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Low cholesterol is a risk factor for attentional impulsivity in patients with mood symptoms

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ABSTRACT

This study examined the relationship between cholesterol levels and impulsivity in a large sample of patients with mood symptoms. Three hundred and one patients with mood, anxiety, and personality disorders completed a battery of psychometric scales including the Barratt Impulsiveness Scale-Version 11 (BIS-11) and the Profile of Mood States (POMS). On the same day of psychometric assessment, blood samples were analyzed for total cholesterol (TC) and high-density lipoprotein cholesterol (HDL-C). Statistical analysis controlling for the confounding effects of age, gender, diagnosis, and current mood symptoms showed that lower TC levels were associated with increased attentional impulsivity. There was a weak linear correlation between TC and attentional impulsivity across the entire range of TC levels (110–295 mg/dL) but a highly significant difference between participants with TC levels lower than 165 mg/dL and the rest of the sample. The current study adds to the growing body of evidence pointing to the association between serum cholesterol and mental health. Considering that attentional impulsivity is a demonstrated risk factor for suicide, patients presenting with low cholesterol and mood symptoms may warrant increased clinical attention and surveillance.

1. Introduction

Impulsivity has been defined as a predisposition toward rapid, unplanned reactions to internal or external stimuli with diminished regard to the negative consequences of these reactions to the impulsive individual or others (Moeller et al., 2001). Impulsivity is directly mentioned in the DSM-IV diagnostic criteria for several disorders and is implied in the criteria for others, including ADHD, personality disorders, mania, and substance abuse/dependence. Impulsivity not only has clinical implications, but also appears to be a relatively enduring trait that characterizes many people without diagnosable psychiatric disorders. Individual differences in the temperamental trait of impulsivity are continuously distributed as well as substantially heritable, and therefore are likely to result from additive or non-additive interaction of genetic variations with environmental influences (Lesch and Merschdorf, 2000; Potenza and Taylor, 2009).

There has been considerable convergence in recent years on the neurobiological substrates of impulsivity. The neuroanatomical circuitry involved in impulsivity includes the prefrontal cortex, orbitofrontal cortex, and distinct sub-regions of the striatum (Dalley et al., 2008). Although the neurochemistry of impulsivity is likely to imply various neurotransmitters, including dopamine, noradrenaline, endocannabinoids, and glutamate (Pattij and Vanderschuren, 2008), the primary role of brain serotonin (5-HT) has clearly emerged from many experimental and clinical studies that have demonstrated an association between decreased 5-HT transmission and increased impulsivity (Carver and Miller, 2006; Paaver et al., 2007).

Deficits in central serotonin transmission could also explain the link between low serum cholesterol and increased impulsivity (Buydens-Branchey et al., 2000; Pozzi et al., 2003; Conklin and Stanford, 2008). Several studies have suggested that serum cholesterol may be a marker for central serotonergic activity (Steegmans et al., 1996; Terao et al., 2000; Vevera et al., 2005). Experimentally decreasing the cholesterol content of cell membranes has been shown to reduce the binding affinity of a serotonin 5-HT1A receptor agonist, alter G-protein coupling of the receptor, and decrease activity of the serotonin transporter (Scanlon et al., 2001; Pucadyil and Chattopadhyay, 2007). Kaplan et al. (1994) found that when monkeys (of the same weight and receiving the same caloric intake) were fed a low-cholesterol diet, they had lower levels of the serotonin metabolite, 5-hydroxyindoleacetic acid (5-HIAA), in their CSF than did monkeys on a high-cholesterol diet.

Compared to negative mood, aggression, suicide and self-harm, impulsivity has received less attention by studies focusing on the emotional and behavioral correlates of low-cholesterol levels (Troisi, 2009). What is more, the results of the few studies that have focused on impulsivity are discordant (Garland et al., 2007) and their generalizability is questionable because they were based on small samples and/or samples characterized by restricted demographic composition (mainly young men) and diagnostic range (primarily drug addiction and deliberate self-harm).

