Središnja medicinska knjižnica

Marčinko, D., Marčinko, V., Karlović, D., Marčinko, A., Martinac, M., Begić, D., Jakovljević, M. (2007) *Serum lipid levels and suicidality among male patients with schizoaffective disorder.* Progress in Neuro-Psychopharmacology and Biological Psychiatry, [Epub ahead of print, Corrected Proof].

Serum lipid levels and suicidality among male patients with schizoaffective disorder

Darko Marčinko*, Vesna Marčinko, Dalibor Karlović, Anita Marčinko, Marko Martinac, Dražen Begić, Miro Jakovljević

Department of Psychiatry, University Hospital Zagreb, Kišpatićeva 12, Zagreb, Croatia

Abbreviations:
- BMI, Body mass index;
- HDL-C, High density lipoprotein cholesterol;
- HDRS-17, Hamilton Depression Rating Scale;
- LDL-C, Low density lipoprotein cholesterol;
- PANSS, Positive and Negative Syndrome Scale
- SSI – Scale for Suicide Ideation.

*Corresponding author: Darko Marčinko, MD, PhD, psychiatrist-psychotherapist
Department of Psychiatry, University Hospital Zagreb, Kišpatićeva 12, 10000 Zagreb
Tel. +385 1 2421 603   Fax. + 385 1 2388 329
E-mail : darko.marcinko@zg.t-com.hr

Abstract
Suicidal behavior in schizoaffective disorder is a serious problem and suicide risk during lifetime ranges between 5%-10%. Neurobiology of suicidal behavior has not been studied sufficiently, and a high number of studies are oriented toward lipid investigation. The aim of our study was to investigate whether there were differences in the level of lipids (cholesterol, HDL-cholesterol, LDL-cholesterol, triglycerides) in hospitalized suicidal (n=20) and non-suicidal (n=20) patients with schizoaffective disorder. The study also included male healthy control subjects (n=20). Hamilton Depression Rating Scale (HDRS-17), and Positive and Negative Syndrome Scale (PANSS) were used to confirm the level of psychopathology in patients with schizoaffective disorder. Severity of suicidality was measured by Scale for Suicide Ideation (SSI) (Beck et al., 1979) at time of admission. Results of the study indicated significantly lower concentrations of cholesterol (p<0.001), LDL-cholesterol (p<0.01) and HDL-cholesterol (p<0.01). There were no differences in the number of previous hospitalisation and previous suicide attempts between suicidal and non-suicidal patients (p>0.05). Duration of the illness was significantly (p<0.05) shorter in suicidal patients. Suicidal patients also had a significantly higher score on HDRS-17 (p<0.001) and PANSS (p<0.01) compared to non-suicidal patients.

Key words: suicidality, lipids, cholesterol, LDL-cholesterol, men, schizoaffective disorder

1. Introduction

Changes in serum concentration of lipids, particularly of cholesterol, are among the most studied biological factors in the field of suicidality. In the early 1990s, analyses of mortality rates in prevention-related clinical trials showed a correlation between low cholesterol and non-illness-related mortality (Muldoon et al., 1990; Lindberg et al., 1992; Neaton et al., 1992). Further analyses in extensive studies demonstrated the occurrence of suicide as a secondary complication, and investigations showed association between low cholesterol and recurrent suicide attempts (Zureik et al., 1996; Partonen et al., 1999). Case-control studies indicated lower cholesterol levels in patients admitted after suicide attempt as compared to admitted non-suicidal patients (Garland et al., 2000; Kim et al., 2002; Diaz-Sastre et al., 2007). Correlation of low cholesterol level with suicidality has also been confirmed in other psychiatric disorders, such as anorexia nervosa (Favaro et al., 2004) and panic disorder (Ozer et al., 2004). Our previous studies confirmed the role of cholesterol in suicidal behavior of patients diagnosed with different form of psychotic disorders (Marčinko et al., 2004, 2005, 2007).

Some studies demonstrated that association of low cholesterol with suicide attempts was more pronounced among violent suicide attempters or those with a history of such attempts (Alvarez et al., 2000; Vevera et al., 2003; Kim and Myint, 2004; Marčinko et al., 2005). One study corroborated causative correlation between low cholesterol and violence in general (Golomb, 1998). There have, however, been some case control studies that failed to show an association between cholesterol level and suicide attempts (Almeida-Montes et al., 2000; Deisenhammer et al., 2004). Also, some previous epidemiological and clinical studies have presented conflicting results on possible associations between low cholesterol levels and heightened rates of death from suicide (Tanskanen et al., 2000; Muldoon et al., 2001).

