

Relation of serum cholesterol, lipid, serotonin and tryptophan levels to severity of depression and to suicide attempts

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Objective: To determine if there is a relation to low serum cholesterol, lipoprotein, serotonin or tryptophan levels in patients with depression who have recently attempted suicide. **Design:** Biochemical and behavioural study. **Setting:** Inpatient and outpatient treatment at the Instituto Mexicano de Psiquiatría. **Participants:** Thirty-three patients with a diagnosis of major depressive episode. Eighteen of these patients had attempted suicide in the month before the start of the study; 15 patients had never attempted suicide. **Outcome measures:** Serum levels of total cholesterol, high-density lipoprotein (HDL), low-density lipoprotein (LDL), triglycerides, serotonin (5-HT) and tryptophan. Scores on Hamilton Depression Rating Scale, Carroll Depression Rating Scale, Beck Hopelessness Scale and Beck Suicide Attempt Severity Scale. **Results:** There were no significant differences between patients who had attempted suicide and those who had not in terms of serum cholesterol, HDL, LDL and triglyceride levels. Serum levels of 5-HT and tryptophan were significantly lower in patients with depression who had a recent suicide attempt than in those patients who had never attempted suicide. A comparison of patients not taking antidepressant medication found serum 5-HT levels to be more than 3 times lower in those patients with a recent suicide attempt than in patients with no history of suicide attempt. **Conclusions:** The study found no difference in lipid profiles between patients who had attempted suicide and those who had not. Low serum levels of 5-HT may increase the risk of suicide attempt in patients who are depressed.

Objectifs : Déterminer s'il y a un lien entre les faibles taux sériques de cholestérol, de lipoprotéines, de sérotonine ou de tryptophane chez les patients dépressifs qui ont essayé récemment de se suicider. **Conception :** Étude biochimique et comportementale. **Contexte :** Traitement en service interne et externe à l'Instituto Mexicano de Psiquiatría. **Participants :** Trente-trois patients chez lesquels on a diagnostiqué un épisode dépressif majeur. Dix-huit avaient essayé de se suicider au cours du mois qui a précédé le début de l'étude et 15 autres n'avaient jamais fait de tentative de suicide. **Mesures de résultats :** Taux sériques de cholestérol total, de lipoprotéines de haute densité (HLD), de lipoprotéines de basse densité (LDL), de

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triglycérides, de sérotonine (5-HT) et de tryptophane. Résultats selon l'Échelle d'évaluation de la dépression de Hamilton, l'Échelle d'évaluation de la dépression de Carroll, l'Échelle de désespoir de Beck et l'Échelle de gravité de la tentative de suicide de Beck. **Résultats** : Il n'y avait pas de différences importantes entre les patients qui avaient essayé de se suicider et ceux qui n'avaient pas fait de tentative de suicide en ce qui concerne les taux sériques de cholestérol, de HDL, de LDL et de triglycérides. Les taux sériques de 5-HT et de tryptophane étaient beaucoup plus bas chez les patients atteints de dépression qui avaient essayé récemment de se suicider que chez ceux qui n'avaient jamais fait de tentative de suicide. Une comparaison entre les patients qui ne prenaient pas d'antidépresseur a révélé que les taux sériques de 5-HT étaient plus que trois fois plus faibles chez les patients qui avaient essayé récemment de se suicider que chez ceux qui n'avaient jamais fait de tentative de suicide. **Conclusions** : L'étude n'a révélé aucune différence entre les profils lipidiques de patients qui avaient essayé de se suicider et de ceux qui n'avaient pas fait de tentative. Les faibles taux sériques de 5-HT peuvent augmenter le risque de tentative de suicide chez les patients déprimés.

Introduction

Cholesterol is especially abundant in the nervous system and is important in many aspects of cellular structure and function. It affects the fluidity of cell membranes, membrane permeability and exchange processes.¹ In mouse brain membranes, the lipid fluidity markedly modulates the binding of serotonin (5-HT); therefore, with low cholesterol levels, the cellular membrane fluidity increases and 5-HT receptors are less exposed to 5-HT in the synaptic cleft.² Some authors have suggested that the overall result of cholesterol depletion in the central nervous system (CNS) includes a reduction in serotonergic neural activity due to the effects of cholesterol at both presynaptic sites (where it increases 5-HT reuptake) and postsynaptic sites (where it decreases 5-HT receptor number and function).³ Evidence for the reduction in serotonergic activity in the CNS comes from an *in vivo* primate study, which demonstrated that monkeys fed a low-fat/low-cholesterol diet had a blunted prolactin response to the 5-HT agonist fenfluramine, indicating a reduction in 5-HT activity.⁴

