Low Serum Cholesterol May Be Associated With Suicide Attempt History

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Objective: This case-control study used both healthy blood donors and psychiatric inpatients as controls and controlled for gender, age, low body mass index, alcohol and nicotine use, and aggressive and impulsive behaviors to examine the association between low serum cholesterol levels and suicide attempts.

Method: At a Spanish general hospital, the recruitment included 417 patients with suicide attempt history (138 men and 279 women), 155 psychiatric inpatient controls without suicide history (68 men and 87 women), and 358 healthy controls (220 men and 138 women). All participants were aged 18 years or older. To study the association between low serum cholesterol levels (fasting < 160 mg/dL) and suicide attempts, odds ratios (ORs) and 95% confidence intervals (CIs) were calculated in univariate analyses. Logistic regression models adjusted ORs for confounding variables in male, female, and total samples. The study was conducted from January 1996 to December 1997.

Results: The ORs in the total sample (for psychiatric and healthy controls respectively) were 1.8 (95% CI = 1.2 to 2.9, p = .007) and 1.9 (95% CI = 1.4 to 2.6, p < .001) for the univariate analyses, and 1.6 (95% CI = 0.95 to 2.6, p = .08) and 1.6 (95% CI = 1.0 to 2.4, p = .04) after variable adjustment. In women, the adjusted OR was 1.8 (95% CI = 0.90 to 3.5, p = .09) for psychiatric controls. In men, the adjusted OR was 2.0 (95% CI = 0.99 to 4.1, p = .05) for healthy controls. All ORs were in the hypothesized direction but some subsamples appeared too small to reach significance.

Conclusion: This study, somewhat limited by the small sample size, suggests that low cholesterol may be associated with suicide attempts. Low cholesterol level in suicide attempts may be more important from a pathophysiologic than from a diagnostic point of view.

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There are more than 30 clinical studies that show an association between increased suicide risk and low total serum cholesterol.[1,2] Assuming that low cholesterol is associated with increased suicide risk, in the context of the stress-diathesis suicide model[3] low serum cholesterol level may increase suicide risk in 2 different ways. It may act as a state factor that would contribute to triggering the suicidal act (stressor), or it may act as a trait factor (diathesis) related to aggression/impulsivity, which would lower the suicide threshold. The second possibility would be consistent with the hypothesis that cholesterol depletion reduces central serotonergic activity.[4–8] Low serotonin has been linked to high aggression/impulsivity,[9,10] and most of the neurochemical evidence points to the involvement of the serotonergic system in suicidal behavior.[10] It has been suggested that a key indicator "of the presence of the diathesis would be a personal history of suicide attempt, an indication that the patient had the propensity to act on suicidal impulses in the past."[11(p1434)]

A meta-analysis concluded that intervention studies and clinical trials using cholesterol-lowering strategies have not demonstrated any relationship between cholesterol level and violent death,[1] although it could be argued that artificially lower levels of cholesterol are not the same as naturally occurring lower cholesterol levels and that patients taking cholesterol-lowering agents had naturally high total cholesterol levels during most of their lives. Some studies on the association between low cholesterol levels and suicide attempts have yielded opposite[12] or negative results.[13] Papakostas et al.[14] have suggested that both increases and decreases in neuronal membrane cholesterol and cholesterol content can lead to alterations in serotonergic function.

Three possible reasons have been suggested to explain the lack of replication in all studies of the association between low cholesterol and suicide attempts: the lack of homogeneity among suicide attempters, the lack of homogeneity among controls, and differences in the characteristics of suicide attempts per se. Regarding lack of homogeneity in defining suicide attempters, some of the prior studies have specifically focused on suicide attempters with a specific psychiatric diagnosis such as depression[15,16] or psychoses.[17] Other studies (e.g., Marcinko et al.[18]) have suggested that only violent suicide attempters had significantly lower cholesterol levels than control subjects and that nonviolent suicide attempters did not.

