Original Article

DOI: 10.7860/JCDR/2013/7592.3734

Biochemistry Section

Cardiovascular Disease Risk in Schizophrenia Patients: A Case Control Study

KEDAR B. JOSHI[1], ANUP NILLAWAR[2], A.P. THORAT[3]

ABSTRACT

Background: The Schizophrenia patients are at higher risk for cardiovascular morbidity and mortality. The aim of this case-control study is to measure Cardiovascular Disease (CVD) risk parameters in patient group and compare it with normal population.

Methodology: We recruited 45 cases of Schizophrenia diagnosed by diagnostic and statistical manual of mental disorders (DSM-IV) criteria and 41 healthy controls from general population. The body mass index, metabolic syndrome parameters, lipid parameters and high sensitive C-reactive protein were measured in both groups. Metabolic syndrome and dyslipidemia prevalence were assessed based on National Cholesterol Education Programme (NCEP) Adult Treatment Panel III (ATP III) guidelines.

Results: The Schizophrenia subjects showed statistically significant high waist circumference, increased triglycerides and decreased HDL cholesterol values. The subjects also showed statistically significant increased hs-CRP values. The prevalence of metabolic syndrome and laboratory dyslipidemia were 28.8% and 51.1% respectively, which were higher compared to control group.

Conclusion: The Schizophrenia subjects are at higher risk for cardiovascular disease events due to high prevalence of metabolic syndrome and dyslipidemia. These patients should be regularly monitored for CVD risk factors and timely referred to physician for further management.

Keywords: Metabolic Syndrome, Dyslipidemia, HS-CRP

INTRODUCTION

Schizophrenia is a neuropsychiatric disorder of uncertain etiology. The genetic factors, inflammation and infection have been identified as contributory factors to disease etiology. In India, the annual incidence rate of Schizophrenia is 4.4 and 3.8 per 10,000 population for rural and urban areas, respectively [1]. Schizophrenics have shorter life period than the general population [2-4] and are associated with higher risk of respiratory, infectious and cardiovascular diseases [5]. Other associated factors with patients are smoking, inadequate diet, sedentary lifestyle and lack of regular physical activity [6,7].

In recent studies, Schizophrenia patients are reported to have higher risk for cardiovascular diseases [8-10] and this risk is shown by presence of metabolic syndrome characteristics and dyslipidemia. There is high prevalence of metabolic syndrome in the patients receiving antipsychotic medication [11,12].

Metabolic syndrome is identified by coincidence of elevated waist circumference, impaired lipid metabolism, hypertension and/or hyperglycemia. This cluster is a well-accepted risk factor for cardiovascular morbidity and mortality [13]. C-reactive protein (CRP), a pentameric protein, is a sensitive marker for low-grade systemic inflammation and raised levels in blood independently, predicts the future risk of CVD [14-16]. Some studies describe the involvement of immune dysfunction and inflammation [17-19] and also raised levels of high sensitive CRP in patients with Schizophrenia [20,21].

In this case-control study, we aimed to measure the CVD risk in Schizophrenic subjects in terms of metabolic syndrome characteristics, dyslipidemia, body mass index and high sensitive CRP.

MATERIAL AND METHODS

A total 45 cases of Schizophrenia diagnosed by DSM-IV criteria, reporting to Psychiatry Out-patients Department of Government Medical College and Hospital, Aurangabad, India, were selected. The duration of disease was noted. The exclusion criteria was mental retardation, chronic inflammatory conditions, treatment with mood stabilizers, pregnant or lactating women and patients already suffering from hypertension, diabetes mellitus or hyperlipidemia. A total 41 age- and sex-matched controls were psychiatrically evaluated and enrolled in the study with no past history of psychiatric illness. Only subjects who were capable of giving written informed consent were recruited in the study. Institutional ethical committee approval was obtained.

Assessments

The demographic and medical information was documented in a standard chart. Characteristics of study population are shown in [Table/Fig-1]. Height (in metres) and weight (in kgs) of subjects was measured and Body mass index was calculated by formula BMI= Weight/(Height)^2. Waist circumference was measured at the level of iliac crest in horizontal plane. The blood pressure was measured using digital sphygmomanometer, on right and left arm in seated position and average values for systolic and diastolic pressure were noted. Fasting plasma glucose, serum lipid parameters and hs-CRP were measured.