Genetic factors have also been investigated as part of the etiology of suicidal behavior (Turecki, 2001). Regarding neurobiological research of suicidal behavior in psychotic disorders, most studies deal with schizophrenia which actually motivated us to conduct this investigation with schizoaffective disorder. The aim of this study was to investigate if there were differences in lipid concentrations (cholesterol, HDL cholesterol, LDL-cholesterol, triglycerides) between suicidal and non-suicidal patients with schizoaffective disorder on hospital treatment, and a healthy, control group.

2. Methods

2.1. Sample

Subjects were male patients (N=40) treated at the Department of Psychiatry, University Hospital Zagreb, during the period of 18 months. Within patients, 20 patients were consecutively admitted suicidal men with schizoaffective disorder, and 20 patients were consecutively admitted men with schizoaffective disorder, without suicidal behavior. The diagnosis of schizoaffective disorder was made according to diagnostic criteria of the International Statistical Classification of Diseases and Related Health Problems, 10th Revision (ICD-10) after performing structured diagnostic psychiatric interview (WHO, 1996). All of the patients have depressed type of schizoaffective disorder. Hamilton Depression Rating Scale, HDRS-17 (Hamilton, 1960) was applied to assess depressive symptoms. Positive and negative syndrome scale, PANSS (Kay et al., 1987) was used to estimate psychotic symptoms. The trained psychiatrists performed clinical evaluation. Patients were classified as suicidal at the hospital admission if a suicidal ideation, or a suicide attempt, or both, was present. Suicidality was assessed positive if item 3 of the HDRS-17 scale was

scored positively. Severity of suicidality was measured by Scale for Suicide Ideation (SSI) (Beck et al., 1979) at the time of admission for all of the participants.

All participants were free of all medications in the previous 3 months. Healthy male subjects (N=20) with no history of psychiatric illness and somatic disorders or diseases were randomly selected as a control group. They were recruited from the general population and were closely matched for age. All subjects gave written informed consent to participate in the study. This study was approved by the Clinical Hospital Center Medical Ethics Committee.

Only patients whose biochemical analyses from the time of admission were available were included in the study. Venous blood samples were collected within 24 hours of admission. None of the patients or control subjects included in the study had used any cholesterol-lowering drugs before the sampling. The exclusion criteria were: hypertension, hypothyroidism, diabetes mellitus, disorders of the lipoprotein metabolism, diagnosis of substance abuse, including alcoholism, eating disorders and organic brain syndrome.

2.2. Assessment

Venipuncture was performed for all subjects between 8 and 9 a.m. after 12 h overnight fast. Immediately after collecting blood samples, serum concentrations of cholesterol, HDL-cholesterol and triglycerides were determined using enzyme method and commercial kits (Olympus Diagnostic, GmbH, Hamburg, Germany) on Olympus AU 600 automated analyzer. Inter-assay laboratory coefficients of variation were 3.2% for cholesterol, 2.5% for triglycerides, and 3.0% for HDL-cholesterol. Reference intervals for the measured parameters were as follows: cholesterol < 5.0 mmol/L, LDL < 3.0 mmol/L, HDL > 1.0 mmol/L, and triglycerides < 1.7 mmol/L. Height and weight of each patient were recorded while they were standing barefoot in light clothes on the medical scale that measures height and weight. Body mass index (BMI) was calculated in the way that body weight in kilograms was divided with squared height value in meters.

2.3. Data analysis

The results were expressed as mean values and standard deviations. Kruskal Wallis one way analysis of variance was applied for statistical processing of the obtained data during comparison of continuous variables across the three subject groups (suicidal patients, non-suicidal patients and healthy controls). Student t-test was used to compare two groups of patients after normal data distribution in some variables had been demonstrated by Kolmogorov-Smirnov test. Nonparametric Spearman correlation coefficient test was applied in searching relations between variables. In all tests, the criterion of significance was $p<0.05$. Statistical processing of results was done by using commercial statistical package SPSS 11 (SPSS for Windows 11.0, SPSS, Chicago, IL, USA).

