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Inflammatory and metabolic changes in persons presenting with First Episode Psychosis- A Prospective Observational Study

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ABSTRACT

Background & objectives: Inflammation plays a significant role in the development of psychotic disorder, and research has shown that patients with first-episode psychosis have increased inflammation (FEP). We analyzed changes in inflammatory status as assessed by CRP,ESR and metabolic profile (BMI, waist circumference, FBS, triglycerides, HDL-cholesterol, and blood pressure) in individuals presenting with First Episode Psychosis over a three-month longitudinal period. We performed a preliminary analysis of changes in the inflammatory status as assessed by C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), and metabolic profile (BMI, waist circumference, FBS, triglycerides, HDL-cholesterol, blood pressure) in individuals presenting with First Episode Psychosis over a three-month longitudinal period.

Methods: 100 FEP patients from Medical College Kolkata were included in a longitudinal study. All participants underwent anthropometric measurements of BMI, waist circumference, blood pressure, and blood CRP, ESR, triglycerides, HDL-cholesterol, and fasting blood sugar at baseline and three months later. For categorical data, descriptive statistics were reported as percentages and mean with standard deviation (for continuous data). One sample t test, Paired t test, and Pearson's correlation test were carried out for analytical statistics.

Results: The majority of people who were diagnosed with First Episode Psychosis experienced an increase in CRP and ESR at the time of initial contact. CRP at first contact and BMI at three months had a significant linear positive moderate connection (r=0.37, p0.05), as did W.C. at three months (r=0.23, p0.05). ESR at first contact had a statistically significant linear positive weak connection with BMI (r=0.27, p0.05), SBP (r=0.26, p0.05), and DBP (r=0.31, p0.05) after three months.

Conclusion: Our preliminary findings suggest that individuals with FEP who have higher levels of inflammation are more likely to experience poorer metabolic outcomes linked to the metabolic syndrome. We advise more study to confirm these findings and that early measures to lower inflammation and keep an eye on changes should be recommended in a person with First Episode Psychosis.

Keywords: *First Episode Psychosis, Inflammation, Metabolic Profile.*

INTRODUCTION

'First-episode psychosis' (FEP) is a term used to describe a person recently identified as acutely psychotic but without any formal diagnosis earlier. It is not recognised by any nosology as an official diagnosis, (i.e.-classificatory system of mental disorder) but refers to the condition in which a person experiences psychosis for the first time in their life. Psychosis is defined as per DCR-10, which is the presence of hallucinations, delusions, or a limited number of severe abnormalities of behavior, such as gross excitement and overactivity, marked psychomotor retardation, and catatonic behavior). For the

entity First Episode Psychosis (FEP) we developed an operational definition based on the current literature. There are three categories of definitions for 'first-episode': (i) first treatment contact; (ii) duration of antipsychotic medication use; and (iii) duration of psychosis. **[1]** For our study we predominantly will rely on the 1st Operational Definition (First treatment contact).[2]

Inflammation plays a significant role in the psychotic disorder, particularly in the development of that illness.According to findings from several research, there is a high correlation between inflammatory abnormalities and first-episode drug-naive psychosis (FEP), which may be independent of the effects of antipsychotic medicines. [3] Elevation in the process of inflammation has also been in the other studies over the past few years increasingly reported in both chronic and first episode psychosis (FEP) cohorts[4-8].C-Reactive Protein (CRP) is an acute-phase reactant protein mainly derived by hepatocytes in response to an increase in circulating pro-inflammatory cytokines [9]. In a recent cross-sectional investigation, hsCRP independently predicted metabolic syndrome, increased waist circumference, and raised triglycerides in individuals with psychosis. [10]. Dopamine malfunction is the only well-accepted therapeutic target in psychosis, and D2 antagonists make up the sole class of drugs used to treat it. Inflammation is supported as a potential novel treatment target by studies done to date, but further study is needed to determine which patients would benefit the most. The only clinical trial that has been done so far using anti-inflammatory drugs in addition to antipsychotics in patients with recent-onset schizophrenia found that patients treated with a combination had significantly better therapeutic outcomes than those treated with antipsychotics and placebo.[11]. Inflammation affects patients with FEP's metabolic outcomes, but very few studies have been done in India. Therefore it is necessary to investigate and determine a connection between inflammatory status and metabolic abnormalities in FEP patients. It is important to consider the inflammatory condition as a potential future indicator of psychosis and a risk factor for a changed metabolic profile. We can also benefit from considering the inflammatory condition as a possible future indication of psychosis onset and a risk factor for an altered metabolic profile. The aim of our study is to look at changes in the inflammatory status as measured by CRP and ESR, as well as changes in the Metabolic Profile (BMI, Waist Circumference, FBS, Triglycerides, HDL-Cholesterol, Blood Pressure) in subjects presenting with First Episode Psychosis over the course of a three-month longitudinal period.

