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ORIGINAL PAPER

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Serum lipid levels in seasonal affective disorder

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Abstract Previous research has assessed the relationship between blood lipid levels and depression with contradictory results. Several studies have linked low cholesterol levels with impulsive, aggressive and suicidal behaviours. The aim of this pilot study was to examine serum lipids in a sample of patients suffering from seasonal affective disorder (SAD). We conducted a retrospective analysis of data on total serum cholesterol and serum triglycerides in 39 SAD patients and 40 non-seasonally depressed or schizophrenic control subjects. Study subjects had to be free of psychotropic drugs for at least 2 weeks. Analysis of covariance (ANCOVA) was performed to assess group differences. After adjustment for significant covariates SAD patients had significantly lower total cholesterol levels (5.21 ± 1.14 mmol/l) than control subjects (5.94 ± 1.11 mmol/l; $p = 0.013$). Moreover, hypercholesterolemia (total cholesterol > 5.20 mmol/l) was significantly less frequent in the SAD group (46.2%) than in the control group (75.0%; $p = 0.012$). Total serum triglycerides did not differ significantly between SAD patients (1.54 ± 1.07 mmol/l) and controls (1.56 ± 0.96 mmol/l; $p = 0.126$). The results of this study support the idea that low cholesterol levels may be of pathogenetic importance in SAD. Further study in larger clinical samples is warranted to clarify our findings.

Key words serum lipids · cholesterol · triglycerides · seasonal affective disorder

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Introduction

Over the past two decades, scientists have discussed the relationship between serum lipids and psychiatric morbidity. Early correlational studies in humans have shown a negative association between aggression and serum cholesterol levels [52, 53]. Experimental studies in non-human primates have suggested a causal relationship between a diet lower in fat and increased agonistic behaviour [11, 18]. Low serum cholesterol has been found in many, but not all, studies among suicide attempters [14]. One study has been able to show lowered cholesterol in patients with violent but not with non-violent suicide attempts [1]. Clinical trials of cholesterol-lowering interventions [31] and observational cohort studies [25, 30, 46] have found a link between low cholesterol and depressive symptoms, but there are also reports, which have demonstrated a positive relationship between cholesterol and depression [33, 34], and studies, which have failed to find a like association [5, 27]. Some authors have proposed that depressive patients have higher serum triglyceride levels [13], but others have not been able to replicate these results [12, 37].

Seasonal affective disorder, winter type (SAD) is a subtype of mood disorder characterised by recurrent major depressive episodes with onset in fall or winter (fall–winter depression), followed by full remission or hypomanic (more seldom manic) episodes during the successive spring and summer period. SAD represents

an important chronobiological research paradigm, but is also clinically significant since epidemiological studies have estimated that the seasonal subtype of depression represents about 10% of all subjects with major depression [24]. The present study was aimed to examine blood lipid levels in a sample of SAD patients and to compare them with a clinical sample of patients with other psychiatric diagnoses.

Method

This investigation included data on serum lipids from the screening visits of different psychopharmacological clinical trials, which had been carried out at the Department of General Psychiatry (Medical University of Vienna, Austria). Blood samples were collected from all subjects by peripheral venipuncture. The Ethics Committee of the Medical University of Vienna gave approval to the single protocols, and all patients provided written informed consent prior to study participation. A total of 39 SAD patients (30 females, 9 males) and 40 acutely ill control subjects (26 females, 14 males) suffering from either non-seasonal major depressive disorder (n = 23) or psychosis (schizophrenia or schizoaffective disorder; n = 17) were included in this evaluation.

Seasonal affective disorder patients had to fulfil the Rosenthal [40] and DSM-IV-TR criteria [2] for SAD. A Global Seasonality Score (GSS) of 11 or higher on the German version of the Seasonal Pattern Assessment Questionnaire [20] and a total score of 22 or higher as measured by the Structured Interview Guide for the Hamilton Depression Rating Scale, SAD version [56] was required; patients with subsyndromal SAD [21] or with axis-I comorbidity were excluded from this analysis. SAD patients and controls were at least 18 years of age and had to be in good overall health; subjects with severe somatic illnesses were not included.

