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ORIGINAL ARTICLE:

Lipid Profile Improvements: Omega-3 Fatty Acids Versus Aripiprazole as Adjuncts to Olanzapine Therapy

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ABSTRACT

OBJECTIVE

To compare the beneficial effects of omega 3 fatty acids (omega 3 FA) and add on aripiprazole in patients taking olanzapine and having deranged lipid profile.

STUDY DESIGN

Comparative study design.

PLACE & DURATION OF STUDY

The study was conducted in Psychiatry department of Sir Ganga Ram Hospital (SGRH), Lahore in a duration of 6 months.

METHOD

Sixty schizophrenic patients (both genders), taking olanzapine and having deranged serum triglyceride and LDL cholesterol were recruited in two groups (Group I and Group II with 30 subjects in each group). Group I was administered 1000 mg omega 3 FA/day/oral at bed time for twelve weeks. Group II was administered aripiprazole 5 mg /day/oral at bed time. Body weight was measured at screening and after 12 weeks. Serum triglyceride and serum LDL cholesterol of both groups were measured at screening (0 day), 6 weeks and after 12 weeks. Collected data was analyzed using SPSS 20.

RESULTS

After 12 weeks Group I showed 19% and Group II showed 15 % reduction in body weight. Group I showed 22 % reduction and Group II depicted 20 % reduction in serum triglyceride. Serum LDL cholesterol showed 20 % and 19 % reduction respectively in Group I and Group II. Body weight, serum triglyceride and LDL cholesterol of Group I and Group II had significantly (≤0.05) reduced as compared with levels at screening.

CONCLUSION

Treatment with omega 3 FA and aripiprazole successfully reduced body weight, serum triglycerides and LDL cholesterol.

KEYWORDS

Schizophrenia, Aripiprazole, Omega 3 Fatty acids, Serum triglycerides, Serum LDL, Olanzapine, metabolic derangements.

INTRODUCTION

Schizophrenia is a chronic psychiatric illness characterized by psychological, social and behavioral malfunction. Alteration in dopamine levels in mesolimbic and mesocortical pathways of brain is the main pathology behind the disease [1].

Symptoms of schizophrenia can be described as positive symptoms, negative symptoms and cognitive symptoms. Positive symptoms include hallucinations and delusions. Negative symptoms are reduced motivation and social withdrawal. Cognitive symptoms account for deficits in working memory and cognitive flexibility. Symptoms mostly appear between 20 -30 years of age [2].

Incidence of schizophrenia in Pakistan varies from 1.5-2.5 % of population with up to 73% patients experiencing relapses of symptoms [3]. The disease burden of schizophrenia can be reduced by efficient management of disease with pharmacological and behavioral interventions. Antipsychotic drugs are classified as typical and atypical antipsychotics (AAPs). AAPs (clozapine, olanzapine, quetiapine, risperidone, aripiprazole etc.) are considered drugs of choice due to comparatively better side effect profile [4].

However, most AAPs have numerous side effects including derangement of glucose and lipid metabolisms, hypertension, obesity, myocarditis and sexual dysfunction. Almost 19 % patients taking atypical AAPs experience derangements of lipid profile and blood sugar levels [5]. Olanzapine is the most commonly prescribed AAP but causes significant weight gain, raised blood sugar and lipid levels [6]. Treatment with aripiprazole and lurasidone has shown better metabolic profile than other AAPs. But mostly psychiatrists are reluctant to switch a stable patient from one AAP to another to improve the metabolic profile. Studies have shown that add on/concurrent therapy with aripiprazole can improve the metabolic profile of schizophrenia patients without affecting the psychotic symptoms[7].

Omega-3 fatty acids alter the phospholipid composition of cell membranes, increase anti-inflammatory cytokines and reduce pro-inflammatory factors. Omega-3 fatty acids are natural antioxidants and have shown promising effects in reducing serum lipid levels in patients with hyperlipidemia by reducing the synthesis of cholesterol and triglycerides in liver[8]. Studies have proved that omega-3 fatty acids improve cognitive function in schizophrenia patients [8,9]. This study was designed to compare the beneficial effects of omega-3 FA and add on aripiprazole in patients taking olanzapine and having deranged lipid profile.

METHOD

Participants

This was a comparative study conducted in Psychiatry department of Sir Ganga Ram Hospital (SGRH), Lahore. Non-Probability, consecutive sampling technique was followed. Sixty patients were recruited in two groups, having 30 patients in each group. Inclusion criteria included age range 20-45 years, both genders, diagnosed patients according to DSM V (Diagnostic and statistical manual of mental disorders) taking olanzapine, with deranged lipid levels (Triglycerides = ≥150 mg/dl, LDL cholesterol = ≥130mg/dl). Patients already taking antihyperlipidemic treatments / omega-3 fatty acids, pregnant/lactating mothers, hypertensive patients and patients with a previous history of ischemic cardiac events were excluded from this study.