METHODOLOGY

It was an observational research conducted in a hospital. We initially created an operational definition for the term First Episode Psychosis (FEP) based on the most recent research. All patients who received a primary psychiatric diagnosis from the department of psychiatry by the consultants on the appropriate day of OPD and had psychotic symptoms for the first time in their lives were selected as FEP cases. The operational definition of FEP was subsequently applied to these patients for our investigation. These first-episode psychotic patients were included in accordance with the inclusion and exclusion criteria (mentioned later). All consecutive patients who met the established FEP criteria were originally checked, and three months later, they were all reviewed.

Patients and caregivers gave their informed permission. According to a semi-structured proforma, sociodemographic data and medical history were obtained. All participants in the trial underwent anthropometric measurements of BMI, waist circumference, blood pressure, and blood CRP, ESR, triglycerides, HDL-cholesterol, and fasting blood sugar (FBS) at the beginning of the study (baseline) and three months later. To assess the severity of the Psychosis, the FEP patients were checked through the Brief Psychiatric Rating Scale (BPRS) at the time of the initial contact and again at the three-month follow-up. In between, these participants underwent treatment depending on the specific treating consultants' preferences and accepted treatment standards. The final step was to assemble all the data and analyze it using conventional statistical techniques while keeping in mind our goals. For categorical data, descriptive statistics were reported as percentages and mean with standard deviation (for continuous data). One sample t test, Paired t test, and Pearson's correlation test were carried out for analytical statistics.

The prevalence or annual incidence of First Episode Psychosis in the Indian Population was not documented. Prevalence could be estimated as 50%. 100 samples altogether were to be calculated.(Estimated using the formula: 4pq/L2, where p is the prevalence of FEP and q is equal to 100 -p; L is the relative inaccuracy. If we fix a relative error of 10%, we get from the preceding formula a sample size of 100.)

Inclusion criteria:

1) Psychosis described as per DCR 10 that is- *the presence of hallucinations, delusions, or a limited number of severe abnormalities of behavior, such as gross excitement and overactivity, marked psychomotor retardation, and catatonic behavior*).

2) All clinically relevant psychotic disorders for first time in life fulfilling the criteria of any psychiatric diagnosis in the rubric of-

- ➢ Schizophrenia and related psychotic disorder (F20-29) and
- ➢ Mood [Affective]Disorder with Psychotic symptoms (F30-39).

3) A person with First Episode Psychosis as per operational definitions applied in our study (i.e.- First treatment contact)

4) Age: 18-55 years.

5) Able to converse in Hindi, English or Bengali and read the level of primary education.
6) Willing to participate in the study and giving informed consent.

Exclusion criteria:
*1)*A person with any preceding or past psychiatric illness.
2) Patients with any history of taking any Psychotropic Drugs- Not Drug Naive prior to contact.
3) FEP patients who were prescribed psychotropic drugs well-known to develop metabolic changes (Like- Olanzapine, Clozapine, Valproate) by the treating consultant in their first contact.
4) Any Organic Psychosis (F06)
5) Substance-induced psychosis (F10-19)
6) Refusal to give consent.
7) Inadequate information regarding the patient.

