Original Article

Lipid Correlates of Attentional Impulsivity in First Episode Mania: Results from an Indian Population

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ABSTRACT

Background: Attentional/cognitive impulsivity has been demonstrated as being associated with an increased risk for suicide and other self-harming behaviors, along with a more severe course in patients with bipolar disorder. That an alteration of the various serum lipid fractions might be associated with increased impulsivity has been proposed in the past, but evidences are ambiguous and mainly based on western population data. **Objective:** The present study was aimed to analyze the attentional impulsivity and various serum lipid fractions in bipolar patients, from an Indian perspective. **Materials and Methods:** At presentation, 60 drug free/naïve first episode Mania patients were rated on the Barratt impulsiveness scale-version 11 and Young Mania Rating Scale; body mass index (BMI) was calculated and blood samples were analyzed for total cholesterol (TC), high density lipoproteins, low density lipoproteins and very low density lipoproteins (VLDL), triglycerides (TG) and apolipoproteins A1 and B. **Results:** The analysis revealed statistically significant negative correlation and inverse linear relationship between TC, TG, VLDL and BMI with attentional impulsivity. **Conclusion:** The present study adds to the growing literature on a complex relationship between lipid fractions and attentional impulsivity. The findings present interesting insights into the possible substrates of human behavior at biochemical levels. The implications are many, including a need to introspect regarding the promotion of weight loss and cholesterol reduction programs in constitutionally vulnerable population.

Key words: *Attentional impulsivity, bipolar, body mass index, lipid*

INTRODUCTION

The construct of impulsivity is multifaceted,[1-3] manifest as "actions which are poorly conceived, prematurely expressed, unduly risky or inappropriate to the situation and that often result in undesirable consequences".[4] Impulsivity, in relation to affective disorders, have been studied extensively and a significantly higher level of impulsivity has been demonstrated in these subjects as compared to a healthy population.[5-10] Researchers have also found an increased impulsivity in euthymic bipolar patients;[11,12] though the acute neurochemical changes in brain probably leads to a particularly overt manifestation of this feature[13-15] during manic episodes.

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The neurobiological basis of this impulsivity has received considerable attention in recent years, in terms of both the anatomical[16,17] as well as the neurochemical[18] foundations. Deficient central serotonergic transmission has been proposed[19-21] as a biological substrate for impulsivity; and a number of studies in past have suggested serum cholesterol to be a surrogate marker[22-24] for the same and demonstrated a correlation between serum cholesterol and various measures of impulsivity[19,20,25-28] across psychiatric diagnoses. Studies have discussed the effects of

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cholesterol on serotonergic function,[29,30] through its influence on the function of membrane-bound serotonergic structures by altering membrane fluidity[31] and reduction in serotonin transporter activity due to their destabilization after cholesterol depletion.[29] Cholesterol depletion also has been found to result in an impaired functioning of 5-HT1A and 5-HT7 receptors.[32,33] Cholesterol is also a major component of lipid rafts, which are of significance in synaptic function;[34] and thus depletion of cholesterol has been shown to have diffuse effects on not only serotonergic functioning, but also on other neurotransmitter systems, including the excitatory amino acid transport,[35] gamma-amino butyric acid transmission[36] and opioid signaling.[37] A tentative conclusion that can be drawn from studies on this aspect is that the interactions between cholesterol and serotonergic functions are almost certain.

Cholesterol consists of various fractions such as high density lipoproteins (HDL), low density lipoproteins (LDL) and very low density lipoproteins (VLDL). When considering impulsivity as a whole, some studies[25,38,39] suggest that the most important lipid fraction is HDL, whereas others[26,40] propose total cholesterol (TC) or the LDL fraction to be the important one. The proposal that even the sub-constructs of impulsivity might have different biological underpinning[41] led to studies exploring the relationship between the former and various cholesterol fractions.[28,42] In a study by Troisi[28] found that in a mixed sample population, attentional impulsivity, as measured on Barratt impulsiveness scale-version 11 (BIS 11) attentional subscale, was the construct negatively correlated with lower cholesterol levels; while Conklin *et al*.[42] in their study found a negative correlation between motor impulsivity and omega-3 fatty acid in the body.