Regarding controls, the majority of the studies have compared groups of suicide attempters with healthy controls without psychiatric disorders.[17,19,20] In a previous case-control study, we compared serum cholesterol levels in suicide attempters (cases) and healthy volunteers (controls) matched by gender, age, and body mass index (BMI).[21] We found that serum cholesterol levels were significantly lower in suicide attempters than in controls, although after gender stratification, the difference remained significant only in men. Matching by gender and BMI allowed us to eliminate some confounding factors in low cholesterol levels, but our prior study still had a weakness: it used a control group with no psychiatric disorders. The majority of suicide attempters have a co-occurring psychiatric disorder.[22,23] Thus, one can argue that a study showing differences between suicide attempters and controls with no psychiatric disorders is contaminated by the potential confounding effects of psychiatric disorders on cholesterol levels. Psychiatric medications are probably not an important confounding factor (some of them are associated with high cholesterol levels but not with low cholesterol levels). However, some psychiatric disorders, particularly major depressive disorder, substance abuse, and eating disorders, have been associated with low serum cholesterol levels in some studies[6,14,24–26] and they are also associated with suicide attempts.

This study considered all of these limitations by taking into consideration the demographic factors associated with low cholesterol (gender and BMI), the psychiatric disorders (using 2 types of controls, healthy volunteers and psychiatric patients), the effects of variables associated with suicide attempts (such as aggression and impulsivity traits, alcohol use disorders, or smoking) and by using relatively large sample sizes, since some prior studies had relatively small samples.[17,19,27]

The primary objective of this case-control study using healthy and psychiatric controls and controlling for confounding factors was to examine whether low cholesterol level acts as a trait factor (diathesis), which lowers the suicide threshold. In summary, we hypothesized that after controlling for confounding factors, there would be a higher prevalence of subjects with low serum total cholesterol levels among individuals with history of suicide attempts than among healthy controls and among psychiatric controls without history of suicide attempts.

METHOD

Sample

All psychiatric patients (aged 18 years or older) were recruited at a Spanish general hospital that provides free medical coverage to a catchment area of 500,000 people. The sample is independent and does not overlap with our prior matched case-control study.[21] A sample of 417 psychiatric patients with a history of at least 1 suicide attempt, including 138 male and 279 female subjects, were recruited during a 2-year span. The psychiatric control group included 155 inpatients without history of suicide attempts, including 68 male and 87 female psychiatric controls admitted to the same psychiatric unit as the subjects with history of suicide attempts. The healthy control group included 358 blood donors (220 men and 138 women) aged 18 years or older from the same hospital, without any history of suicide attempts, psychiatric treatment, or psychiatric diagnoses. Blood donation in Spain is a nonprofit, altruistic procedure. To ensure the safety of donors and patients, there are stringent exclusion criteria for blood donation, which include most illnesses and pharmacologic treatments. Written informed consent was obtained after a complete description of the study (conducted from January 1996 to December 1997) was given to all subjects. The institutional review boards of Ramon y Cajal University Hospital and Fundacion Jimenez Diaz University Hospital approved the study.

Assessments

As recommended by the U.S. National Institute of Mental Health, a suicide attempt was defined as a self-destructive behavior with the intention of ending one's life, independent of the resulting damage.[28] Clinical DSM-IV diagnoses were obtained with the Mini-International Neuropsychiatric Interview, version 5.0.[29] Table 1 includes the most important diagnoses that may

Table 1. Characteristics of Male and Female Suicide Attempters, Psychiatric Controls, and Healthy Controls[a]

	Females			Males		
Characteristic	Healthy Controls (N = 138)	Psychiatric Controls (N = 87)	Suicide Attempters (N = 279)	Healthy Controls (N = 220)	Psychiatric Controls (N = 68)	Suicide Attempters (N = 138)
Young age[b]	57 (79)	32 (28)	60 (166)	57 (126)	37 (25)	43 (59)
Low BMI[c]	22 (30)	37 (32)	50 (139)	7 (16)	21 (14)	27 (37)
Ever smoking	50 (69)	61 (53)	63 (176)	44 (96)	78 (53)	77 (106)
Impulsivity traits[d]	36 (49)	41 (36)	76 (211)	30 (67)	54 (37)	75 (103)
Aggressive behavior[e]	20 (28)	63 (55)	62 (174)	26 (57)	65 (44)	68 (94)
Major depressive disorder[f]	…	38 (33)	60 (168)	…	31 (21)	65 (89)
Substance use disorders	…	10 (9)	16 (46)	…	34 (23)	51 (70)
Eating disorders	…	1 (1)	18 (49)	…	1 (1)	2 (3)
Age, mean ± SD, y	34.9 ± 11.9	43.1 ± 12.8	35.4 ± 13.6	34.9 ± 10.8	41.3 ± 13.3	39.7 ± 14.0
BMI, mean ± SD, kg/m^2	24.5 ± 3.6	24.8 ± 6.0	23.1 ± 4.9	26.3 ± 3.7	25.7 ± 5.2	24.6 ± 3.9
Impulsivity score, mean ± SD	41.8 ± 13.7	43.3 ± 13.0	57.3 ± 15.7	40.5 ± 14.0	48.6 ± 16.6	56.9 ± 16.7
Aggressive behavior score, mean ± SD	10.7 ± 1.8	13.1 ± 3.7	14.1 ± 4.7	11.1 ± 2.2	14.8 ± 4.8	15.5 ± 6.4