American Heart Association/National Heart, Lung, and Blood Institute Scientific Statement (AHA/NHLDI) guidelines criteria [13] were used for defining metabolic syndrome, as it is simple to use in clinical setting [Table/Fig-2]. For clinical diagnosis of metabolic syndrome; waist circumference, triglycerides, HDL-C, blood pressure and fasting blood glucose were measured. Categorical cut off points are given in [Table/Fig-2]. Presence of any 3 of 5 criteria given in [Table/Fig-2] constitute the diagnosis of metabolic syndrome. We used lower waist circumference cut off points (>90 cm in men and >80 cm in women), as these lower values are appropriate for Asian countries. National Cholesterol Education Programme (NCEP), Adult Treatment Panel III (ATP III) guidelines were used to define laboratory dyslipidemia (total cholesterol >200mg/dl and LDL >160mg/dl).

STATISTICAL ANALYSIS

The data was analysed by GraphPad Prism software. The numerical data was presented as mean ± standard deviation (mean ± SD). The statistical significance was calculated using student's t-test for continuous variables and by Fisher's Exact test for categorical data. The two-tailed p-value <0.05 was considered to be statistically significant.

RESULTS

The statistical comparison of physical and laboratory parameters are shown in [Table/Fig-3]. Difference in body mass index of patients and control group was not statistically significant.

Among metabolic syndrome parameters, the increase in waist circumference and triglycerides and decrease in HDL level were significant in patient group. The systolic and diastolic BP and fasting glucose levels showed no difference. Among lipid parameters, total cholesterol and LDL levels showed no difference while high sensitive CRP level was significantly high in patient group.

The prevalence of metabolic syndrome and laboratory dyslipidemia was 28.8 and 51.1 percent respectively, which was statistically significant.

Characteristics	Subjects (45)	Controls (41)
Age in years (mean±SD)	38.5 ± 1.3	35.8 ± 11.3
Gender Male, n (%) Female, n (%)	 29 (65) 16 (35)	 21 (51) 20 (49)
Duration of disease, years (mean±SD)	14.6 ± 7.8	-----

[Table/Fig-1]: Characteristics of study population

Measure (any 3 of 5 constitute diagnosis)	Categorical Cutoff points
Elevated waist circumference*	≥90cm in men ≥80 cm in women
Elevated Triglycerides	≥150 mg/dl or on drug T/t for elevated TGs
Reduced HDL-C	<40 mg/dl in men <50 mg/dl in women
Elevated blood pressure	≥130 mm Hg systolic or ≥85 mm Hg diastolic or on antihypertensive T/t
Elevated fasting glucose	≥100 mg/dl or on drug T/t for elevated glucose

[Table/Fig-2]: American Heart Association/National Heart, Lung, and Blood Institute Scientific Statement Criteria for clinical diagnosis of metabolic syndrome
HDL-C, high density lipoprotein cholesterol; TGs, triglycerides; T/t, treatment.
*Lower cut off points recommended for Asian countries

Parameter	Subjects (45)	Controls (41)	(p-value)
BMI (mean ± SD)	27.3 ± 4.7	26.5 ± 4.4	NS
Waist circumference (mean ±SD)	87.2 ± 12.3	81.1 ± 11.3	0.0192*
Triglycerides (mean ± SD)	118.8 ± 26.5	96.5 ± 36.8	0.0017*
HDL (mean ± SD)	36.8 ± 9.5	42.2 ± 10.3	0.0133*
Systolic BP (mean ± SD)	124.5 ± 10.2	122.3 ± 9.9	NS
Diastolic BP (mean ± SD)	81.5 ± 9.3	78.2 ± 8.5	NS
Fasting glucose (mean ± SD)	95.5 ± 25.9	87.3 ± 18.5	NS
Metabolic syndrome, n (%)	13 (28.8)	3 (7.3)	0.0126*†
Lipids Total cholesterol (mean ± SD) LDL (mean±SD)	 150.6 ± 45.6 119.8 ± 23.8	 144.8 ± 38.9 112.3 3± 17.9	 NS NS
Laboratory dyslipidemia, n (%)	23 (51.1)	4 (9.7)	0.0001*†
High sensitive CRP (mean ± SD)	4.1 ± 3.1	2.63 ± 0.9	0.0025*

[Table/Fig-3]: Statistical comparison of physical and biochemical parameters in study population
BMI-Body Mass Index; HDL-High Density Lipoprotein; BP-Blood Pressure; LDL Low Density Lipoprotein; CRP-C reactive Protein Measured in mg/L
* p value statistically significant (< 0.05); † p value found by Fisher's Exact test. NS-Not Significant

DISCUSSION

In this study, we aimed to measure the cardiovascular disease risk in Schizophrenia subjects. Apart from metabolic alterations, other factors like sedentary life, smoking and physical inactivity play a major role in increasing the cardiometabolic risk in Schizophrenia subjects. These factors are strongly associated with Schizophrenia [10].