Inflammatory Status- was measured by **CRP** and **ESR.**

Marker	***Elevated Inflammatory Status***
CRP	More than 10 mg/liter **[12]**
ESR	More than 10mm/hr (for Male) More than 12mm/hr (for female) *[According to Dacie and Lewis Practical Hematology,12thEdition]* **[13]**

Metabolic Profile- was examined by measuring **blood pressure, Triglycerides, HDL-C, FBS,** and **Waist Circumference, BMI.**

Metabolic Profile	**Altered Metabolic Status**
i)Blood Pressure	More than 130/85 mm Hg
ii)Triglycerides	More than 150 mg/dl
iii)HDL-C	Less than 40 mg/dl for Men Less than 50 mg/dl for Women
iv)FBS	More than 110 mg/dl
v) Waist Circumference	Greater than 102cm (40 inch) for Men Greater than 88cm (35 inch) for Women

[According to NCEP ATP III GUIDELINE] **[14]**

vi) BMI	Over 23 kg/m2 for Indian Population **[15]**

RESULTS
Of the 100 participants, 53% were males and 47% were females. 37% of our individuals were single, whereas 59% were married. 32% of patients were from rural backgrounds, 13% from semi-urban backgrounds, and 55% of patients were from metropolitan backgrounds.

At first contact, the mean CRP value was 13.82 +/- 3.77, and after three months, it was 5.88 +/- 2.93(shown in figure 1). The mean CRP value at First Contact and the three-month follow-up showed a significant difference ($p<0.05$, Confidence Interval C.I.-95%). Initially the mean ESR value was 20.11 +/- 12.27, and after three months, it was 9.27 +/- 3.76(shown in figure 1). Between the mean ESR value at first contact and the three-month follow-up, there was a sizable difference. The percentage of patients with elevated SBP increased to 33% after three months. The subjects' average BMI at the time of first contact was 21.71 +/- 2.92 Standard Deviation (S.D.). The mean BMI value after three months of follow-up was

21.81 +/- S.D. 2.93(shown in figure 2). The mean BMI value at these two time points showed a significant change. BMI at three months was 0.10 units higher than BMI at first contact when measured against the mean. ($p<0.05$, 95% C.I.).

The subjects' mean W.C. value at First Contact was 85.87 +/- 8.35 Standard Deviation (S.D.). After a three-month follow-up, the subjects' mean W.C. value became 86.32 +/- S.D. 8.26(shown in figure 2). W.C. at 3 months was 0.45 units greater than W.C. at First Contact (95% C.I.) when mean value was taken into account showing a significant difference . Only 5% of participants exhibited increased TGL upon first interaction. TGL values were thought to increase when they exceeded 150 mg/dl. TGL at 3 months was 35.23 units greater than TGL at first contact, taking mean value into account ($p = 0.05$, 95% C.I.) indicating a considerable difference between these two values .16% of the subjects' HDL-C was lower at the initial interaction. Less than 50 mg/dl for females and 40 mg/dl were deemed to be lower values for HDL-C. The proportion of patients with decreased HDL-C increased to 37% after three months.The percentage of individuals with increased FBS increased to 56% after three months. At the time of first contact, the subjects' mean FBS value was 94.79 +/- Standard Deviation (S.D.) 11.67. Following a three-month follow-up, the participants' mean FBS value was 110.44 +/- S.D. 11.35. The mean FBS value at First Contact and Three Month Follow Up differed significantly. According to the National Cholesterol Education Program (NCEP) Adult Treatment Panel III (May 2001) definition, metabolic syndrome is present if three or more of the following five criteria are met: waist circumference over 40 inches/102 centimeters (men) or 35 inches/88 centimeters (women), blood pressure over 130/85 mmHg, fasting triglyceride (TG) level over 150 mg/dl, fasting high-density lipoprotein (HDL) cholesterol level less than 40 mg/dl (men) or 50 mg/dl (women) and fasting blood sugar over 110 mg/dl. Extent of metabolic syndrome among subjects at first contact and three-month follow up is shown in figure 3.