Coming back to affective disorders, in these patients disruptions in lipid levels have been demonstrated. Patients with manic disorders have been shown to have a lower cholesterol levels[43,44] and some studies have also found an increased triglyceride (TG) level in them;[45,46] when compared with matched healthy controls. In the light of ongoing discussion, we might now ask a pertinent question: Can this derangement be affecting the disease manifestations and course as such?

The importance of studying impulsivity in these patients with bipolar disorder (BD) is highlighted by the finding of Jiménez *et al*.[47] of it exerting a significant role in cognitive and functional impairment in patients with BD and by Swann *et al*.[48] of a higher attentional impulsivity being associated with a more severe course and outcome in them. Hence, considering that a high score on measures of attentional/cognitive impulsivity sub-construct is a demonstrated risk factor for suicide and other self-harming behaviors[49,50] and that a higher attentional subscale value in BIS 11 was associated with a more severe course;[50] patients presenting with low cholesterol, attentional impulsivity and mood symptoms warrant increased clinical attention and surveillance.

The present authors intended to study the relationship between attentional impulsivity, measured using BIS 11; and various serum lipid fractions. Present study tried to circumvent a number of limitations in the past studies. Most of the studies investigating the relationship between cholesterol and impulsivity so far have been conducted in the west. The western diet has a higher fat and lower fiber content,[51] and the population follows a sedentary life-style; compared with the developing countries. Therefore their generalizability to developing countries is questionable. As evident from their sample characteristics, most of the subjects had a body mass index (BMI) above 23, which is much higher compared with the definition of the Indian standards for normal weight. What happens in the normal, or low normal range of BMI is therefore not clear. The past studies did not adequately control for the effects of other factors, which might have influenced the blood lipid levels, like substance abuse.[25,27] In the past, it has been proved that both impulsivity[18] and cholesterol levels[52] can be affected by drugs like mood stabilizers. Past studies also failed to control for drug status.[25,27,28] Most of the studies until date included patients with diagnosis other than affective disorders,[25-27] or studied a mixed sample.[28] They tried to study the manifestations of impulsivity like self-harming behavior, violence or suicidality; but none differentiated between the premeditated and impulsive components of these acts, as suggested by Barratt *et al*.[41] None of the studies in past correlated the sub-scales of the BIS 11 in subjects with impulsivity, with the cholesterol fractions, except for one by Troisi.[28] Finally, only TC, HDL and LDL have been studied in detail; but the other fractions as TG and VLDL were not studied in most. As TG levels are elevated in patients with affective disorders[45,46] and that obesity and impulsivity have been found to be linked in some studies,[53,54] the past studies have neglected this blood lipid fraction in their assessment of impulsivity.

This is the first study, to the best of our knowledge, investigating the relationship between the various lipid fractions and measures of attentional impulsivity as the basic construct, in a homogenous sample of the first episode mania, in a representative developing-country population and with a modest sample size.

MATERIALS AND METHODS

The index study was conducted at a postgraduate teaching hospital and a leading tertiary care referral psychiatric facility in the eastern part of the India. The study population consisted of 60 first episode manic patients diagnosed as per International Classification of Diseases-10 Diagnostic Criteria for Research[55] criteria, by a psychiatrist having a postgraduate qualification in psychiatry. Subjects were excluded if they had a comorbid neurological disorders or general medical conditions such as diabetes mellitus, liver disease, renal disease, hypertension and thyroid dysfunction etc., if they were taking oral contraceptives and beta blockers, or if they were over 65 years of age, or if they had a past history of cholesterol abnormality.

The socio-demographic data was obtained. Height and weight were recorded using standard scales and BMI was calculated. A sample of 5 ml of venous blood was collected between 8 and 9 in the morning, after the subjects have fasted for 12 h. The blood was analyzed on the same day, within 2 h of collection, during which the sample was stored at room temperature. TC, HDL, LDL, VLDL and Serum TG estimation was done by enzymatic method (using cholesterol esterase, cholesterol oxidase and peroxidase) and apolipoproteins (Apo) A1 and B fractions were measured using immunoturbidometry.