There is also evidence for an association between reduced 5-HT activity and aggressive, impulsive and suicidal behaviour.⁵ In studies designed to reduce the prevalence of myocardial infarction by lowering cholesterol levels, increased mortality from suicide, accidents and violence was an unexpected finding.⁶⁻¹² This relation has been also reported in some smaller studies done in psychiatric patients.¹³⁻¹⁶ In other studies, however, no relation between low cholesterol levels and aggressive, impulsive and suicidal behaviour was found.¹⁷⁻²¹

Other studies have found a correlation between low serum cholesterol and lipoprotein levels, on one hand,

and the occurrence and severity of major depressive episodes, on the other.^{22,23} Other studies, however, have failed to confirm this finding.²⁴⁻²⁷

The objective of our study was to determine if lipid profile, serum 5-HT levels and serum tryptophan levels differ between patients who are depressed and have had a recent suicide attempt and patients who are depressed but nonsuicidal.

Methods

Subjects

We studied 33 inpatients and outpatients, both male and female, at the Instituto Nacional de Psiquiatria, who met *Diagnostic and Statistical Manual of Mental Disorders, 4th edition (DSM-IV)* criteria²⁸ for a major depressive episode, moderate to severe, single or recurrent, who were or were not taking antidepressant medication. In those patients who were taking antidepressant medication, the duration of the treatment varied from 2 months to just a few days or even hours. We excluded patients with a history of manic episodes, schizophrenia, or alcohol or drug abuse or dependence. All patients gave their written informed consent, as required by the institutional review board.

Of the 33 patients, 18 had attempted suicide within the previous month and 15 had never attempted suicide. Each patient was interviewed by 2 different psychiatrists at 2 different times. A general physical examination and a complete laboratory profile were requested and, if indicated, an electroencephalogram, electrocardiogram, computed tomographic examination and immunological pregnancy test were performed. Subjects who had any medical illness or were pregnant

were excluded from the study. (None of the 33 patients included in the analysis were pregnant or ill.) The following rating scales were applied: Hamilton Depression Rating Scale (HDRS; 17-item version);²⁹ Carroll Depression Rating Scale;³⁰ Beck Hopelessness Scale;³¹ and Beck Suicide Attempt Severity Scale.³²

Lipid profile

After a 12-hour fasting period, blood samples were drawn by venipuncture (between 7:30 am and 9:00 am). Each blood sample was left to clot at room temperature. Serum specimens were held at 4°C until analysis within 6 hours of collection. Each serum sample was assayed for total serum cholesterol, triglyceride, low-density lipoprotein (LDL-C) and high-density lipoprotein (HDL-C) levels. Lipoprotein fractions were separated by conventional precipitation methods using phosphotungstate and magnesium for HDL,³³ and polyvinyl sulfate for LDL.³⁴ The supernatants were assayed immediately after precipitation, or stored at -70°C if the analysis was delayed. Total cholesterol and triglyceride concentrations were determined by enzymatic methods.^{35,36} All methods were standardized according to the program for internal and external quality assessment coordinated by the World Health Organization special program of research development and research training in human reproduction (Brugge, Belgium).

5-HT and tryptophan levels

For serum 5-HT sample preparation, 10 mL of blood was collected into a silicone glass tube containing 100 µL of 10% sodium EDTA and centrifuged at 3000 rpm (1900 ~ g) for 15 minutes at room temperature. Without shaking the tube, approximately half of the volume of the intermediate part of the serum (avoiding the small platelets in the upper part) was transferred with a polyethylene pipette to a microcentrifuge tube and kept at -70°C. Of this, 250 µL was placed into a microcentrifuge tube, to which 50 µL of 25% ascorbic acid was added and briefly mixed by vortexing. To this, 50 µL of 3.4 mol/L perchloric acid was added and the tube vortex mixed for 10 seconds, allowed to sit for 10 minutes at 4°C and then spun for 5 minutes at 10 000 ~ g. The supernatant was filtered through a 4.5-µm porous membrane of which a 5-µL aliquot was used for chromatographic separation.³⁷