Instruments

The data regarding age, sex, past medical history, family history, physical examination, and clinical examination were recorded in the case report form. Patients in Group I were administered omega-3 fatty acids 1000 mg/day (capsule form), with meals for twelve weeks [6]. Patients were advised to take medication at bedtime. Patients in Group II were administered aripiprazole [11] 5 mg/day with meals for twelve weeks. Dose was started with 5mg/day and reviewed after every six weeks. Patients were advised to take medication at bedtime. Fasting blood sugar, serum cholesterol and serum triglyceride were carried out at baseline, 6 weeks and 12 weeks[6]. Body weight was measured at baseline and at the end of 12 weeks. Compliance was ensured by pill count and diary cards. Follow up was done after every two weeks, and medicine for next two weeks was provided. During every follow up patients were asked

about any unpleasant effects of new medicines and advised accordingly.

Spontaneously reported treatment-emergent adverse events (TEAEs) were recorded throughout the twelve-week period. Physical examination, monitoring of medications and adverse events were done at baseline and weeks 6 and 12. All the patients were asked to report in psychiatry OPD in case of any drug related side effects and at the completion of trial period.

Procedure

After informed consent the patients (having stable schizophrenia symptoms on olanzapine but deranged lipid levels) were divided into two groups; Group I and Group II with 30 individuals in each group. Patients were enrolled according to inclusion criteria and randomly assigned in a 1:1 ratio to two study groups (Group I was administered omega 3 fatty acids 1000 mg/da**y** and Group II aripiprazole [10] 5-15 mg/day) using a computerized random number table generator to obtain a trial sequence. The statistician generated the random allocation sequence and the investigators enrolled the patients. Both groups were measured for the variables mentioned above and record was entered to SPSS version 22.

All the quantitative variables were presented by mean ± SD. The mean difference among serum triglycerides and cholesterol was compared by Independent Sample t-test according to normality of data. The comparison of outcome variables on 3 different time points (0, 6 and 12 weeks) was compared by repeated measure ANOVA. Therapeutic effectiveness was assessed by chi-square test. P-value ≤ 0.05 was considered as significant.

RESULTS

The results showed that among sixty patients with schizophrenia 26 were males and 34 were females. Age ranged from 23-45 years. All patients belonged to middle to lower socioeconomic status. Screening body weight of Group I was 77.96 ± 9.45 kg (mean ± SD) and of Group II was 75.93 ± 4.56 kg (see figure 1). After 12 weeks body weight of Group I was 71.34 ± 8.27 kg and Group II showed a weight of 68.76 ± 5.6 kg (Fig. 1). Both groups showed a significant reduction ((p ≤ 0.05) in body weight after 12 weeks. Comparison of both treatments showed no significant difference after 12 weeks.

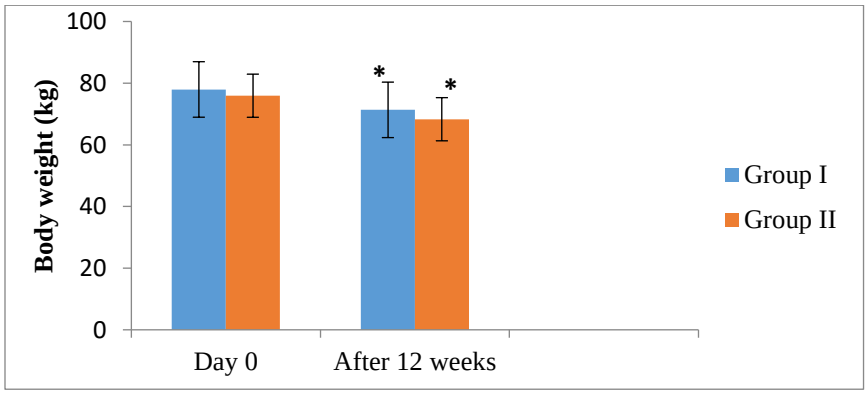

Fig.1. Comparison of Body weight (kg) of Group I and Group II, n=30.

Serum triglycerides were measured at screening (Day 0), at 6 weeks and after 12 weeks of both groups. On day 0 serum triglycerides of Group I was 218.16 ±3 9.14 mg/dl and Group II 213.51± 40.63 (see figure

2). At 6 weeks serum triglycerides of Group I reduced to 193.43 ± 39.16 mg/dl (≤ 0.05 significant as compared to day 0) while that of Group II was 191.06 ± 42.14 mg/dl (≤ 0.05 significant as compared to day 0). After 12 weeks serum triglyceride levels of both groups were significantly reduced as compared to day 0 and were 171.40 ± 35.33 mg/dl for Group I and 170.72 ± 42.07 mg/dl for Group II (Fig. 2). No significant difference was observed between two treatment groups after 12 weeks.