On the same day, young mania rating scale (YMRS) and BIS 11 were applied on the subjects. All the subjects were rated on self-administered BIS 11. BIS 11 is the most commonly used self-report measure for assessing impulsivity in both clinical and research settings. The subscales were introduced into the scale in BIS version 10, in recognition of the multidimensional nature of impulsivity, evident after factor analytic studies. BIS 11 is a further improvement on that with the labeling of "Attentional Impulsiveness" subscale, defined as an inability to focus attention or concentrate.[56] There are 30 personal statements in the BIS 11, as listed by Patton *et al.*,[57] designed to assess general impulsiveness taking into account the multi-factorial nature of the construct. Items are rated from 1 (absent) to 4 (most extreme) and scores range from 30 to 120. The BIS 11 identifies three components of impulsivity. Attentional/cognitive impulsivity is a lack of cognitive persistence with an inability to tolerate cognitive complexity; motor impulsivity is a tendency to act on the spur of the moment; and non-planning impulsivity refers to a lack of sense of the future.

Statistical analysis

The data was analyzed using the SPSS version 16 (SPSS, Inc., Illinois, USA). The frequency counts of the categorical variables were done; and the mean and standard deviation of the continuous variables were calculated across the sample. Kolmogorov-Smirnov test was used to test the normal distribution of all the cholesterol fraction values. Relationship between the various lipid fractions and score on attentional impulsivity subscale of BIS 11 was investigated in bivariate exploratory analysis using Pearson's correlation. Linear regression analysis was applied on the variables emerging to be significantly correlated with the latter.

RESULTS

The study sample consisted of 50 male and 10 female subjects (n = 60). Out of the 60, 17 were drug free for at-least one month prior to the date of collection of their blood samples and 43 were drug naïve. 9 had a significant family history of either an affective disorder or a psychotic disorder. The sample mean age was 26.88 ± 7.13 years and the mean BMI (kg/m^2) was 18.53 ± 2.40 [Table 1]. All the cholesterol values and BIS scores were normally distributed (Kolmogorov-Smirnov test $P > 0.05$).

Bivariate correlation revealed BIS 11 attentional scale scores to correlate negatively and significantly with TC, TG, VLDL and Apo B levels [$P < 0.05$; Table 2], indicating that a lower values of these were associated with increased attentional impulsivity. Linear relationship emerged between the attentional score and TC, TG, VLDL ($P < 0.05$) and BMI ($P < 0.01$) when we conducted linear regression analysis to explore these associations further and the beta was found to be negative in all cases [Table 3].

Table 1: Socio-demographic, clinical and laboratory characteristics of subjects for continuous variables (*N*=60)

Variables (*N* = 60)	Mean ± SD
Age (years)	26.88±7.13
BMI (kg/m²)	18.53±2.40
TC (mg/dl)	139.48±36.74
TG (mg/dl)	89.15±38.58
HDL (mg/dl)	39.23±8.43
LDL (mg/dl)	83.90±30.80
VLDL (mg/dl)	17.87±8.33
Apo A1 (mg/dl)	220.67±38.54
Apo B (mg/dl)	134.38±44.30
YMRS	27.93±9.12
BIS 11 attentional score	19.78±4.19
BIS 11 motor score	25.60±4.79
BIS 11 non-planning score	26.88±4.77
BIS 11 total score	72.27±9.38

SD – Standard deviation; BMI – Body mass index; BIS 11 – Barratt Impulsiveness Scale-version 11; TC – Total cholesterol; TG – Triglycerides; HDL – High density lipoproteins; LDL – Low density lipoproteins; VLDL – Very low density lipoproteins; Apo – Apolipoproteins; YMRS – Young mania rating scale

Table 2: Pearson's correlation between lipid values and BIS 11 scores (*N* = 60, df = 57)

Variables	TC	TG	HDL	LDL	VLDL	Apo A1	Apo B	BMI
BIS11 attentional	−0.261*	−0.314*	−0.050	−0.194	−0.335*	−0.214	−0.268*	−0.417**

TC – Total cholesterol; TG – Triglycerides; HDL – High density lipoproteins; LDL – Low density lipoproteins; VLDL – Very low density lipoproteins; Apo – Apolipoproteins; BIS 11 – Barratt Impulsiveness Scale-version 11; BMI – Body mass index. *$P < 0.05$; **$P < 0.01$