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The present study was designed to overcome the methodological limitations of past research. We studied the relationship between cholesterol levels and impulsivity in a large sample of participants with a wide range of non-psychotic psychiatric disorders, not limiting our focus on those conditions characterized by extreme levels of impulsivity such as borderline personality disorder or substance abuse. Our sample included participants of both sexes and age spanning from adolescence to late adulthood. We took into account the confounding effect of present mood state on the assessment of impulsivity and distinguished between the different components of impulsivity when analyzing the data. Finally, we measured both total cholesterol (TC) and high-density lipoprotein cholesterol (HDL-C) to ascertain if a specific cholesterol fraction (pro-atherogenic or anti-atherogenic) was associated with impulsivity. Our hypothesis was that lower cholesterol levels were associated with greater impulsivity. The strong evidence linking impulsivity (Neufeld and O'Rourke, 2009) and cholesterol levels (Lester, 2002) to suicide risk attests to the clinical relevance of studying the relationship between cholesterol levels and impulsivity.

2. Method

2.1. Participants

Participants were 301 (204 women and 97 men) consecutive patients referred to the day hospital of the psychiatric clinic of the University of Rome Tor Vergata between January 2006 and December 2008. The diagnostic composition of the sample included 180 patients with mood disorders (159 with unipolar depression and 21 with bipolar depression), 98 with anxiety disorders, and 23 with cluster B personality disorders. Diagnostic assessment was made by experienced clinical psychiatrists who administered to each participant the Structured Clinical Interview for DSM-IV Axis I Disorders (SCID-CV) (First et al., 1997) and the Schedule for Interviewing DSM-IV Personality Disorders-IV (SIDP-IV) (Pfohl et al., 1997).

Participants were excluded if they (1) had a DSM-IV principal or comorbid diagnosis of psychotic disorders, mental retardation, and eating disorders; (2) were following a cholesterol-lowering diet and/or were using lipid-lowering medications. Participants with psychotic symptoms or mental retardation were excluded because their mental state might interfere with self-assessment of impulsivity. Participants with eating disorders were excluded because their altered eating habits might impact on cholesterol levels. The University Intramural Ethical Committee approved all procedures and protocols, and written informed consent was obtained after the procedures had been fully explained and before clinical assessment.

2.2. Measures

Weight and height were measured using a standard scale to calculate the body mass index (BMI). Blood samples (5 ml) were drawn by a trained physician on weekdays between 07:30 and 08:30 am after the participants had fasted for at least 12 h. Samples were immediately delivered to the University Hospital laboratory and analyzed for TC and HDL-C. On the same day that the fasting plasma sample was collected, each participant completed a battery of psychometric scales including the Barratt Impulsiveness Scale-Version 11 (BIS-11) (Patton et al., 1995; Fossati et al., 2001) and the Profile of Mood States (POMS) (McNair et al., 1992).

The BIS-11 is a 30-item self-report questionnaire 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). Therefore, the possible scores range from 30 to 120; nonpsychiatric controls generally score in the range of 50–70. The BIS-11 identifies three components of impulsivity. Attentional/cognitive impulsivity is a lack of cognitive persistence with inability to tolerate cognitive complexity; motor impulsivity is a tendency to act on the spur of the moment; and nonplanning impulsivity refers to a lack of sense of the future. To control for the confounding effect of current mood on the assessment of impulsivity, participants were asked to complete the POMS. They were asked to carefully read each of 65 items, then respond to a 5-point Likert scale ranging from 1 (not at all) to 5 (extremely) based on how they were feeling the day they completed the inventory. The total mood disturbance score (POMS-TMD) was calculated by summation of the five negative affect scales (fatigue, depression, tension, anger, confusion) and subtraction of the vigor scale. A higher POMS-TMD corresponds to higher levels of mood disturbance.

