elevations are not likely to trigger coronary heart disease (CHD).

Key words: Schizophrenia, lipid profile, antipsychotics.

INTRODUCTION

Schizophrenia is a mental disorder characterized by a breakdown of thought processes and by a deficit of typical emotional response accompanied by significant social and/or occupational dysfunction with a global prevalence of about 0.3-0.7%[1]. Schizophrenia is a multifactorial disorder and a combination of genetic and environmental factors have been shown to play a role in the development of the condition[2]. Nevertheless, regardless of the causes of schizophrenia, antipsychotic drugs are mostly effective in alleviating the symptoms. Antipsychotic medications

have been distinguished into two groups – typical and atypical, and their actions have been shown to be directly related to their affinities for the dopamine D2 receptor suggesting that the properties of this receptor are disturbed in schizophrenia[3].

Antipsychotic treatment is associated with metabolic side effects that include various degrees of weight gain, dyslipidaemia and susceptibility to type 2 diabetes[4]. In addition, patients with chronic psychotic disorders have increased CHD mortality[5,6] and adverse CHD risk profiles[7,8]. Although it is difficult to separate the contributions of illness, lifestyle, and medication factors to these risks, there is now a pressing clinical need to monitor patients treated with antipsychotic medications for metabolic disturbance.

Some previous studies have associated dyslipidaemia with schizophrenia on antipsychotic medications, some of which presented conflicting reports and argument[9,10,11,12]. Existing antipsychotic drugs have been shown to further contribute to the aggravation of metabolic disorder with greater severity recorded for atypical drugs[12,13]. Recent studies confirmed that medication non-adherence is more common among outpatients with schizophrenia and is associated with poor quality of life[14]. This may affect the degree of associated metabolic disorder. Furthermore, most of these studies were conducted in developed countries, and we are not certain how these generalize findings apply to the developing economy where health resources are relatively inadequate. In this study we try to determine a link, if any, between the development of dyslipidaemia among schizophrenic out-patients on antipsychotic medications attending one of our tertiary Teaching Hospitals in Nigeria.

MATERIALS AND METHODS

The protocol for this study was approved by the Research and Ethic committee of the Ladoke Akintola University of Technology teaching hospital, Osogbo, Osun state, Nigeria**.**

A total of seventy-two subjects consisting of 24 schizophrenic patients attending psychiatry clinic of Ladoke Akintola University Teaching Hospital, Osogbo, Nigeria who are on typical antipsychotic medications, 24 schizophrenics not on any medication and 24 healthy controls were recruited for the study after given their informed consent.

The inclusion criteria include a diagnosis of schizophrenia using the Mini International Neuropsychiatric Interview (M.I.N.I); those between aged 18 - 60 years old; those receiving the same typical antipsychotic medications for at least 24 weeks; sedentary, non-obese (BMI <26) and waist to hip (W/H) circumference ratio of <0.8 were enrolled in the study.

The exclusion criteria include co-morbid mood disorder; history of illicit substance use within the last 1 month; pregnancy; patients with other endocrine disorders and metabolic disorders.

Written informed consent was obtained from each selected subject before they are included in the study.

After an overnight fast, 10ml of venous blood was collected at the antecubital fossa in sitting position without stasis into lithium heparinized bottle. Plasma was obtained after centrifugation at 3500r.p.m for 10 minutes and immediately stored at -20^{oC} until they were analyzed.

Total plasma cholesterol and triglycerides were determined enzymatically using kits from Randox laboratory Ireland UK[15,16]. HDL (high-density lipoprotein) – cholesterol was measured (when triglycerides were <4 mmol/L) after low-density lipoproteins, very low density lipoprotein) (LDL, VLDL) and chylomicron fractions were precipitated quantitatively by addition of phosphotungstic acid in the presence of magnesium ions. After centrifugation, the cholesterol concentration in the HDL (high density lipoprotein) fraction, which remained in the supernatant, was analyzed[17]. Quality control was ensured by the use of control materials from Randox laboratory and Human Company of Germany. LDL-cholesterol was calculated using Friedwald formula (LDL Cholesterol=Total Cholesterol–(Triglyceride/5 + HDL Cholesterol)[18]. The cardiovascular risk ratio was calculated from the values of lipids profile obtained[19].