[a]Data presented as % (N), except where noted.
[b]Young age: < 35 years.
[c]Low BMI: ≤ 22 kg/m^2.
[d]Impulsivity traits measured with Barratt Impulsiveness Scale and dichotomized using cut points generated with ROC curves.[30]
[e]Aggressive behavior measured with Brown-Goodwin Lifetime History of Aggression and dichotomized using cut points generated with ROC curves.[30]
[f]Unipolar major depressive disorder after excluding bipolar patients.
Abbreviations: BMI = body mass index, ROC = receiver operating characteristic.
Symbol: … = not applicable.

Table 2. Univariate Analyses of the Association Between Low Total Serum Cholesterol Levels and History of Suicide Attempts

	Total Sample			Females			Males		
Value	Healthy Controls (N = 358)	Psychiatric Controls (N = 155)	Suicide Attempters (N = 417)	Healthy Controls (N = 138)	Psychiatric Controls (N = 87)	Suicide Attempters (N = 279)	Healthy Controls (N = 220)	Psychiatric Controls (N = 68)	Suicide Attempters (N = 138)
Low cholesterol, % (N)[a]	20 (71)	20 (31)	32 (133)	25 (34)	16 (14)	32 (88)	17 (37)	25 (17)	33 (45)
Attempters' OR	1.9	1.8	…	1.4	2.4	…	2.4	1.5	…
95% CI	1.4 to 2.6	1.2 to 2.9	…	0.90 to 2.3	1.3 to 4.5	…	1.5 to 4.0	0.75 to 2.8	…
p Value	< .001	.007	…	.14	.006	…	.001	.33	…

[a]Low serum cholesterol: < 160 mg/dL.
Symbol: … = not applicable, cases for analysis.

confound differences between patients with history of suicide attempts and those without. In all subjects, weight and height were measured to calculate the BMI. A BMI ≤ 22 was defined as low. Young age (< 35 years) was used to control for the association between age and low cholesterol.

Impulsivity was measured with the Spanish version of the Barratt Impulsiveness Scale, version 11 (BIS-11).[31] History of aggression was measured with the modified Brown-Goodwin Lifetime History of Aggression.[32–34] Subjects were classified as impulsive or not, and as having aggressive history or not, by dichotomizing scores using cut points generated with receiver operating characteristic (ROC) curves.[30] The degree of planning of the suicide attempt was measured with the planning subscale of the Beck Suicide Intent Scale.[30,35,36] The expected lethality of the attempt was measured with the expected lethality subscale of the Beck Suicide Intent Scale.[35] Risk and protective/rescue factors were measured with the Weisman and Worden scale.[37]

Fasting serum cholesterol levels were measured using the hospital laboratory. Individuals were grouped using a cut-off point of 160 mg/dL of serum cholesterol, previously described in the literature[14,24] as a biological marker for suicide risk.

Data Analysis

Statistical analyses were conducted using the computer software Statistical Package for the Social Sciences, version 14.0 (SPSS Inc., Chicago, Ill.). Univariate analyses, in the total sample and then after gender stratification, compared the frequency of subjects with low cholesterol levels among subjects with history of suicide attempts compared to healthy and psychiatric controls by using odds ratios (ORs) and 95% confidence intervals (CIs). Significance was measured using Fisher exact tests (Table 2).