Table 3: Linear regression analysis of relation between TC, TG, VLDL, Apo B and BMI; and BIS 11 attentional impulsivity subscale score (dependent variable)

Variable	β	*t*	*P*	*R*	R^2	Adjusted R^2
TC	−0.302	−2.409	0.019*	0.302	0.091	0.075
TG	−0.339	−2.740	0.008**	0.339	0.115	0.099
VLDL	−0.355	−2.894	0.005**	0.355	0.126	0.111
Apo B	−0.255	−2.005	0.050	0.255	0.065	0.049
BMI	−0.438	−3.715	0.000**	0.438	0.192	0.178

TC – Total cholesterol; TG – Triglycerides; VLDL – Very low density lipoproteins; Apo – Apolipoproteins; BIS 11 – Barratt Impulsiveness Scale-version 11; BMI – Body mass index

DISCUSSION

In the present study, the sample size was modest and constituted of only first episode manic patients. A first hypomanic or manic episode has been considered as a valid construct for predicting BD.[58,59] Hence the present study selected only first episode mania patients to obtain a homogenous sample, representative of those with BD; who are relatively free from the confounding effects of prolonged medication (mood stabilizers, antipsychotics and antidepressants), as well as the metabolic effects associated with the disorder itself.[43,44,60-63] The mean YMRS score was found to be 27.93 ± 9.12. A score of <10 on YMRS has been used as a cut-off value in defining euthymic subjects in various studies on bipolar patients.[64,65] Hence, all the subjects in the present study were symptomatic at the time of induction.

Troisi[28] had found a significant negative correlation between TC and score on attentional subscale of BIS 11, especially at the lower end of the TC range (<165 mg/dl). Conklin and Stanford[27] subdivided the scores on BIS 11 and found a negative and significant correlation between TC and LDL levels and attentional impulsivity, measured on BIS 11. Studies exploring similar psychological constructs using manifestations rather than scores on BIS *per se* found that TC levels were negatively correlated with executive control and sustained attention[66] and a lowering cholesterol levels had an adverse effect on cognitive functions.[67] Pozzi *et al*.[26] found lower levels of TC to be a significant predictor of impulsivity and Henderson *et al*.[68] reported higher serum LDL cholesterol and a recent increase in TC to be associated with comparatively better memory performance. Chakrabarti *et al*.[69] found significantly lower levels of TC and LDL in patients with a history of violent crimes compared with those without, in an Indian sample. Thus, in line with previous studies, the role of TC in impulsivity was reconfirmed by the present authors. We further refined the findings on the role of TC and confirm that attentional impulsivity was associated with a lower TC level. We further propose that these two are linearly related to each other and a lower TC level predicted a higher attentional impulsivity, at least within the cholesterol range of the present study population.

However, the present study did not find a role of LDL in manifestation of attentional impulsivity, as demonstrated by several authors in the past.[27,68,69] We hypothesize that this was due to a lack of homogeneity in the past studies in terms of clinical sample, drug status and manifestations and measurements of impulsivity. Conversely, the previous studies do not mention a relation between the VLDL fraction, TG levels and attentional impulsivity, while our study predicts a lower VLDL and TG values those with attentional impulsivity. This is a novel finding and was probably obtained because the association between blood lipids and features of impulsivity varied with the characteristics of the population (food habit, lifestyle etc.).[70] TGs are the major lipids in fat deposits and are implicated in obesity, diabetes and coronary heart diseases. The VLDLs act as vehicles for carrying TGs from the liver to the extra-hepatic tissues[71] and an increased TG leads to a higher BMI and obesity. Liao *et al*.[72] studied subjects with a psychiatric diagnosis of either Schizo-affective disorder or BD and concluded that TG was found to correlate negatively with violent behavior, though they did not specifically address the issue of impulsivity. Our findings and those of Liao *et al*.[72] might be related through a complex mechanism encompassing violence, impulsivity and serotonin function.[21]

Regarding the role of Apo B in impulsivity, insufficient data exists. In an article in 2004 Chakrabarti *et al*.[69] had found a lower Apo B level in Indian males with a history of violent crime compared with those without. However, these authors did not differentiate between premeditated and impulsive violence and hence the results cannot be generalized. We believe this aspect requires future replication and elaboration.