Analytical measurements were made with a high-per-

formance liquid chromatography (HPLC) system consisting of a Waters Associates (Milford, MA) Model 510 pump, Wisp 710 autosampler, refrigerating unit, 470 programmable fluorescence detector with an excitation wavelength of 278 nm and emission wavelength of 335 nm, a response time of 1.5 seconds, slit widths set at 18 nm, a gain program (0 to 6 minutes ~ 1; 6 to 13 minutes ~ 100) and Maxima version 3.3 software (for system control, data acquisition and reduction, operating via System Interface Module). Separation was done with a Waters Guard Pak with Nova-Pak C18 inserts and a Waters stainless-steel column (4 µm, 150 mm × 3.9 mm I.D.) Nova-Pak C18. The mobile phase (flow rate of 1 mL per minute) was a mixture of buffer-acetonitrile (90.5:9.5 V/V). The buffer consisted of a mixture of 12.6 mmol/L of citric acid, 11.60 mmol/L of dibasic ammonium phosphate, 2.34 mmol/L sodium octil sulphonate, 1.11 mmol/L sodium EDTA and 3.32 mmol/L dibutylamine phosphate. The pH of the mobile phase was adjusted to 3.7 with 2N sodium hydroxide after the addition of acetonitrile.

Standard stock solutions of 5-HT (1 mg/mL) and tryptophan (4 mg/mL) were prepared as described elsewhere.³⁸ From the stock solutions, standard solutions were prepared for 5-HT (concentration range of 1 to 100 ng/mL) and for tryptophan (concentration range of 1 to 14 µg/mL) in aqueous solution. Calibration curves were processed the same way as the samples. The retention times were 5 minutes for tryptophan and 7.84 minutes for 5-HT.

The intra-assay variation coefficients of the method were 1.77% for tryptophan ($n = 19$, 8.55 µg/mL) and 5.30% for 5-HT ($n = 19$, 40.65 ng/mL). Inter-assay variation coefficients were 3.08% for tryptophan ($n = 5$, 8.98 µg/mL) and 5.24% for 5-HT ($n = 4$, 43.75 ng/mL). The minimum quantifiable level was 0.4 ng/mL for 5-HT and 0.005 µg/mL for tryptophan, in the conditions of referred gain. Data on recovery percentages for each compound were, for tryptophan: 1 µg/mL, 87.39%; 8 µg/mL, 96.12%; 14 µg/mL, 98.85%; and for 5-HT: 20 ng/mL, 95.62%; 100 ng/mL, 99.80%.

A mixture of metoxy indoles in aqueous solution were directly injected into the HPLC to show that there were no compounds overlapping with the 5-HT and tryptophan peaks.

Statistical analysis

For dependent variables (cholesterol, LDL-C, HDL-C, triglycerides, 5-HT, tryptophan and HDRS), group

comparisons were performed using analysis of covariance (ANCOVA). The covariate variable was body mass index. Another 2×2 factorial analysis of covariance was performed with medication status as the second factor. Pearson correlation coefficients were calculated to test for a linear relation between the variables. Logistic regression analysis was used to calculate relative risk (variables were dichotomized using median split).

Results

Of the 18 patients who had attempted suicide, 13 were women and 5 were men; of the 15 patients who had never attempted suicide, 12 were women and 3 were men. Table 1 shows the demographic, clinical and total scores for both groups. ANOVA showed no significant differences in age or body mass index between the 2 groups. However, in the group who had recently attempted suicide, it did show a higher number of lifetime suicide attempts (1.6 [standard deviation 1.3] versus 0.0 [SD 0.0]; $F_{1,31} 21.74, p < 0.001$), a higher number of previous depressive episodes (3.3 [SD 14.47] v. 0.93 [SD 1.0]; $F_{1,31} 5.59, p = 0.02$), and a higher number of previous inpatient events (i.e., admissions to hospital) (0.5 [SD 0.8] v. 0.0 [SD 0.0]; $F_{1,31} 6.29, p = 0.01$).

There were no significant differences between groups in severity of depressive episodes. The total scores on the HDRS were 23.88 (SD 5.69) for those who had attempted suicide and 27.2 (SD 6.69) for those who had never attempted suicide ($F_{1,31} 2.35, p = 0.13$). For the

Carroll Depressive Scale, the total scores were 33.5 (SD 7.52) in those patients who had attempted suicide and 30.26 (SD 8.65) in nonsuicidal patients ($F_{1,31} 1.31, p = 0.25$). Patients who had attempted suicide had a higher score on the Beck Hopelessness Scale, although the differences were not significant (Table 1).