Logistic regression allows univariate analyses to be adjusted for confounding factors. The dichotomous independent variables that were considered confounding variables for the presence/absence of low cholesterol levels were the

Table 3. Logistic Regression Analysis Comparing Patients With History of Suicide Attempts Versus Psychiatric Controls

Variable	OR	95% CI	Wald χ^2 Test (all df = 1)
Total sample[a] (N = 572)			
Low cholesterol[b]	1.6	0.95 to 2.6	3.1 (p = .08)
Young age[c]	1.8	1.1 to 2.8	6.5 (p = .01)
Impulsivity traits[d]	2.7	1.8 to 4.1	21.9 (p < .001)
Schizophrenia[e]	0.32	0.19 to 0.54	18.5 (p < .001)
Major depressive disorder	2.7	1.8 to 4.2	21.7 (p < .001)
Females[f] (N = 366)			
Low cholesterol[b]	1.8	0.90 to 3.5	2.7 (p = .09)
Young age[c]	3.0	1.7 to 5.4	14.4 (p < .001)
Impulsivity traits[d]	3.6	2.1 to 6.2	21.5 (p < .001)
Aggressive behavior[g]	0.57	0.32 to 1.0	3.7 (p = .05)
Major depressive disorder	2.7	1.6 to 4.7	12.8 (p < .001)

[a]The logistic regression analysis selected variables using a backward selection procedure and only significant or close to significant variables are described. Hosmer-Lemeshow $\chi^2 = 3.6$, df = 7, p = .83.
[b]Low serum cholesterol: < 160 mg/dL.
[c]Young age: < 35 years.
[d]Impulsivity traits measured with Barratt Impulsiveness Scale and dichotomized using cut points generated with ROC curves.[30]
[e]Schizophrenia or other nonaffective psychosis.
[f]The logistic regression analysis selected variables using a backward selection procedure and only significant or close to significant variables are described. Hosmer-Lemeshow $\chi^2 = 6.2$, df = 8, p = .62.
[g]Aggressive behavior measured with Brown-Goodwin Lifetime History of Aggression and dichotomized using cut points generated with ROC curves.[30]
Abbreviation: ROC = receiver operating characteristic.

Table 4. Logistic Regression Analysis Comparing Patients With History of Suicide Attempts Versus Healthy Controls

Variable	OR	95% CI	Wald χ^2 Test (all df = 1)
Total sample[a] (N = 775)			
Low cholesterol[b]	1.6	1.0 to 2.4	4.2 (p = .04)
Female gender	2.9	2.0 to 4.2	31.7 (p < .001)
Young age[c]	0.37	0.25 to 0.54	24.5 (p < .001)
Low BMI[d]	3.3	2.1 to 5.1	29.3 (p < .001)
Impulsivity traits[e]	4.2	2.9 to 6.0	58.7 (p < .001)
Aggressive behavior[f]	4.2	2.9 to 6.1	56.2 (p < .001)
Ever smoker	1.6	1.1 to 2.3	5.4 (p = .02)
Males[g] (N = 358)			
Low cholesterol[b]	2.0	0.99 to 4.1	3.8 (p = .05)
Young age[c]	0.3	0.1 to 0.5	15.9 (p < .001)
Low BMI[d]	3.3	1.5 to 7.2	8.5 (p = .004)
Impulsivity traits[e]	4.7	2.6 to 8.4	27.7 (p < .001)
Aggressive behavior[f]	3.2	1.8 to 5.7	15.8 (p < .001)
Ever smoker	2.6	1.4 to 4.6	9.5 (p = .002)

[a]The logistic regression analysis selected variables using a backward selection procedure and only significant or close to significant variables are described. Hosmer-Lemeshow $\chi^2 = 5.6$, df = 8, p = .69.
[b]Low serum cholesterol: < 160 mg/dL.
[c]Young age: < 35 years.
[d]Low BMI: ≤ 22 kg/m^2.
[e]Impulsivity traits measured with Barratt Impulsiveness Scale and dichotomized using cut points generated with ROC curves.[30]
[f]Aggressive behavior measured with Brown-Goodwin Lifetime History of Aggression and dichotomized using cut points generated with ROC curves.[30]
[g]The logistic regression analysis selected variables using a backward selection procedure and only significant or close to significant variables are described. Hosmer-Lemeshow $\chi^2 = 10.93$, df = 8, p = .21.
Abbreviations: BMI = body mass index, ROC = receiver operating characteristic.

presence/absence of low BMI, young age, history of ever smoking, history of aggressive behaviors, and impulsive traits. When comparing with psychiatric patients without history of suicide attempts, additional confounding variables were the presence/absence of a diagnosis of depressive, substance use, or eating disorders. In summary, whenever a univariate analysis indicated a significant or close to significant association between low cholesterol and history of suicide attempts versus healthy or psychiatric controls, logistic regressions were performed using presence or absence of history of suicide attempts as the dependent variable to control for confounding variables. The Hosmer-Lemeshow goodness-of-fit test was used to examine the fitness of the logistic regression models. We conducted the logistic regression in the total sample and then after gender stratification given the known gender differences in suicide attempt characteristics.