Prevalence of metabolic syndrome in subject group was found to be 28.8%, which is significantly higher than control group. The increased level of triglycerides and decreased HDL cholesterol in subjects caused such high prevalence. Prevalence of dyslipidemia was 51.1% in these subjects. These subjects are at high risk for CVD events and need timely evaluation of their biochemical parameters. This will help in early intervention and better outcome.

High sensitive CRP is a well-established sensitive marker which indicates low-grade systemic inflammation. Raised levels of CRP in blood independently, predict the future risk of cardiovascular disease. There are increasing evidences in literature which emphasize immune activation and raised CRP levels in Schizophrenia cases. This study found significant increase in blood CRP levels in Schizophrenia subjects. The study also suggests that CRP may play a role in underlying inflammation and inflammation is a possible contributing factor in disease pathogenesis.

LIMITATIONS

As this is a case-control study, causal relation could not be developed. Type of antipsychotic drug was not taken into account, hence effect of drugs could not be evaluated. Also, for patient population, the factors like physical activity or dietary habits were not controlled hence, effect of these factors on CVD risk could not be described.

CONCLUSION

The study concludes that Schizophrenia patients are at high risk for cardiovascular disease events in future. These patients are more likely to develop physical disturbances, metabolic syndrome and dyslipidemia. This study underlines the importance of timely referral of patients to physicians for further evaluation. The patients will benefit from timely biochemical evaluation and adequate treatment.

REFERENCES

[1] NN Wig, Vijoy K Varma, SK Mattoo, PB Behere, HR Phookan, AK Misra, et al. An incidence study of Schizophrenia in India. *Indian J Psychiatry.* 1993 Jan-Mar; 35(1): 11–17.
[2] McGrath J, et al: Schizophrenia: a concise overview of incidence, prevalence, and mortality. *Epidemiol Rev.* 2008, 30:67–76.
[3] Sperling W, Biermann T: Mortality in patients with Schizophrenia. *Lancet.* 2009, 374(9701):1592. author reply 1592–3.
[4] Tiihonen J, et al: 11-year follow-up of mortality in patients with Schizophrenia: a population-based cohort study (FIN11 study). *Lancet.* 2009, 374(9690): 620–27.
[5] Leucht S, Burkard T, Henderson J, Maj M, Sartorius N. Physical illness and Schizophrenia: a review of the literature. *Acta Psychiatr Scand.* 2007; 116 (5): 317–33.
[6] Saha S, Chant D, McGrath J. A systematic review of mortality in Schizophrenia. Is the differential mortality gap worsening over time? *Arch Gen Psychiatry.* 2007; 64(10):1123–31.
[7] Barnett AH, Mackin P, Chaudhry I, et al. Minimising metabolic and cardiovascular risk in Schizophrenia: diabetes, obesity and dyslipidaemia. *J Psychopharmacol.* 2007; 21(4): 357–73.
[8] Dita Protopopova, Jiri Masopust, Radovan Maly, Martin Valis & Jan Bazant. The prevalence of cardiometabolic risk factors and the ten-year risk of fatal cardiovascular events in patients with Schizophrenia and related psychotic disorders Psychiatria Danubina, 2012; Vol. 24, No. 3, pp 307-3131.
[9] Mas Ayu Said, Ahmad Atim Sulaiman, et al. Metabolic syndrome and cardiovascular risk among patients with Schizophrenia receiving antipsychotics in Malaysia. *Singapore Med J.* 2012; 53(12); 801
[10] LUÍS FERREIRA, ADRIANA BELO, CASSIANO ABREU-LIMA. A case-control study of cardiovascular risk factors and cardiovascular risk among patients with Schizophrenia in a country in the low cardiovascular risk region of Europe [103]; *Rev Port Cardiol.* 2010; 29 (10): 1481-93.
[11] Susanne Kraemer, Anette Minarzyk, Thomas Forst, Daniel Kopf and Hans-Peter

Hundemer. Prevalence of metabolic syndrome in patients with Schizophrenia, and metabolic changes after 3 months of treatment with antipsychotics -results from a German observational study Kraemer, et al. *BMC Psychiatry.* 2011, 11:173 ;http://www.biomedcentral.com/1471-244X/11/173.