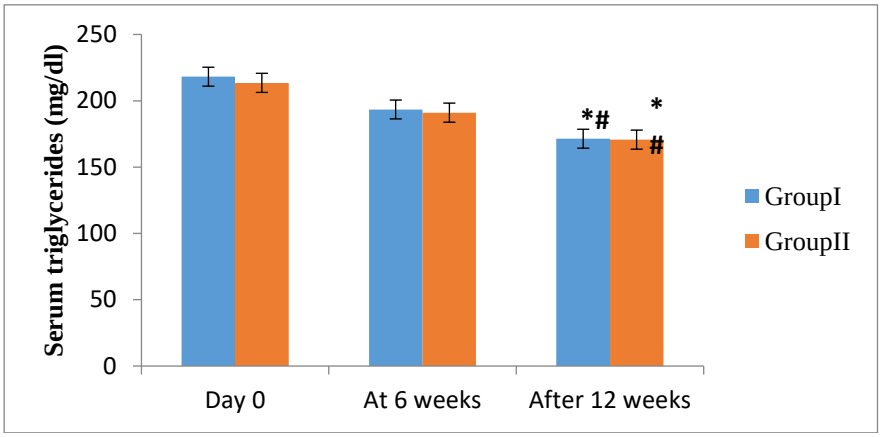

Fig.2. Comparison of serum triglyceride (mg/dl) of Group I and Group II n=30.

Serum LDL cholesterol values were measured at screening (Day 0), at 6 weeks, and after 12 weeks of both groups. At screening, serum LDL cholesterol of Group I and Group II were 184.23 ± 33.88 mg/dl and 183.20 ± 35.11 respectively. Fig 3 showed comparison of Mean ± SD of both groups. At 6 weeks serum LDL cholesterol of Group I was 165.16 ± 33.07 mg/dl (significance ≤ 0.05) and serum LDL cholesterol value of Group II was 163.79 ± 32.22 mg/dl (significance ≤ 0.05). After 12 weeks serum LDL cholesterol of Group I reduced to 147.56 ± 30.76 mg/dl and Group II showed reduction to 148.52 ± 30.31 mg/dl both of these results are significant (≤ 0.05) as compared to the results of Day 0 (Fig. 3). Comparison of both treatments showed no significant difference (≤ 0.05) after 12 weeks.

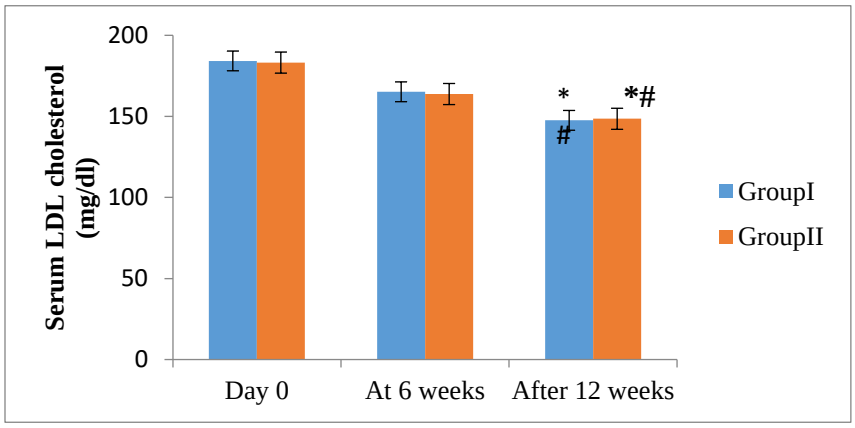

Fig.3. Comparison of serum LDL cholesterol (mg/dl) of Group I and Group II n=30.

Spontaneously reported treatment-emergent adverse events (TEAEs) were recorded throughout the twelve-week period. Physical examination, monitoring of medications and adverse events were done at baseline and weeks 6 and 12. Both treatment strategies were well tolerated.
No considerable side effects were reported by the patients.

DISCUSSION

Schizophrenia is a psychological disorder with multiple risk factors, i.e. genetic, epigenetic, and environmental. History of other mental illnesses, type A personality, migration, history of trauma in early life, and drug addiction also play an important role in precipitating psychoses [12]. Despite the significant advancements in the treatment of schizophrenia recently, therapeutic resistance in schizophrenia patients ranges from 5 to 60% [13]. Olanzapine is an atypical antipsychotic drug (APD) commonly prescribed for treatment of schizophrenia. However, its use is associated with the risk of metabolic syndrome, including hyperlipidemia, hyperglycemia, hypertension and weight gain[14].