Statistical analysis: All values were entered into EPI INFO (version 6.4a database). Values are expressed as mean ± SD, the statistical significance of the mean differences between groups was assessed by Student's t-test. Valve of $p< 0.05$ was taken as a measure statistical significance.

RESULTS

The study was carried out with schizophrenic subjects not on medication (n=24), schizophrenic subjects on medication (n=24) and controls subjects (n=24). The anthropometric data for the subjects and controls are presented in Table 1. They show no significant difference.

Table 1. Anthropometric and clinical parameters (mean±SD) of Schizophrenic subjects and control

	Control Subjects (n=24)	Schizophrenic without Medication (n=24)	p^1 value	Schizophrenics on Medication (n=24)	p^2 value
Age(years)	48.4±2.8	44.7±3.2	0.6872	45.4±2.8	0.6911
Height (cm)	178.9±1.6	172.5±1.9	0.7016	175.8±1.2	0.7872
Weight (kg)	77.3±0.9	73.1±1.1	0.8109	74.1±1.3	0.8287
BMI (Kg/m2	24.2±0.1	24.6±0.3	0.8978	24.0±0.5	0.8876
Systolic BP	127.2±2.7	129.2±3.1 (mmHg)	0.8251	125.7±2.9	0.7858
Diastolic BP	81.7±1.9	84.5±2.4 (mmHg)	0.7709	85.7±1.7	0.8381
Waist	81.1±3.2	86.7±1.2 Circumference (cm)	0.6997	84.9±2.9	0.8114
Hip	94.5±2.4	98.1±1.9 Circumference (cm)	0.6809	97.3±1.5	0.6398
W/H ratio	0.86±0.01	0.88±0.02	0.8142	0.87±0.02	0.8391

Significant level , p < 0.05
P^1= Control compared with Schizophrenic without Medication
P^2= Control compared with Schizophrenic on Medication

Table 2. The p value when the (mean ± SD) of the measured parameters subjects

	Control Subjects (n=24)	Schizophrenic without Medication (n=24)	p^1 value	Schizophrenic on Medication (n=24)	p^2 value
Triglyceride	1.57 ± 0.34	1.60 ± 0.41 (mmol/L)	0.7721	3.21 ±0.20	0.0017
Total Cholesterol	3.68 ± 0.22	3.51 ± 0.43 (mmol/L)	0.6193	3.97 ±0.23	0.5182
HDL Cholesterol	1.90 ± 0.21	1.87 ± 0.15 (mmol/L)	0.7105	1.83 ± 0.17	0.6801
VLDL Cholesterol	0.71 ± 0.01	0.73 ± 0.07 (mmol/L)	0.8001	1.46 ± 0.19	0.0020
LDL Cholesterol	1.47 ± 0.19	1.32 ± 0.11 (mmol/L)	0.5215	1.50 ± 0.15	0.6191
HDL.C /T C	0.52 ± 0.02	0.53 ± 0.05	0.8602	0.46 ± 0.03	0.7014

Significant level , p < 0.05
P^1= Control compared with Schizophrenic without Medication
P^2= Control compared with Schizophrenic on Medication

The mean± SD plasma concentrations of triglyceride (TG) level (3.21 ±0.20 mmol/L) for schizophrenic subjects on medication was significantly increased ($p<0.01$) compared to the controls(1.57 ± 0.34mmol/L), also the mean± SD plasma concentrations of triglyceride (TG) level (3.21 ±0.20 mmol/L) for schizophrenic subjects on medication was significantly increased ($p<0.01$) compared to the schizophrenic subjects not on any medication (1.60 ± 0.41mmol/L).