All study subjects had to be free of psychotropic drugs at the time of the blood tests for at least 2 weeks (4 weeks for fluoxetine, 3 months for depot neuroleptics). Three data sets of potential control patients, who had been prescribed cholesterol-lowering drug treatment, were not selected for this evaluation. A total of 32 control patients (80%) had received psychotropic medication in the time-frame of 3 months before inclusion: 18 controls (45%) had been treated with neuroleptics, 13 (32.5%) of those with atypical antipsychotics. A total of 21 (50%) control subjects had been treated with antidepressants, 11 had received mirtazapine (tricyclic antidepressants had not been prescribed in this sample). In total, 8 SAD patients (20.5%) had received psychopharmacologic medication in the last 3 months before the study: all these patients had been treated with antidepressants (one with mirtazapine). No SAD patient had previously been on antipsychotics. Hyperlipidemia was here defined according to the National Cholesterol Education Program, Adult Treatment Panel III (NCEP ATP-III) [10]: total serum cholesterol above 5.2 mmol/l, total serum triglycerides above 2.3 mmol/l.

Variables used in the analysis (group, sex, age, body mass index (BMI), cholesterol, triglycerides, fasting state) were tested for outliers, departures from normality and linearity, multicollinearity, heteroscedasticity, heterogeneity of regression and equality of slopes (i.e. a significant group-by-covariate interaction). Analysis showed moderate positive skewness and kurtosis and a significant Kolmogorov–Smirnov test for triglycerides and BMI. The natural logarithmic transformation (ln) was therefore applied to these two variables for the following statistical procedure. Analysis of covariance (ANCOVA) was calculated with SPSS 12.0 [45] using a general linear model with either cholesterol or triglycerides as the dependent variable, group (SAD or controls) as independent variable and sex, age, BMI and fasting state as covariates. Covariates were evaluated by prior multiple regression with stepwise backward elimination. Non-significant covariates in the model were deleted. Further analysis included Student's t-test, Fisher's exact test and Pearson's χ^2. The $p \leq 0.05$ level of significance was adopted. All statistical comparisons were two-tailed.

Results

Mean age in the SAD group was trendwise lower (39.3 ± 13.3 years) than in the control group (44.5 ± 14.7 years; $t = -1.642$, $df = 77$, $p = 0.105$). Mean GSS for SAD patients was 15.4 ± 3.1. Similar to other published SAD material from Middle Europe [59] a relatively high percentage (43.6%) of SAD patients was diagnosed with the atypical features specifier and only 17.9% obtained the melancholic features specifier according to DSM-IV-TR.

Analysis by ANCOVA, adjusting for age and BMI, demonstrated significantly lower total serum cholesterol levels (5.21 ± 1.14 mmol/l) in the SAD group than in controls (5.94 ± 1.11 mmol/l; $F = 6.466$, $df = 1$, $p = 0.013$). Furthermore, hypercholesterolemia was significantly less frequent in SAD patients (46.2%) than in the control group (75.0%; exact probability: $p = 0.012$). There was no statistically significant difference in total serum triglycerides between SAD patients (1.54 ± 1.07 mmol/l) and controls (1.56 ± 0.96 mmol/l; $F = 2.395$, $df = 1$, $p = 0.126$). Covariates for this analysis were sex, BMI and fasting state. The rate of patients with hypertriglyceridemia showed no significant difference between SAD (15.4%) and control patients (14.3%; exact probability: $p = 1.000$) Fig. 1.

Homogeneity of the control group was tested by analysing differences between patients with non-seasonal major depression and those with psychosis: However, there was neither a significant difference between these two subgroups in regard to total serum cholesterol (non-seasonal depression: 6.08 ± 1.19 mmol/l, psychosis: 5.74 ± 0.99 mmol/l; $t = 0.975$, $df = 38$, $p = 0.336$) nor total serum triglycerides (non-seasonal depression: 1.35 ± 0.71 mmol/l, psychosis: 1.78 ± 1.16 mmol/l; $t = -1.312$, $df = 26.230$, $p = 0.201$).

Weight gain and metabolic disorders are frequently associated with antipsychotic treatment [22, 29]. To rule out any potential long-term effects of previous treatment we compared differences between control subjects with and without prior neuroleptic treatment: There was no statistically significant difference in regard to total serum cholesterol (neuroleptics: 5.68 ± 1.06 mmol/l, no neuroleptics: 6.14 ± 1.13 mmol/l; $t = 1.315$, $df = 38$, $p = 0.196$) or total serum triglycerides (neuroleptics: 1.75 ± 1.13 mmol/l, no neuroleptics: 1.35 ± 0.72; $t = -0.253$, $df = 33$, $p = 0.219$) between these two groups. Regarding the prior use of atypical antipsychotics there was also no significant difference on cholesterol levels (atypical antipsychotics: 5.92 ± 1.15 mmol/l, no atypical antipsychotics:

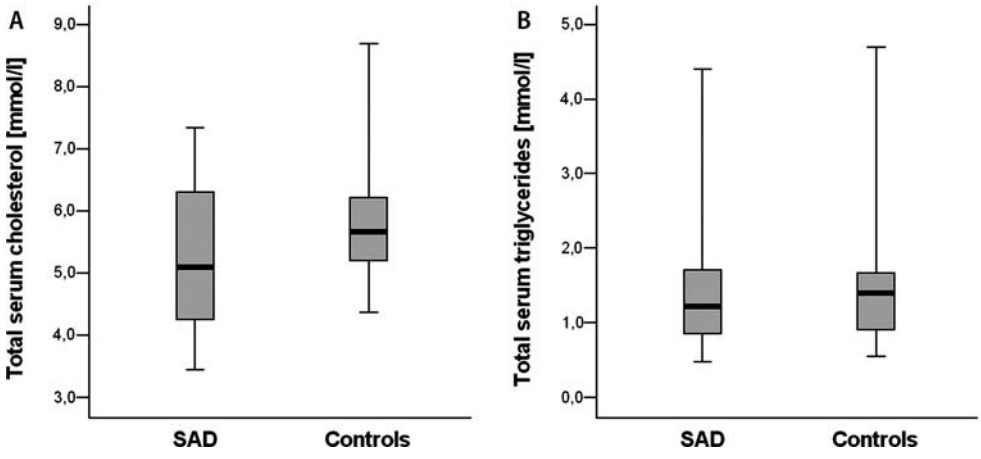

Fig. 1 (**A**) Total serum cholesterol levels (mmol/l) in 39 SAD patients and 40 control patients ($p = 0.021$). **(B)** Total serum triglyceride levels (mmol/l) in 39 SAD patients and 35 controls ($p = 0.546$). The upper edge of the box indicates the 75th percentile of the data, the lower hinge the 25th percentile. The line in the box indicates the median value. The ends of the whiskers represent the minimum and maximum data values. SAD, seasonal affective disorder

5.94 ± 1.11 mmol/l; $t = 0.074$, $df = 38$, $p = 0.941$) or triglyceride levels (atypical antipsychotics: 1.64 ± 0.94 mmol/l, no atypical antipsychotics: 1.51 ± 1.00 mmol/l; $t = -0.396$, $df = 33$, $p = 0.695$). Certain antidepressants (e.g. mirtazapine and tricyclic antidepressants) can promote weight gain and may have unfavourable effects on lipid parameters [28]: However, there was no statistically significant difference in regard to cholesterol (mirtazapine: 6.02 ± 0.97 mmol/l, no mirtazapine: 5.90 ± 1.17 mmol/l; $t = -0.296$, $df = 38$, $p = 0.769$) or triglyceride levels (mirtazapine: 1.32 ± 0.80 mmol/l, no mirtazapine: 1.67 ± 1.02 mmol/l; $t = 0.994$, $df = 33$, $p = 0.328$) between control subjects with or without this medication.

Seasonal affective disorder patients and controls were also separately compared with published data on hyperlipidemia of 115,837 persons from the Viennese general population, who underwent voluntary health screening tests in Vienna in 2001 [26]: We observed a lower rate of hypercholesterolemia in the SAD group than expected (observed vs. expected rate: 46.2% vs. 65.9%; $\chi^2 = 6.767$, $df = 1$, $p = 0.009$), but no significant difference in the rate of hypertriglyceridemia (15.4% vs. 23.3%; $\chi^2 = 1.367$, $df = 1$, $p = 0.242$). As for the control group there were no significant differences in regard to the rates of hypercholesterolemia (75.0% vs. 65.9%; $\chi^2 = 1.474$, $df = 1$, $p = 0.225$) and hypertriglyceridemia (14.3% vs. 23.3%; $\chi^2 = 1.591$, $df = 1$, $p = 0.207$).

Discussion

To our best knowledge, this is the first study investigating serum lipids in patients with SAD. Our main finding is that mean serum cholesterol in SAD patients is significantly lower than in non-SAD psychiatric patients. Serum triglycerides were not found to be different between SAD patients and controls. The observation that lipid levels appeared to be quite similar between the two subgroups of the control patients, and the fact that only the rate of hypercholesterolemia in the SAD group differed from the general population, substantiate that the findings of this study are not due to a bias of the control group.