3. Results

Results of the study are presented in table 1. There were no statistically significant differences for BMI and age values between subject groups ($p>0.05$). Analysis showed that total cholesterol values in suicidal patients were statistically significantly lower than in non-suicidal patients and the control group ($p=0.000$). Triglyceride levels in suicidal patients were not statistically significantly different compared to non-suicidal patients and the control group ($p=0.255$). HDL-cholesterol concentrations in suicidal patients were statistically significantly lower than in non-suicidal patients and the control group ($p=0.007$), also the values of LDL-cholesterol ($p=0.001$). In suicidal patients, PANSS values were statistically significantly higher than in non-suicidal patients ($p=0.004$), and the HDRS-17 score was also statistically

significantly higher in suicidal patients than in non-suicidal ones (p=0.000). We have no found correlation between suicidality (measured by SSI) and symptom severity (measured by PANSS, p=0.127 and HDRS, p=0.992). We searched further for a possible correlation between biological variables and the score in SSI and did not find any significant correlation except for cholesterol. Serum cholesterol and SSI score gave a significant negative correlation (Spearman R=-0.867, p=0.005). Also, we have no found correlation between HDRS score and lipid fractions (p>0.05). We have noted in the table, the number /the frequency/ of previous suicide attempt and done correlations between the frequencies of suicide and lipid profiles. There were no significant correlations for any lipid marker (p>0.05). There were no differences in the number of previous hospitalization and previous suicide attempts between suicidal and non-suicidal patients (p>0.05). Duration of the illness was significantly (p=0.027) shorter in suicidal patients.

4. Discussion
4.1. Principal findings
Results of the study showed differences between suicidal and non-suicidal patients with schizoaffective disorder both on biological and clinical levels. Suicidal patients had statistically significantly lower levels of cholesterol and LDL, while triglyceride and HDL values were lower but without a statistically significant difference in relation to non-suicidal patients with schizoaffective disorder. Also, suicidality negatively correlated to the level of cholesterol which emphasize the possible role of this biological marker in the complex process of suicidality. Decreased cholesterol concentrations in suicidal patients were consistent with previous study results (Kim et al., 2002; Kunugi et al, 1997; Marčinko et al., 2004, 2005, 2007; Modai et al, 1994). Provided that these results are confirmed on a larger number of samples, they could be of assistance in recognizing suicidal behavior in routine clinical practice. Several different mechanisms have been stated in the literature to account for the correlation between low cholesterol level and suicidality. Although biological mechanisms of association between low cholesterol and suicidality have not been completely elucidated, reduced serum cholesterol level may be accompanied by changes in viscosity and function of serotonin receptors and transporters, as well as by decreased serotonin precursors (Engelberg, 1992). According to a frequently cited study by Engelberg (1992), low cholesterol level may be related to decreased lipid microviscosity in neural membranes and may reduce serotonin receptor exposure on the membrane surface, which leads to reduced function of serotonin receptors. The consequence of inhibited serotonin neurotransmission is lower inhibition of impulsive and aggressive behavior, which may trigger suicidal behavior. In line with two earlier investigations of depression symptoms and suicidality in psychotic patients (Walsh et al., 2001; Aguilar et al., 2003), our study also confirmed that suicidal patients had more pronounced depressive symptoms compared to non-suicidal patients, which was evident in higher HDRS-17 score. Suicidal patients may have less appetite, which in turn results in lower intakes of certain nutrients such as lipids and, hence, further intensifies vulnerability to depressive and suicidal patterns of behavior but we were not found correlation between lipid profiles and depressive symptoms and could not confirmed the hypothesis. The lack of correlation between HDRS score and cholesterol could be explained by many confounders (e.g., poor physical health, dietary habits, social and economical conditions) important in the context of suicidality.
Suicidal patients also had a significantly higher score regarding the scale of psychotic symptoms (PANSS), which reflect enhanced severity of schizoaffective disorder. Also, we

have no found correlation between suicidality and symptom severity, measured by PANSS and HDRS which could be explained by the fact that underlying vulnerability to suicidal behavior may consist of interrelated different psychological and biological characteristics. One of important characteristic should be duration of the illness and we have found significantly shorter duration of the illness in suicidal patients. The risk of suicidal behavior in psychosis is stressed in the earlier course of the illness (Brown, 1997) what is important in the prevention activities.

As far as we know, our results are the first to show the relationship between reduced cholesterol and suicidality in schizoaffective disorder. Since a majority of individuals with schizoaffective disorder never attempt suicide, suicidal behavior is viewed as an outcome of the possible interaction between biological diathesis and transient mood and/or psychotic states or life event triggers. Such a model emphasizes the role of a biological predisposition (in the form of lower cholesterol functioning) to lack of behavioral control, that make patients more vulnerable to acting on suicidal ideation.