Similarly, the mean± SD plasma concentrations of VLDL Cholesterol level (1.46 ± 0.19 mmol/L) for schizophrenic subjects on medication was significantly increased (p<0.01) compared to the controls (0.71 ± 0.01 mmol/L), also the mean± SD plasma concentrations of VLDL Cholesterol level (1.46 ± 0.19 mmol/L) for schizophrenic subjects on medication was significantly increased (p<0.01) compared to the schizophrenic subjects not on any medication (0.73 ± 0.07mmol/L).

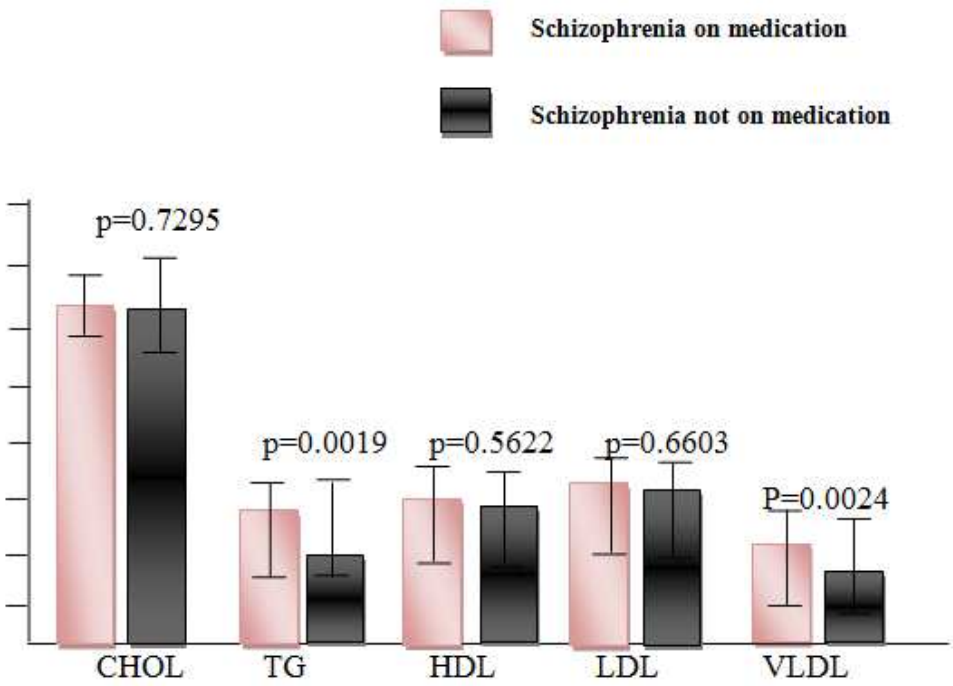

Fig 1: Comparison between schizophrenia on medication and non medication lipid profile

DISCUSSION

Epidemiological studies have shown that dyslipidaemia is a powerful risk factor for coronary heart disease[20]. Dyslipidaemia has been associated with schizophrenia in previous studies, some of which presented a conflicting results[9,10,11]. Furthermore, most of these studies were conducted in developed countries, and we are not certain how these findings are applicable in the developing economy where health resources are relatively inadequate.

We found that plasma concentrations of triglyceride (TG) was significantly higher in medicated schizophrenic patients compared with the controls group (p<0.01). The main source of this increase in TG concentration is evidently endogenous. Under normal conditions, fatty acid released by digestion of dietary fat together with cholesterol are absorbed and re-esterified to form triacylglycerols and cholesterol esters. These together with phospholipids and apolipoproteins are secreted into the systemic circulation via the lymphatics as chylomicrons. Thus, exogenous TG is transported from intestine as chylomicrons. The enzyme lipoprotein lipase located on capillary wall is activated and immediately hydrolyses triacylglycerol from chylomicrons into glycerol and fatty acid. The chylomicron remnants, now rich in cholesterol are taken up by the liver[21]. Although, studies have shown that the small intestine is capable of utilizing endogenous substances for TG synthesis in the presence and absence of dietary lipids[22], the clear appearance of the fasting plasma from the study subject showed that the observed increased plasma TG levels were not of dietary origin.