CRP at the time of the initial contact and BMI three months later showed a significant linear positive moderate connection ($r=0.37$, $p<0.05$)(shown in table 1). Accordingly, greater CRP values at the time of the initial interaction are linked to higher BMI levels three months later. CRP at initial contact and W.C. at three months also had a statistically significant linear positive weak connection ($r=0.23$, $p<0.05$). This indicates that higher CRP is Obesogenic.

ESR at first contact and BMI at three months had a statistically significant linear positive weak connection ($r=0.27$, p0.05)(shown in table 1). Accordingly, greater ESR values at the time of the initial interaction are linked to higher BMI levels three months later. Between ESR at first contact and SBP at three months, a statistically significant linear positive weak connection ($r=0.26$, $p<0.05$) is found. In other words, greater ESR values at the beginning of the relationship correspond to higher SBP after three months. ESR at initial contact and DBP at three months also had a statistically significant linear positive moderate connection ($r=0.31$, $p<0.05$). Accordingly, greater ESR values at the beginning of the relationship correspond to higher DBP after three months. CRP at First Contact and TGL at Three Months Did Not Correlate Significantly, though ($r=0.02$, $p=0.80$).

Correlation between changes in inflammation and changes in metabolic markers

The difference in CRP and the difference in metabolic indicators did not significantly correlate linearly. ($p>0.05$)(shown in table 2). Between the difference in ESR and waist circumference, there was a statistically significant linear positive moderate connection ($r=0.23$, p0.05). This implies that greater changes in W.C. are linked to greater changes in ESR.

However, no additional significant association between differences in ESR and other metabolic indicators (such as differences in TGL, HDLC, FBS, SBP, and DBP) was discovered.

Figure: 1 Mean CRP and ESR at First Contact and Three-month Follow up

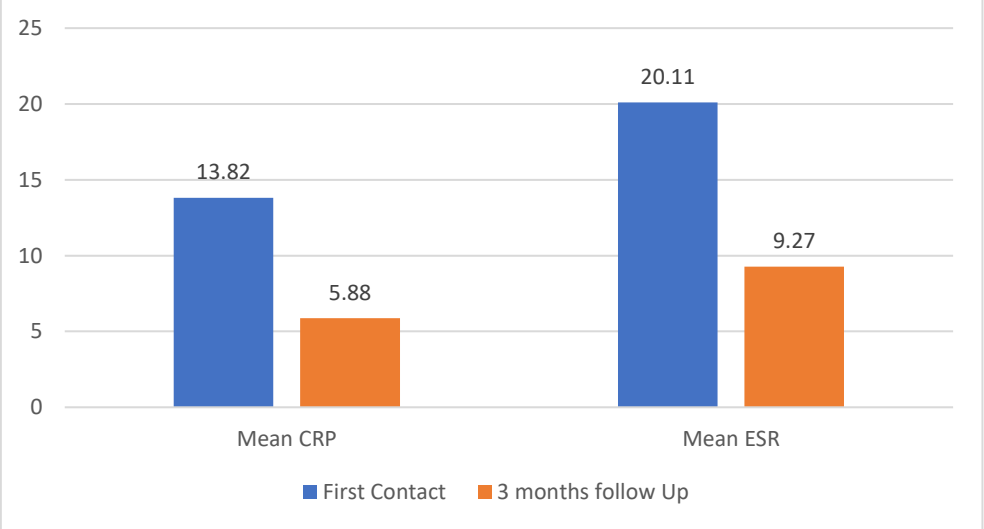


Figure 2: Mean Distribution of Metabolic Markers at First contact and after 3 months