4.2. Unanswered questions and future research

Limitations of this study were a relatively small patient sample and the lack of information on patients' nutritive habits, which we plan to perform in one of our further investigations that will include a larger number of schizoaffective patients. In the present study there are no data available regarding several other factors that may contribute to the alterations in serum cholesterol in suicidal patients, such as genetic factors and cigarette smoking.

5. Conclusions

Our results show that lipids have an important role in distinguishing suicidal from non-suicidal patients which, if confirmed on a higher number of patients and in more studies, may be of considerable clinical significance. A better understanding of the neurobiology of suicide can facilitate the detection of the population of patients who have a high risk to attempt suicide, and to develop better treatment interventions for these patients.

References.
- Aguilar EJ, Leal C, Acosta FJ, Cejas MR, Fernández L, Gracia RA. Psychopathological study of a group of schizophrenic patients after attempting suicide. Are there two different clinical subtypes? Eur Psychiatry 2003;18:190–192
- Almeida-Montes LG, Valles-Sanchez V, Moreno-Aguilar J, Chavez-Balderas RA, Garcia-Marin JA, Cortes Sotres JF, Hheinze-Martin Heinze-Martin???? G. Relation of serum cholesterol, lipid, serotonin and tryptophan levels to severity of depression and to suicide attempts. J Psychiatry Neurosci 2000;25:371-377.
- Alvarez JC, Cremniter D, Gluck N, Quintin P, Leboyer M, Berlin I, Therond P, Spreux-Varoquaux O. Low serum cholesterol in violent but not in non-violent suicide attempters. Psychiatry Res 2000;95:103-108.
- Beck AT, Kovacs M, Weissman A. Assessment of suicidal intention: The scale of suicide ideation. J Consult Clin Psychology 1979;47:343-352.
- Brown S. Excess mortality of schizophrenia: a meta-analysis. Br J Psychiatry 1997;171:502-508.

- Deisenhammer EA, Kramer-Reinstadler K, Liensberger D, Kemmler G, Hinterhuber H, Fleischhacker WW. No evidence for an association between serum cholesterol and the course of depression and suicidality. Psychiatry Res 2004;121:253-261.
- Diaz-Sastre C, Baca-Garcia E, Perez-Rodriguez MM, Garcia-Resa E, Ceverino A, Saiz-Ruiz J et al. Low plasma cholesterol levels in suicidal males: A gender- and body mass index-matched case-control study of suicide attempters and nonattempters. Prog Neuropsychopharmacol Biol Psychiatry 2007, In Press.
- Engelberg H. Low serum cholesterol and suicide. Lancet 1992;339:727–9.
- Favaro A, Caregaro L, Di Pascoli L, Brambilla F, Santonastaso P. Total serum cholesterol and suicidality in anorexia nervosa. Psychosom Med 2004;66:548-552.
- Garland M, Hickey D, Corvin A, Golden J, Fitzpatrick P, Cunningham S, Walsh N. Total serum cholesterol in relation to psychological correlates in parasuicide. Br J Psychiatry 2000;177:77-83.
- Golomb BA. Cholesterol and violence: is there a connection? Ann Intern Med 1998;128:478-487.
- Hamilton MA. Rating scale for depression. J Neurology, Neurosurgery and Psychiatry 1960;23:56–62
- Kay SR, Fiszbein A, Opler LA. The positive and negative syndrome scale (PANSS) for schizophrenia. Schizophr Bull 1987;13:261.
- Kim YK, Lee HJ, Kim JY, Yoon DK, Choi SH, Lee MS. Low serum cholesterol is correlated to suicidality in a Korean sample. Acta Psychiatr Scand 2002;105:141-148.
- Kim YK, Myint AM. Clinical application of low serum cholesterol as an indicator for suicide risk in major depression. J Affect Disord 2004;81:161-166.
- Kunugi H, Takei N, Aoki H, Nanko S. Low serum cholesterol in suicide attempters. Biol Psychiatry 1997;41:196– 200.
- Lindberg G, Rastam L, Gullberg B, Eklund GA. Low serum cholesterol concentration and short term mortality from injuries in men and women. BMJ 1992;305:277-279.
- Marčinko D, Martinac M, Karlović D, Lončar Č. Cholesterol serum levels in violent and non-violent young male schizophrenic suicide attempters. Psych Danubina 2004;16:161-164.
- Marčinko D, Martinac M, Karlović D, Filipčić I, Lončar Č, Pivac N, Jakovljević M. Are there differences in serum cholesterol and cortisol concentrations between violent and non-violent schizophrenic male suicide attempters? Colleg Antropologicum 2005;29:153-157.
- Marčinko D, Pivac N, Martinac M, Jakovljević M, Mihaljević-Peleš A, Muck-Šeler D. Platelet serotonin and serum cholesterol concentrations in suicidal and non-suicidal male patients with first episode of psychosis. Psychiatry Res 2007;150:105–108.
- Modai I, Valevski A, Dror S, Weizman A. Serum cholesterol levels and suicidal tendencies in psychiatric inpatient. J Clin Psychiatry 1994;55:252–254.
- Muldoon MF, Manuck SB, Matthews KA. Lowering cholesterol concentrations and mortality: a quantitative review of primary prevention trials. BMJ 1990;301:309-314.
- Muldoon MF, Manuck SB, Mendelsohn AB, Kaplan JR, Belle SH. Cholesterol reduction and non-illness mortality: meta-analysis of randomized clinical trials. Br Med J 2001;322:11–5.
- Neaton JD, Blackburn H, Jacobs D, Kuller L, Lee DJ, Sherwin R, Shih J, Stamler J, Wentworth D. Serum cholesterol level and mortality findings for men screened in the Multiple Risk Factor Intervention Trial. Multiple Risk Factor Intervention Trial Research Group. Arch Intern Med 1992; 152:1490-1500.