The concurrent significant increase in plasma VLDL-Cholesterol compared with the controls (p<0.01) also showed that the elevated plasma TG concentration was of endogenous origin. VLDL-Cholesterol is known to be synthesized in the liver. Where two molecules of acyl-CoA, formed by the activation of fatty acids by acyl-CoA synthetase combine with glycerol 3-phosphate to form phosphatidate (1,2-diacylglycerol phosphate). This takes place in two stages, catalyzed by glycerol-3-phosphate acyltransferase and 1-acylglycerol-3-phosphate and diacylglycerol acyltransferase to 1,2-diacylglycerol and then triacylglycerols[23]. Most of the activity of these enzymes resides in the endoplasmic reticulum of the cell. The regulation of TG and biosynthesis is also driven by the availability of free fatty acids. Those that escape β-oxidation are preferentially converted to phospholipids, and when this requirement is satisfied they are used for TG synthesis. In the present study, we speculate that expression of one or more of these

central enzymes involved in the biosynthesis of VLDL-Cholesterol in medicated schizophrenic patients are stimulated by antipsychotic agents. The elevated plasma VLDL-Cholesterol concentration in our study is similar to that of Hardy et al., who compared different antipsychotic treatments[24].

The exact mechanism by which antipsychotics modulate plasma TG via VLDL-Cholesterol has not been fully demonstrated in humans. However, recent animal experiments show that antipsychotics elevate plasma TG levels by up-regulating the expression of lipogenic Sterol Regulatory Element-Binding Proteins (SREBP)- controlled ones and induces key enzymes controlling liver lipid synthesis and VLDL-Cholesterol by the liver include: the fed-state rather than the starved-state; the feeding of diets high in carbohydrate (particularly if they contain sucrose or fructose), leading to high rate of lipogenesis and esterification of fatty acids; high levels of circulating free fatty acids; ingestion of ethanol; and the presence of high concentration of insulin and low concentration of glucagon, which enhance fatty acid synthesis and esterification and inhibit their oxidation. Further metabolism by removal of triacylglycerol and esterification of cholesterol, converting VLDL to LDL may occur steadily in medicated schizophrenic patients. This is evident by insignificant difference in plasma LDL ($p>0.05$). Schmid et al., also observed no significant difference in the plasma concentration of LDL in rats treated with Olanzapine[25] while Idonije et al., reported significant increase in plasma LDL concentration in humans treated with Clozapine compared with the apparently normal subjects[17].

Similarly, no significant difference was observed in plasma total cholesterol in medicated schizophrenic patients compared with the controls. This suggests that the medication or the condition itself did not have significant effect on HMG-CoA reductase, the rate-limiting enzyme of cholesterol level in schizophrenia[12, 26], it is also note-worthy that plasma HDL-Cholesterol concentration in our study subject is essentially the same with that obtained for the control subjects ($p>0.05$).

CONCLUSION

In view of our present findings, there is most likely that antipsychotic agents (typical) used to ameliorate schizophrenic disorders will cause increase in some plasma lipid profiles (TG and VLDL-Cholesterol). Decreased plasma concentration of HDL and increased LDL-Cholesterol has been found to be a potential risk factor for coronary heart disease. Since plasma total cholesterol, LDL and HDL concentrations in medicated schizophrenic patients in our study were essentially the same with the values obtained for apparently normal control; it is difficult to conclude that medicated schizophrenic patients are also at risk of coronary heart disease only on the basis of significant elevated endogenous TG and VLDL-cholesterol.

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