Following the indication of one of the reviewers, we compared cholesterol levels among subjects with history of suicide attempts compared to healthy and psychiatric controls by using analysis of variance (ANOVA).

RESULTS

Cholesterol levels were significantly different in healthy controls (mean = 195.9, 95% CI = 191.43 to 200.36), psychiatric controls (mean = 187.3, 95% CI = 180.68 to 193.95), and suicide attempters (mean = 189.1, 95% CI = 184.92 to 193.30) (ANOVA F = 3.2, df = 2, p = .042). Age and BMI had a significant effect on cholesterol levels (age: ANOVA F = 110.5, df = 1, p < .001; BMI: ANOVA F = 12.3, df = 1, p < .001). Post hoc k-matrix analyses showed that cholesterol levels were significantly lower among suicide attempters than among healthy controls (contrast estimate, 6.8; p = .031), but there were no statistically significant differences when suicide attempters were compared to psychiatric controls. Moreover, a continuous distribution does not help to classify the subjects.

Table 2 describes the univariate analyses in the total sample including both genders. Low cholesterol was associated with suicide attempt in the total sample with significant ORs when using healthy controls (OR = 1.9, 95% CI = 1.4 to 2.6) and psychiatric controls (OR = 1.8, 95% CI = 1.2 to 2.9). Tables 3 and 4 describe the logistic regression models that control for confounding variables. Compared to psychiatric controls, suicide attempters had an adjusted OR for low cholesterol of 1.6 and this result approached significance (p = .08) (Table 3). Compared to healthy controls, suicide attempters had an adjusted OR for low cholesterol of 1.6 (p = .04) (Table 4).

Female Subjects

Women with a history of suicide attempts had a significantly higher frequency of low levels of cholesterol than

other female psychiatric patients (OR = 2.4; Table 2). When this OR was adjusted for confounding factors in the logistic regression model, the OR decreased to 1.8 and was close to being significant (Table 3).

Women with a history of suicide attempts had a higher frequency of low levels of cholesterol than healthy women, but the univariate OR of 1.4 did not reach significance (Table 2). Thus, no logistic regression analysis was performed.

Male Subjects

Men with a history of suicide attempts had a higher frequency of low levels of cholesterol than other male psychiatric patients but the OR of 1.5 was not significant (Table 2). Thus, no logistic regression analysis was performed.

Men with a history of suicide attempts had a higher frequency of low levels of cholesterol than healthy men, and the univariate OR of 2.4 was significant (Table 2). The OR was 2.0 and within the limits of significance (p = .05) after adjusting for confounding factors (Table 4).

Exploring the Effects of Low Cholesterol as a State Marker Rather Than a Trait Marker

Although all ORs were in the hypothesized direction in the total sample, 2 of the 4 ORs after gender stratification did not reach significance. One could argue that our selection of low cholesterol levels as a trait marker was wrong and that it would have been better considered a state marker. To consider low cholesterol levels as a state marker, some psychiatric patients had to be reclassified. Some of the patients with a history of suicide attempt were recruited at admission with no current suicide attempt and for these analyses were considered as noncurrent suicide attempters. The sample sizes for current suicide attempters were 268 women and 131 men. The sample sizes used in these analyses as psychiatric controls were 103 female and 77 male psychiatric patients with no current suicide attempts.

All the ORs after gender stratification appeared to be similar when they were recalculated using the alternative definition. The new OR comparing current female attempters versus female healthy controls was 1.4, versus 1.4 in the prior analysis. The new OR comparing current female attempters versus female psychiatric controls was 1.9, versus 2.4 in the prior analysis. The new OR comparing current male attempters versus male healthy controls was 2.5, versus 2.4 in the prior analysis. The new OR comparing current male attempters versus male psychiatric controls was 1.5, versus 1.5 in the prior analysis.