We also found a significant negative correlation

between obesity and attentional impulsivity. Troisi[28] in 2011 measured the BMI and failed to find any significant correlation between BMI and other measures of impulsivity. In that study, the mean BMI was 24.35 ± 4.50 kg/m^2, whereas in the present study, it is 18.53 ± 2.40 kg/m^2. Gunstad *et al*.[53] studied 408 healthy adults and found that overweight and obese adults with BMI >25 performed poorer on tasks involving executive functioning, when compared to normal weight adults. Nederkoorn *et al*.[73] studied impulsivity in Dutch women and found significantly higher impulsivity on behavioral measures, but not on self-report measures, in obese subjects. The mean BMI of the two groups were 39.0 ± 5.3 and 22.5 ± 2.2 respectively, but the cause-effect relationship between obesity and impulsivity was not clarified in this study. A study by Bauer *et al*.[54] in 2012 examined the association between BMI and the genetic, neuropsychological and psychiatric indicators of impulsivity in formerly substance abusers and concluded that an elevated BMI is associated with genetic, neurophysiological, psychiatric and psychological indicators of impulsivity. Most of these studies dealt with western population and western life-style which is grossly different from the Indian one. Another important difference was that their subjects had much higher BMI compared to the present study sample. Neither of these studies focused on attentional impulsivity; nor did they examine specifically the relationship between impulsivity and BMI in individuals on the lower side of the BMI range. The mean BMI of our study sample was 18.53 ± 2.40 kg/m^2, which was much lower than the normal mean BMI of the population of the above mentioned studies. Therefore, we hypothesize that in individuals at the lower end of the BMI range, in whom the blood TG and VLDL levels are also on the lower side; BMI and impulsivity have an inverse relationship. This is in line with the proposal by Kaplan *et al*.[74] of an evolutionary rationale, in which a lower fat store would prompt the organism to be more active, vigilant and may be, impulsive and risk taking in order to win in the struggle for survival.

LIMITATIONS

The present study suffered from a number of limitations. The sample size was modest (N = 60), but a bigger sample would have provided with more reliable findings. Secondly, the sample had an underrepresentation of the female gender, urban population and subjects from a more affluent background. Some variables like the exact diet and levels of physical activity, which might affect lipid profiles and obesity and other measurements of obesity, such as the waist-hip ratio were not considered. The study used self-report measures of impulsivity (BIS 11), which depends on individual responses and thus might have been influenced by the affective states of the subjects. The study measured cholesterol levels, which have been hypothesized to be acting as a surrogate marker for omega-3 fatty acids.[75] A direct measurement of the latter, thus, would have given more robust results.

CONCLUSION

The current study demonstrates the presence of significant negative correlation between levels of TC, TG, VLDL, Apo B and BMI; and attentional impulsivity in the first episode mania subjects. These correlations followed a linear curve with a negative slope. This is also the first study, to the best of our knowledge, to report a predictive value for various serum lipid fractions and BMI regarding attentional impulsivity, at least in a population with an average BMI at the lower end of normalcy.

This raises an important question regarding the safety of weight loss and lipid lowering therapies in this clinical population, because "the absence of a significant effect of treatment on non-illness mortality alone does not exclude the possibility of cholesterol reduction having any adverse effects on psychological well-being or quality of life"[20] and as found in this study, a falling lipid level predicted an increasing attentional impulsivity in them. The study, thus, adds to the growing body of evidence regarding a complex association between serum cholesterol and mental health and may provide a word of caution regarding an increased risk of impulsivity in patients with BD with "unnecessary" lipid lowering attempts; thus proving detrimental to their well-being.

Future directions

In future, this aspect should be explored further using a larger sample size taking into account objective measures of diet, physical activity levels and include other measures of obesity. The studies in the future also need to apply objective measures of impulsivity, encompassing different techniques, to increase sensitivity and specificity of the measurement. Further, the future studies should also measure omega-3 fatty acid levels in addition to the cholesterol fractions, as suggested by Garland *et al*.[75]

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