2.3. Statistical analysis

The Kolmogorov–Smirnov test was used to test the normality of the distribution of TC levels and BIS scores. Analysis of variance (ANOVA) and analysis of covariance (ANCOVA) were used to compare groups on continuous dependent variables. Homogeneity of variance was tested by the Levene's test. In order to minimize the likelihood of a type-I error, an overall multivariate analysis of covariance (MANCOVA) using all the BIS-11 subscales and total score as dependent variables was performed to compare participants with lower and higher cholesterol levels. The overall significance of MANCOVA was assessed by means of the *F*-test in association with Wilks's lambda. Significant MANCOVA was followed up by separate ANCOVAs on each of the dependent variables. Partial $\hat{\eta}^2$ was used as a measure of effect size. Multivariate regression analysis was used to assess the relationship between TC levels and BIS scores while controlling for the possible confounding effects of age, gender, diagnosis, and current mood symptoms. Collinearity diagnostics based on eigenvalues of the scaled and uncentered cross-products matrix, variation inflation factors (VIF) and tolerances for individual variables was used to exclude multicollinearity among the independent variables. Analysis was performed on a personal computer using SPSS for Windows, version 17.0 (SPSS, Inc., Chicago, Ill.).

Table 1
Descriptive data for the entire sample ($N = 301$).

	Mean	SD	Minimum	Maximum
Age (years)	38.89	12.63	17	68
Body mass index	24.35	4.50	17.39	36.52
POMS-TMD	75.35	48.09	-27	196
BIS total score	68.22	11.05	43	101
Attentional impulsivity	18.68	4.37	9	30
Motor impulsivity	20.97	5.32	10	43
Nonplanning impulsivity	28.55	4.77	16	41
TC (mg/dL)	194.20	38.20	110	295
HDL-C (mg/dL)	53.53	15.85	19	108

Legend: POMS-TMD, POMS total mood disturbance score; TC, total cholesterol; HDL-C, high-density lipoprotein cholesterol.

3. Results

Table 1 reports descriptive data for the entire sample. Both TC levels and BIS total scores were normally distributed (TC: $D(301) = 0.04$, $p = 0.20$; BIS: $D(301) = 0.05$, $p = 0.20$). Based on the Adult Treatment Panel III (ATP III) of the National Cholesterol Education Program (2002), 60% of the participants had "desirable" TC levels (<200 mg/dL), 27% had "borderline high" levels (200–239 mg/dL), and 13% had high levels (≥240 mg/dL). Based on the BIS-11 categorical scores (Stanford et al., 2009), 38% of the participants were classified as highly impulsive (BIS total score >71). Preliminary analyses aimed at ascertaining if gender and psychiatric diagnosis were associated with significant differences in either cholesterol levels or impulsivity scores. Two-ways ANOVAs with gender and diagnosis as between-group factors did not show any significant main or interaction effects on TC levels and BIS scores with the exception of higher HDL-C levels in women (Table 2). BMI was not correlated with any of the BIS scores (r ranging from −0.06 to 0.08).

Table 3 reports second-order partial correlations between cholesterol levels and impulsivity scores while controlling for the effects of age and mood state. There was a negative and significant correlation between TC levels and the BIS attentional impulsivity subscale, but the strength of the correlation was weak ($r = -0.16$). HDL-C levels were correlated with none of the impulsivity measures. To control for the confounding effects of gender and diagnosis, the relationship between TC levels and attentional impulsivity was re-assessed by conducting multivariate regression analysis. Age and POMS-TD score were included among predictors. Multivariate regression analysis confirmed the negative and significant correlation between TC levels and attentional impulsivity (Table 4).

The findings of correlation analysis were confirmed and strengthened by categorical comparisons between participants with lower and higher cholesterol levels. Participants with the lowest quartiles of the TC and HDL-C distributions were compared with the rest of the sample on the BIS subscales and total score by conducting MANCOVAs with age and POMS-TMD as covariates. Participants with lower TC levels (<165 mg/dL, $N = 76$) scored higher than the rest of the sample ($N = 225$) on impulsivity scores (Wilks's lambda = 0.96, $F(4, 294) = 2.98$, $p = 0.02$). Follow-up ANCOVAs showed a marginal significant difference for the BIS total score ($F(1, 297) = 4.05$, $p < 0.05$) and a highly significant difference for the attentional impulsivity subscale ($F(1, 297) = 11.68$, $p < 0.001$, partial $\hat{\eta}^2 = 0.04$). Lower and higher TC groups did not differ in terms of gender composition (chi-square = 0.02, df = 1, $p = 0.89$) and psychiatric diagnosis (chi-square = 0.36, df = 2, $p = 0.83$). There were