Exploring the Effects of Violent Suicide Attempts

Some authors have suggested that low cholesterol level was only associated with violent suicide attempts. We tested that within our sample of current suicide attempters, and we found an association bordering significance in male (OR = 2.9, 95% CI = 1.0 to 8.1, p = .05) but not in female attempters (OR = 1.4, 95% CI = 0.6 to 3.6, p = .47). This comparison of violent (scores ≥ 2 in the expected lethality subscale of the Beck Suicide Intent Scale) versus nonviolent suicide attempters had small sample sizes (men: 17 violent attempters vs. 114 nonviolent attempters, and women: 20 violent attempters vs. 231 nonviolent attempters).

DISCUSSION

Principal Findings

The sample size of the total sample appeared large enough to show an association between suicide attempts and low cholesterol after using psychiatric and healthy controls and adjusting for confounding variables. The psychiatric controls were better controls, in the sense that they shared more confounding factors with the suicide attempters, while the healthy controls were blood donors requiring the exclusion of most illnesses and pharmacologic treatments.

The sample size of the male or female samples did not appear large enough. As in our prior study,[21] we found a significant association between low cholesterol and male suicide attempts when using healthy men as controls. Thus, this association appears to be robust. As we indicated in the prior section, the lack of association between male low cholesterol and suicide attempts when using male psychiatric controls may be due to the small number of male psychiatric controls.

In women the univariate OR was significant when using psychiatric controls, and the multivariate OR was close to significance in the logistic regression. As indicated in the Limitations section, it is very likely that the lack of significance in women when compared with healthy controls was due to the small sample size, which was partly resolved by adding female controls from a prior study.

Gender Effects

We suspect that low cholesterol is associated with suicide attempts, but, when comparing the prior matched study and the results after gender stratification in this one, the only replicated finding that we have is the significant difference between male attempters and male healthy controls. Thus, it is possible that gender may modulate the association between total cholesterol and suicide.

Other authors have found gender-specific relationships between low cholesterol and suicidal behavior, or have analyzed samples of individuals of 1 gender only.[17,38,39] Golier et al.[39] observed that men with cholesterol levels above the 25th percentile were less likely to have made a serious suicide attempt than men with low cholesterol levels when age, weight, race, socioeconomic status, alcohol

use, and depression were controlled for. However, they found no association between cholesterol level and attempted suicide in women. Bocchetta et al.[38] reported that the proportions of men with a history of prior suicide attempts, especially if violent, and of men with a history of completed suicide in a first-degree relative were significantly higher among those men with cholesterol levels in the lowest quartile. They could not find any significant association among women. Soeda et al.[40] reported that low cholesterol increased the likelihood of having scores higher than 3 in the General Health Questionnaire (GHQ-12), suggesting worse mental health, only in males. Although previous studies on the association between gender and serum cholesterol have been inconclusive, some authors have observed that male gender is associated with lower cholesterol levels in several psychiatric disorders.[41,42]

Currently, we are not sure how gender may modulate the association between low cholesterol and suicide attempts. However, we think that gender stratification in the analyses may be important, since each gender had different associated variables in the logistic regression models (the logistic regression models in female attempters versus healthy controls and in male attempters versus psychiatric controls are not presented, since low cholesterol was not significant in the respective univariate analyses).

Limitations

All the ORs were in the predicted direction, meaning that patients with a history of suicide attempts always had significantly higher frequency of low cholesterol levels than healthy or psychiatric controls. In spite of the relatively larger sample size than in prior studies, this study may be still underpowered. In the total sample, the logistic regression models using healthy controls provided a significant OR for low cholesterol, but it was only close to significant in the model using psychiatric controls.

The univariate OR comparing women with a history of suicide attempts and female healthy controls was 1.4 and had a nonsignificant p value of .14. However, after adding female healthy controls from our previous study[21] (N = 109) to the female healthy control sample used in the present study (N = 138), we found that women with a history of suicide attempts (88/279, 32%) had a significantly higher frequency of low levels of cholesterol than did healthy women (59/247, 24%; p = .05), with a univariate OR of 1.5 (95% CI = 1.0 to 2.2). The adjusted OR was 1.3 (95% CI = 0.9 to 2.0) and lost significance (p = .17) after adjusting for confounding factors. This suggests that the lack of significance in the univariate analysis was due to the relatively small number of female healthy controls.

The OR comparing men with a history of suicide attempts and psychiatric controls was 1.5 and had a nonsignificant p value (p = .33). As the number of male psychiatric patients without a history of suicide attempts was relatively small (N = 68), it is not surprising that an OR of this size was not significant. Unfortunately, we lack any other sample of male psychiatric patients to increase the sample size and verify this hypothesis.