[12] Waleed M Sweileh, Sa'ed H Zyoud, Salah A Dalal, Sami Ibwini, Ansam F Sawalha and Iyad Ali .Prevalence of metabolic syndrome among patients with Schizophrenia in Palestine; Sweileh et al. *BMC Psychiatry.* 2012, 12:235; http://www.biomedcentral.com/1471-244X/12/235.

[13] Grundy SM, Cleeman JI, Daniels SR, Donato KA, Eckel RH, Franklin BA, et al. Diagnosis and management of the metabolic syndrome: an American Heart Association/National Heart, Lung, and Blood Institute Scientific Statement. *Circulation.* 2005, 112:2735-52.

[14] Wolfgang Koenig, Malte Sund, Margit Fröhlich, Hans-Günther Fischer, Hannelore Löwel, Angela Döring, et al. Pepys C-Reactive Protein, a Sensitive Marker of Inflammation, Predicts Future Risk of Coronary Heart Disease in Initially Healthy Middle-Aged Men : Results From the MONICA (Monitoring Trends and Determinants in Cardiovascular Disease) Augsburg Cohort Study, 1984 to 1992 *Circulation.* 1999; 99; 237-42.

[15] Shaista Malik, Nathan D. Wong, Stanley Franklin, Jose Pio, Carol Fairchild, Roland Chen. Cardiovascular Disease in U.S. Patients with metabolic syndrome, diabetes, and elevated C-reactive protein DIABETES CARE, Volume 28, Number 3, March 2005; 690-93.

[16] Nader Rifai and Paul M. Ridker High-Sensitivity C-Reactive Protein: A Novel and Promising Marker of Coronary Heart Disease Clinical Chemistry 47:3 403–11 (2001).

[17] Potvin S, Stip E, Sepehry AA, Gendron A, Bah R,Kouassi E. Inflammatory cytokine alterations in Schizophrenia: a systematic quantitative review. *Biol Psychiatry.* 2008; 63: 801-8.

[18] Muller N, Schwarz MJ. Immunology in schizophrenic disorders. *Nervenarzt.* 2007; 78:253-6.

[19] Saetre P, Emilsson L, Axelsson E, Kreuger J, Lindholm E, Jazin E. Inflammation-related genes upregulated in Schizophrenia brains. BMC Psychiatry 2007;7:46.

[20] Faith Dickerson Cassie Stallings, Andrea Origoni, Crystal Vaughan, Sunil Khushalani, Shuojia Yang, Robert Yolken. C-reactive protein is elevated in Schizophrenia Schizophrenia Research 143 (2013) 198–202.

[21] RK Solanki, Paramjeet Singh, Mamta Singh, Mahip Sinha, Mukesh Kumar Swami, Shakuntla Saini. C-Reactive Protein (CRP) in patients with Schizophrenia: Are they related with symptomatology? *Journal of Mental Health & Human Behavior.* 2010 15(1): 6-10.

PARTICULARS OF CONTRIBUTORS:
1. Assistant Professor, Department of Biochemistry GMC Aurangabad, Maharashtra, India.
2. Associate Professor, Department of Biochemistry, SBKS Medical College, Vadodara, Gujarat, India.
3. Professor and Head, Department of Biochemistry, GMC Aurangabad Maharashtra, India.

NAME, ADDRESS, E-MAIL ID OF THE CORRESPONDING AUTHOR:
Dr. Kedar B. Joshi,
Plot 124, Omkar Niwas, Shastri Nagar, Garkheda Aurangabad, Maharashtra-431005, India.
Phone: 09922919177, E-mail: drjoshikedar@gmail.com

FINANCIAL OR OTHER COMPETING INTERESTS: None.

Date of Submission: **Sep 06, 2013**
Date of Peer Review: **Oct 20, 2013**
Date of Acceptance: **Nov 09, 2013**
Date of Online Ahead of Print: **Nov 25, 2013**
Date of Publishing: **Dec 15, 2013**