Lipid profile

Table 2 shows the results of the lipid profile of both groups. There were no significant differences between groups in serum levels of cholesterol, LDL-C, HDL-C and triglycerides. For further analysis, we compared the serum lipid profiles of women in both groups and men in both groups; however, no statistical differences were found.

5-HT and tryptophan

The group of patients who attempted suicide had significantly lower levels of serum 5-HT (10 [SD 8.6] ng/mL) compared with the nonsuicidal group (35.94 [SD 23.36] ng/mL; $F_{1,33} 19.77, p < 0.001$). Similarly, levels of serum tryptophan were significantly lower in the group of suicidal patients (8.39 [SD 2.1] $\mu\text{g/mL}$) compared with the nonsuicidal group (10.18 [SD 2.2] $\mu\text{g/mL}$); $F_{1,33} 5.8, p = 0.02$.

Table 3 presents data on serum 5-HT and tryptophan levels and medication status of each group. It was observed that in those patients being administered antidepressant medication, those who had recently

Table 1: Demographic and clinical characteristics, and rating scale scores, of patients with depression who have or have not attempted suicide

Variable	Mean (and standard deviation)	
	Patients who have attempted suicide, $n = 18$	Patients who have never attempted suicide, $n = 15$
Age	32 (12.9)	31.9 (8.8)
Number of suicide attempts*	1.6 (1.3)	0
Number of previous major depressive episodes†	3.3 (3.7)	0.9 (1.0)
Number of previous inpatient events‡	0.5 (0.8)	0
Body mass index, kg/m^2 §	21.4 (5.0)	23.6 (4.9)
Hamilton Depressive Rating Scale score§	23.9 (5.7)	27.2 (6.7)
Carroll Depressive Rating Scale score§	33.5 (7.5)	30.3 (8.7)
Beck Hopelessness Scale score§	13.5 (4.3)	11.4 (7.2)
Beck Suicide Attempt Severity Scale score	16.1 (3.8)	—

* $p < 0.001$

† $p = 0.02$

‡ $p = 0.008$

§not significant

attempted suicide had lower serum levels of 5-HT (12.45 [SD 9.73] ng/mL) than those patients who had never attempted suicide (38.12 [SD 24.37] ng/mL; $F_{1,11} 7.90$, $p = 0.01$). There was also no significant difference in serum tryptophan levels between the suicidal patients taking medication (8.39 [SD 2.79] $\mu\text{g/mL}$) and the nonsuicidal patients taking medication (9.43 [SD 1.5] $\mu\text{g/mL}$; $F_{1,11} 0.47$, $p = 0.5$).

When we compared serum 5-HT and tryptophan levels in patients who were not taking antidepressant medication, serum 5-HT levels were found to be 3 times lower in suicidal patients (9.38 [SD 7.85] ng/mL) compared with those who had not attempted suicide (35.14 [SD 24.15] ng/mL; $F_{1,20} 11.30$, $p < 0.01$). No significant difference was found in serum tryptophan levels between the suicidal group (8.39 [SD 1.52] $\mu\text{g/mL}$) and the nonsuicidal group (10.45 [SD 2.41] $\mu\text{g/mL}$; $F_{1,14} 1.7$, $p = 0.02$).

The relative risk of suicide attempt in those patients with 5-HT serum levels equal to or below 12.51 ng/mL and free of antidepressant medication was 1.55 ($p < 0.05$). For tryptophan, the relative risk of suicide attempt in those with serum levels below 8.9 $\mu\text{g/mL}$ and free of

antidepressant medication was 1.16 ($p > 0.05$).

We made a correlation between lipid profile, rating scales and serum levels of 5-HT and tryptophan in all patients. We found a coefficient of $r = -4.8$ [$t = -2.44$; $p = 0.024$] between serum levels of 5-HT and the number of previous suicide attempts. The correlation between 5-HT levels and the risk of suicide attempt was small and nonsignificant ($r = -0.35$, $t = -1.71$; $p = 0.10$). The rest of the correlation coefficients were found to be rather small and nonsignificant, i.e., less than 0.4.