- Ozer OA, Kutanis R, Agargun MY, Besiroglu L, Bal AC, Selvi Y, Kara H. Serum lipid levels, suicidality, and panic disorder. Compr Psychiatry 2004;45:95-98.
- Partonen T, Haukka J, Virtamo J, Taylor PR, Lonnqvist J. Association of low serum total cholesterol with major depression and suicide. Br J Psychiatry 1999;175:259-262.
- Tanskanen A, Vartiainen E, Tuomilehto J, Viinamaki H, Lehtonen J, Puska P. High serum cholesterol and risk of suicide. Am J Psychiatry 2000;157:648-650.
- Turecki G. Suicidal behavior: is there a genetic predisposition? Bipolar Disord 2001;3:335–349.
- Vevera J, Zukov I, Morcinek T, Papezova H. Cholesterol concentrations in violent and non-violent women suicide attempters. Eur Psychiatry 2003;18: 23-27.
- Walsh E, Harvey K, White I, Higgittt A, Fraser J, Murray R. Suicidal behaviour in psychosis: prevalence and predictors from a randomized controlled trial of case management. Br J Psychiatry 2001;178: 255–60.
- World Health Organization. International Statistical Classification of Diseases and Related Health Problems, Tenth Revision. Switzerland: Geneva; 1996.
- Zureik M, Courbon D, Ducimetiere P. Serum cholesterol concentration and death from suicide in men: Paris prospective study I. BMJ 1996;313:649-651.

Table 1. Differences in demographic, biological and clinical parameters between suicidal (N=20) and non-suicidal (N=20) patients with schizoaffective disorder and the control group (N=20) (mean ±SD).

	Suicidal (N=20)	Non-suicidal (N=20)	Controls (N=20)	Between-group comparisons, significance level (p)
BMI	25.12±2.06	26.07±1.91	25.61±1.98	0.721
Age	28.90±8.76	37.35±12.21	29.85±7.57	0.056
Cholesterol (mmol/L)	4.43±0.67	6.05±1.20	6.00±1.18	0.000
Triglycerides (mmol/L)	1.68±0.91	2.49±1.95	2.32±1.88	0.255
HDL-cholesterol (mmol/L)	1.04±0.30	1.29±0.29	1.37±0.49	0.007
LDL-cholesterol (mmol/L)	2.71±0.48	3.65±1.10	3.64±1.09	0.001
Previous suicide attempts				0.114
Positive	6	2		
Negative	14	18		
Duration of the illness (year)	6.60±7.04	12.65±9.43		0.027
Previous hospitalization (number)	2.20±1.85	2.25±2		0.935
PANSS (score)	90.75±15.19	80.75±14.56		0.004
HDRS-17 (score)	29.45±9.89	16.15±10.15		0.000