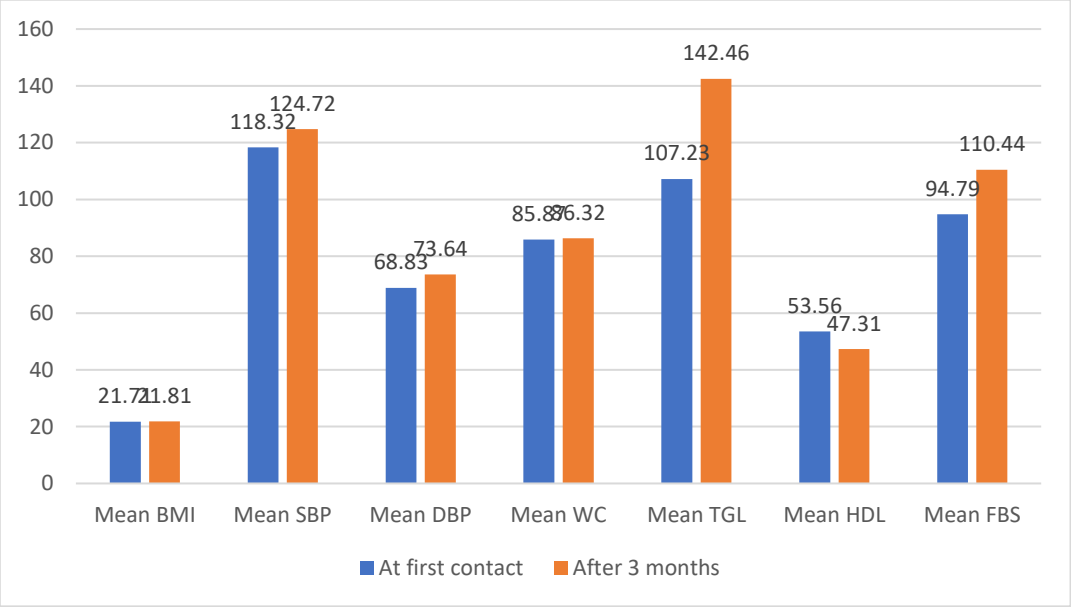


Figure :3 Extent of Metabolic Syndrome among subjects at First Contact and Three-month Follow up

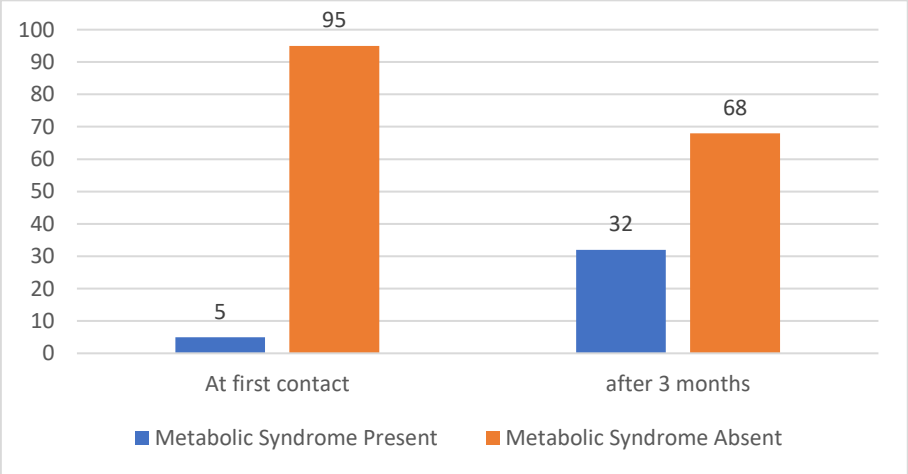


Table :1 Correlation between Inflammatory Status at First contact and metabolic Profile after three- months

Variable	BMI 3M	WC 3M	TGL 3M	HDL 3M	SBP 3M	DBP 3M	FBS 3M
CRP 0M							
Pearson Correlation(r)	0.37	0.23	0.02	.00	0.19	0.17	0.14
P value	**0.001**	**0.01**	0.80	0.94	0.05	0.18	0.15
ESR 0M							
Pearson Correlation(r)	0.27	0.18	0.10	0.12	0.26	0.31	0.15
P value	**0.002**	0.07	0.28	0.20	**0.002**	**0.001**	0.12

Table :2 Correlation between changes in inflammation and changes in metabolic markers