Variables Not Studied That May Be Confounding Factors

We need to acknowledge that we did not study other lipids. Other authors have speculated that the association with increased suicide risk is with other serum lipids rather than with total cholesterol levels (e.g., low high-density lipoprotein cholesterol) in female attempters,[43] or with low levels of omega-3 and omega-6 essential fatty acids in self-harm patients.[27] Furthermore, low omega-3 polyunsaturated fatty acid intake has been associated with increased risk of depression[44] or suicide.[45] Another possible confounding factor is apolipoprotein E.[46,47] Certain mutations of genes, such as apolipoprotein B, 7-dehydrocholesterol reductase or ABCG1 (ATP binding cassette transporter G1), which are involved in cholesterol homeostasis, have been linked to aggression[20] and violent behavior, including self-harm,[48] attempted[20] and completed suicide, and homicide.[49]

Unanswered Questions and Future Research

The limited sample size of violent attempters does not allow for definitive exploration of the effects of this type of suicide on the association between low cholesterol and suicide risk. It is possible that low cholesterol may be more frequent; the order of frequency may be violent attempters > attempters > psychiatric controls > healthy controls, but a huge sample of thousands of patients would be required to test that hypothesis. Moreover, taking into account the differences between men and women in logistic regression models, we think that gender stratification is needed in this area of research.

The limited sample size does not allow for establishing whether low cholesterol may influence suicide risk as a state versus a trait marker. Our results suggest that the selection of the trait marker hypothesis may be reasonable.

In the present study there are no data available regarding several other factors that may contribute to the alterations in serum cholesterol in suicide attempters, such as genetic factors or pharmacologic treatment. Future studies will need to consider them. It must be remembered that psychiatric medications are not likely to cause low cholesterol levels, but some of them, particularly some antipsychotics or mirtazapine,[50] may increase cholesterol levels. It is possible that this may mask some cases of low cholesterol levels.

It has been reported that there is a significant increase in cholesterol levels in depressed patients after treatment.[25,51] In a recent study, Gabriel[26] analyzed the effect of pharmacologic treatment on total cholesterol levels in

patients with acute episodes of major depressive disorder and manic or hypomanic episodes. He observed that total cholesterol levels significantly increased in patients with acute episodes of major depressive disorder after treatment, while they decreased in patients with manic or hypomanic episodes. This will need to be further investigated in future longitudinal studies.

Another remaining question is whether suicide attempts are preceded or followed by low cholesterol levels. Since most suicide attempts take place in the context of a depressive disorder, it has been suggested that attempters may have less appetite as a consequence of depressive symptoms, which in turn results in lower intake of certain nutrients.[45]

Prospective studies with long follow-up periods are needed to clarify the obscure relationship between cholesterol levels and suicide. Ideally, they should include data regarding pharmacologic treatment, comorbid medical conditions that may influence cholesterol levels, and genetic factors. They should also take into account other possible confounding factors, such as psychiatric diagnoses and other lipids (essential or polyunsaturated fatty acids). It will not be easy to pursue these types of studies unless larger multicenter studies are funded.

Conclusions for Clinicians

Low cholesterol levels may be associated with suicide attempts but more studies are needed to clarify the subject and pursue additional confounding factors more thoroughly. Current research cannot confirm that low cholesterol levels can be used for predicting suicide risk. The logistic regression model can be used to calculate how many of the subjects were classified correctly (accuracy). The logistic regression model of women with attempt histories versus female psychiatric controls classified only 79% of the subjects correctly. The logistic regression model of men with attempt histories versus male healthy controls classified only 78% of the subjects correctly. Thus, better models are needed, taking into account other confounding variables, until the accuracy (sensitivity and specificity) is appropriate for the clinical world. Another statistical approach, ROC curves, also suggested that low cholesterol levels may not be suitable as diagnostic predictors of suicide. The use of cholesterol levels in the ROC curves provided low area under the curve (AUC) values to separate suicide attempters versus psychiatric patients (AUC = 0.45) and suicide attempters versus healthy controls (AUC = 0.45).

Currently, one can hypothesize that the importance of low cholesterol level in suicide attempts may be greater from the pathophysiologic than the diagnostic point of view. If low cholesterol is a trait marker of suicide attempts, that may help us to better understand the pathophysiology of suicide attempts and develop preventive interventions.

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