Different plausible hypotheses can be put forward to explain the results of our study: One of the first theories concerning the pathogenesis of SAD suggested an involvement of the pineal hormone melatonin. Besides a delay of dim light melatonin onset [8, 41] and a supersensitive melatonin suppression to light [35], SAD patients display increased serum concentrations [19] and elevated daytime levels of melatonin [9, 23]. Interestingly, melatonin is also thought to lower serum cholesterol as demonstrated in vitro [32], in animal models [16, 44] and in clinical studies in humans [42, 50]. A possible mechanism for melatonin's cholesterol-lowering properties is its reduction of lipoprotein lipase [4, 55]. In addition, melatonin directly inhibits cholesterol synthesis and blocks low-density lipoprotein receptor activity [32], enhances catabolism of cholesterol to bile acids [6] and might also influence serum lipid content by inhibition of oxidative modification of lipoproteins [54].

Reduced cholesterol and SAD are both pathogenetically connected with serotonergic neurotransmission: A serotonergic dysfunction in SAD patients has been determined by the paradigm of tryptophan depletion as well as by neurochemical, genetic and neuroimaging studies [58]. Interestingly, newer research demonstrates that low cholesterol levels are associated with a reduction of central serotonergic activity [47, 48] and with changes in the function of key elements of the serotonergic system such as the serotonin transporter molecule [43] or specific serotonin receptors [38]. Moreover, cholesterol-lowering treatment can provoke a temporary serotonergic dysfunction [51].

As described above, reduced serum cholesterol, aggression, impulsivity, depression and suicidality all seem to be interlinked [3, 49]: The development of psychopathological symptoms is most probably mediated by impairment of the serotonergic system. Con-

sistent with these findings and the results of the present study we have recently published a report on anger attacks (sudden spells of inappropriate anger accompanied by vegetative and behavioural features) in SAD [57]: SAD patients experience anger attacks significantly more often and with higher intensity than patients suffering from non-seasonal depression. This study adds to a growing body of evidence that links cholesterol levels with pathologic mood states and aggression. In the case of SAD, such a connection may be unified by the common pathway of melatonin dysregulation.

This pilot study is limited by the retrospective approach and the relatively small sample size in the SAD and control group. The comparisons with the general population have to be interpreted with caution because it was not possible to correct them for important confounding factors like sex and age. A sample bias cannot be completely ruled out because patients included in this evaluation were selected study patients eligible for clinical trials at a university hospital. Furthermore, we were unable to match SAD patients and control subjects for possible differences in regard to physical activity and lifestyle. Despite the discontinuation period of at least 2 weeks for any psychotropic medication in our study a possible influence of prior drug treatment on lipid measurements has to be discussed: However, our analyses of lipid levels regarding prior treatment with psychotropic drugs provide no statistically significant or even numerically relevant difference between controls with or without prior (atypical) antipsychotics or weight gain promoting antidepressants that could explain our main finding of lower cholesterol in SAD patients. Moreover, control patients with non-seasonal depression and those with psychosis did not show significant differences in regard to serum lipids, which could be expected, if there was a differential effect of treatment.

It is rather unlikely that the phenomenon of lowered cholesterol levels in our cohort of SAD patients was merely due to psychopathological changes during depression, given the fact that a larger percentage of SAD patients suffered from atypical depression (with increased appetite and weight) than from melancholic depression. Decreased appetite as a consequence of depression would probably lead to a reduction of both cholesterol and triglycerides.

Unlike the blood tests of our SAD group, which were carried out exclusively during fall and winter, the measurements of our controls were stratified throughout the year. Therefore it would not be entirely improbable that our results have been influenced by physiological seasonal fluctuations. However, numerous studies have demonstrated total cholesterol to be higher in the winter than in the summer in healthy humans [15, 36, 39], which is not reflected by our results. Thus, seasonal fluctuations would suggest that our results might underestimate the actual magnitude of difference between patients with SAD compared to controls.

Further research should be aimed to replicate our results in a larger sample of SAD patients in contrast with a matched normal population. Moreover, it is yet unknown, whether lowered cholesterol represents a state or trait marker of SAD patients. As previous studies have tried to find a specific pattern of altered lipid composition in depressive disorder (e.g. lower high-density lipoproteins, higher or lower ratio of total cholesterol to high density lipoproteins, decrease of polyunsaturated omega 3 fatty acids and an increase of the omega 6/omega 3 ratio) [7, 17, 60], it would be worthwile to perform additional analyses of lipoprotein fractions with comparisons between summer and winter in SAD, which could yield important insights into the pathogenetic relationship between blood lipids and seasonal depression.

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