Aripiprazole an atypical APD is also used clinically as add-on therapy to reduce metabolic side effects of olanzapine without affecting its therapeutic effects [15]. Multiple studies have shown beneficial effects of omega 3 FA in reducing the manifestations of metabolic syndrome caused by different factors[16].
Out of 60 patients only 5 (8 %) showed normal metabolic parameters this is strong evidence that olanzapine leads to derangements in serum triglycerides (mg/dl) and serum LDL cholesterol (mg/dl). These results are consistent with the observations of Samyukta K et al. who have shown symptoms of metabolic syndrome in up to 60 % of patients taking olanzapine[17].

Significant reduction in body weight was observed in both groups as compared to screening. Similar reduction is reported in body weight in other studies by omega 3 FA [6] and aripirazole[7].
Group I (omega 3 fatty acids 1000 mg/day) showed 22 % reduction in serum triglyceride levels. This result is similar to the 27 % reduction in serum triglyceride levels reported by Xu F et al. 2018[6]. Group II (aripiprazole 5mg/day) exhibited almost 20 % decline in serum triglyceride levels after 12 weeks. This result of Group II (aripiprazole 5mg/day) is in line with the study conducted by Henderson DC et al. 2009, who have documented 26 % reduction of serum triglyceride levels after add on therapy with aripiprazole[7].
Serum LDL cholesterol levels of Group I (omega 3 fatty acids 1000 mg/day) were reduced up to 20 % after 12 weeks as compared to the baseline value. Similar results were reported by other studies[6,18].

These serum triglyceride and serum LDL cholesterol lowering effect of Omega 3 FA can be attributed to their metabolic effects as reduced triglyceride synthesis, reduced addition of triglycerides into lipoprotein particles and decreased triglyceride secretion. Omega-3 FA also reduce hepatic lipogenesis, increase catabolism of apoB-100 and increase β-oxidation of fatty acids[19].

They also activate the transcription factors by increased efficiency of 5' AMP-activated protein kinase (AMPK) and help to regulate the nutrients involved in lipid metabolism pathways. The AMPK is considered as a sensor of energy status which regulates the partitioning process among lipogenesis and lipid oxidation. The genetic expression of enzymes involved in synthesis of fatty acids is suppressed (acetyl-coA carboxylase and fatty acid synthetase)[18].

Omega 3 FA have also been proven to reduce TNF (tumor necrosis factor) alpha levels. TNF alpha leads to increased triglyceride levels by increasing the synthesis of triglycerides and reducing the clearance of lipoproteins from circulation. Omega-3 FAs act as ligands for G protein receptors and decrease pro-inflammatory effects produced by TNF-alpha. Therefore, omega-3 FAs reduce TNF-alpha concentration by suppressing tissue inflammation caused by macrophages. These anti-inflammatory activities can lead to inhibition of triglyceride synthesis and enhance its clearance[6].
Serum lipid levels of Group II (aripiprazole 5mg/day) were also significantly reduced and showed a reduction of almost 19 % after 12 weeks as compared to the levels at day 0. Similar lipid lowering effect of aripiprazole is seen in multiple studies [7,20].

The reducing effect of aripiprazole on serum triglyceride and serum LDL cholesterol can be explained by its actions at different receptors. Blockade of histamine receptors and 5- HT2C by antipsychotics is considered the cause of weight gain produced by these medications[21].
These findings are relatable to 5-HT2C receptors knockout mice which are more prone to develop weight gain and insulin resistance. Aripiprazole acts as an agonist at 5-HT1A and 5-HT2C receptors. The drug shows no antihistaminic effects. These properties are considered responsible for drug's positive effects on metabolic syndrome [15].

CONCLUSION

Treatment with omega 3 FA and aripiprazole has successfully reduced the body weight, serum triglycerides and serum LDL cholesterol. This study indicates the protective effects of both treatment options against metabolic adverse effects of olanzapine. Omega 3 FA have shown comparable results to aripiprazole therapy which is a standard treatment option prescribed to improve lipid profile and deranged blood glucose levels as an add on therapy clinically.

Future Recommendations

This study provides a strong indication for evaluation of beneficial effects of omega 3 FA on disease symptoms and pathogenesis to provide better and safer treatment options for long standing diseases like schizophrenia. Synergistic effects of omega 3 FA and add on aripiprazole should also be evaluated. Schizophrenia patients should be encouraged to include natural sources of Omega 3 FAs in their diet.

Conflict of interest

All authors declared no conflict of interest exist.

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None

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6.	Uzma Qayyum	Punjab Institute of Mental Health (PIMH), Lahore, Pakistan.	Patient assessment, data collection