Discussion

Our results show no correlation between suicide attempt, depression severity and occurrence of major depressive episodes, and serum levels of cholesterol, LDL-C, HDL-C and triglycerides. Mean values were not different in the 2 groups. When the results were compared taking into account body mass index and sex, the results were the same. This is consistent with the studies of Oxenkrug et al,²⁴ Yates and Wallace,²⁵ Strandberg et al,²⁶ and Ploekinger et al,²⁷ whose results show that cholesterol and lipid profile were not different between suicidal, depressed subjects and controls. Although the study of Papassotiropoulos et al¹⁶ found a relative risk of 1 for the occurrence of suicide in those subjects with mean cholesterol values less than 166 mg/dL, total cholesterol in those subjects who had attempted suicide was 247 (SD 41) mg/dL and 200 (SD 32) mg/dL in those with affective disorder; both were higher than in healthy controls (186 [SD 33] mg/dL) and in those with adjustment disorder (176 [SD 38] mg/dL).

Our results are consistent with secondary prevention studies. None of them, including a meta-analysis of 7 studies,¹³ showed an increase in deaths from suicide, accidents or violence. In addition, results of large longi-

Table 2: Values of serum lipid profile between patients who are depressed and have attempted suicide and patients who are depressed but have not attempted suicide*

Lipid	Serum levels, mg/dL; mean (SD)	
	Patients who have attempted suicide, $n = 18$	Patients who have never attempted suicide, $n = 15$
Cholesterol	176.12 (35.2)	176.84 (22.2)
HDL-C	38.70 (9.9)	37.53 (9.3)
LDL-C	100.00 (34.1)	112.21 (21.3)
Triglycerides	155.50 (71.9)	140.00 (59.0)

*All values were not significantly different between the 2 groups.

Table 3: Serum 5-HT and tryptophan levels in patients who are depressed and have attempted suicide and patients who have not attempted suicide

Variable	Mean (and SD)			
	Patients being treated with antidepressant medication		Patients not taking antidepressant medication	
	Attempted suicide	Never attempted suicide	Attempted suicide	Never attempted suicide
Levels of 5-HT, ng/mL	12.45* (9.73)	38.12 (24.37)	9.38‡ (7.85)	35.14 (24.15)
Levels of tryptophan, $\mu\text{g/mL}$	8.39† (2.79)	9.43 (1.50)	8.39§ (1.52)	10.45 (2.41)

* $p = 0.01$ (compared with nonsuicidal group)
 † $p = 0.5$ (compared with nonsuicidal group)
 ‡ $p < 0.01$ (compared with nonsuicidal group)
 § $p = 0.02$ (compared with nonsuicidal group)

tudinal studies have not been consistent in the association between low cholesterol and violent death.¹ On the other hand, we found a significant difference in serum 5-HT and tryptophan levels between subjects with recent suicide attempt and those who had never attempted suicide, even in those who were receiving antidepressant medication (some of them for months). This means that serum levels of 5-HT and tryptophan may be a biological marker for risk of suicide attempt.

Our results are consistent with studies that report that a dysfunction in serotonergic transmission as the cause of impulsive aggression and suicide.³⁹ We also observed a significant correlation between the number of previous suicide attempts and serum 5-HT levels ($r = -0.48$), but a nonsignificant correlation with the lethality of suicide attempt or with total HDRS scores. This suggests that lower levels of serum 5-HT are related more to the recurrence of suicide attempts than to the lethality of self-aggression or severity of depressive episodes.

Another important finding was that serum tryptophan levels were lower in those patients with a recent suicide attempt. This is consistent with the results of Raucoules et al,⁴⁰ Maes et al,⁴¹ Quintana,⁴² Mauri et al,⁴³ and Lucca et al.⁴⁴ This finding also points towards a relation between low serum tryptophan levels and aggressive behaviour, as suggested by Cleare et al.⁴⁵

Two studies have found a relation between seasonal variation in serum L-tryptophan availability and violent suicide occurrence and homicide.^{46,47} Interestingly, in our study, the suicide attempts occurred in the summer, when the circannual levels of tryptophan are lower.

We consider that our results are important when taking into account the relation between serum tryptophan and brain 5-HT content; Sarrias et al⁴⁸ reported the relation between serum and cerebrospinal fluid 5-HT levels to be $r = 0.411$ ($p < 0.02$). Such relations supports the use of peripheral measures in case-control and pharmacological studies in suicide and affective disorders, and guarantee further studies to elucidate if this biochemical parameter is a trait or a state biological marker of suicide behaviour.

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