Variable	Diff. BMI	Diff. WC	Diff. TGL	Diff. HDL	Diff. SBP	Diff. DBP	Diff. FBS
Diff. CRP							
Pearson Correlation(r)	0.15	0.06	0.23	.01	.02	-0.07	.12
P value	0.13	0.52	0.82	0.85	.81	0.43	.20

Diff. ESR							
Pearson Correlation(r)	.09	0.23	0.05	0.03	0.04	0.20	0.10
P value	0.33	**0.003**	0.59	0.73	0.63	0.03	0.31

DISCUSSION

At first contact, the majority of the subjects had elevated CRP and ESR levels; however, three months later, the majority of the subjects had returned to their normal CRP levels. The mean CRP and ESR values at the three-month follow-up and First Contact were significantly different. (Figure-1) At First Contact, all inflammatory indicators (including CRP and ESR) were elevated; however, three months later, they all returned to normal. Similar results were obtained in the earlier investigation **[16]**. Therefore, it can be claimed that psychosis is an inflammatory condition during the time of the First Episode.

After three months, all the factors affecting the metabolic profile altered dramatically, showing a short-term, unfavorable metabolic result (Figure). CRP at the time of the initial contact and BMI three months later showed a significant linear positive moderate connection ($r=0.37$, $p<0.05$). Accordingly, greater CRP values at the time of the initial interaction are linked to higher BMI levels three months later. CRP at initial contact and W.C. at three months had a statistically significant linear positive weak connection ($r=0.23$, $p<0.05$). This indicates that greater CRP values at the time of the initial exposure are linked to higher W.C. three months later. ESR at first contact and BMI at three months had a statistically significant linear positive weak connection ($r=.27$, $p<0.05$). Accordingly, greater ESR values at the time of the initial interaction are linked to higher BMI levels three months later. CRP at First Contact and TGL at Three Months Did Not Correlate Significantly, though ($r=0.02$, $p=0.80$). This outcome differs from those of the most recent study conducted by Russell, A., et al. **[16]**

However, there is generally no connection between inflammatory marker alterations and the result of metabolic markers. Between the difference in ESR and waist circumference, there was a statistically significant linear positive moderate connection ($r=0.23$, p0.05). This implies that greater changes in W.C. are linked to greater changes in ESR. Waist circumference grows more in those who have bigger increases in ESR.

The advantages of this study include using fasting blood samples, the variety of metabolic indicators assessed and the longitudinal design. It's important to acknowledge some restrictions as well. Initially it was not possible to study the entire set of variables that were available. inflammatory response; for instance, we lacked information on other drugs (other than antipsychotics) and on physical health issues. Second, It's possible that the three-month follow-up period was too little to detect changes in some of the measures looked at. Finally, because of the naturalistic study design, we were unable to standardize the course of therapy, and it is possible that the length of the illness or the type of medication used had a difference in the impact on metabolic parameters.

Regarding clinical implications, this study supports the notion that it may be critical to identify FEP patients who are at higher risk of inflammation, which if treated well initially, can have lesser anabolic side effects. Our findings imply that the key to identifying those at higher risk of developing metabolic disorders is assessing inflammation. This shows that monitoring inflammation earlier in the course of an illness is necessary, for instance by including CRP in routine blood testing [17]. In order to investigate a potential advantage of these treatments as a prophylactic approach, future trials of adjuvant, anti-inflammatory therapies in psychosis should include reporting of anthropometric and metabolic results.

Our findings imply that FEP patients who have higher levels of inflammation, as determined by CRP, are more likely to experience poorer metabolic outcomes associated with anabolic changes and which in turn can result in cardiovascular events, which are known to increase mortality. While more study is required to confirm these findings, early treatments to minimize inflammation and track changes have to be taken into consideration.

CONCLUSION

Our preliminary findings suggest that individuals with FEP who have higher levels of inflammation are more likely to experience poorer metabolic outcomes linked to the metabolic syndrome. We advise more study to confirm these findings and that early measures to lower inflammation and keep an eye on changes should be recommended in a person with First Episode Psychosis.

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