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A Case-Control Study of the Association Between Hypocholesterolemia and Depressive Symptoms in a Mexican Population from Los Altos Sur, Jalisco

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Abstract

Mental disorders have significantly increased worldwide, with depression affecting over 280 million people. Up to 60% of individuals with major depressive disorder experience concurrent anxiety, both of which can lead to suicide. While social and cultural factors contribute to mental disorders, recent studies link these conditions to genetic, neurophysiological, and biochemical factors, including serum lipid levels. This study investigates the association between serum lipid levels and depressive symptoms in the Los Altos Sur region of Jalisco, Mexico. Forty-two participants with depressive symptoms and eighty-four controls were recruited. Participants underwent psychometric assessments and lipid profile assays. The results showed significant differences between cases and controls in total cholesterol, triglycerides, LDL, and VLDL levels. Cases had higher rates of hypocholesterolemia and more frequent depressive and anxiety symptoms, as well suicidal risk. Hypocholesterolemia was significantly associated with depressive symptoms. Differences for cases grouped by depressive symptoms and hopelessness were found in HDL. Physical activity was found as a protective factor for depressive and anxiety symptoms. This study demonstrates the association of serum lipid levels with mental health conditions, suggesting that cholesterol levels are related to increased vulnerability to depression and hopelessness. Understanding these associations can aid in early identification and intervention for at-risk populations.

Keywords: depression; anxiety; suicidal behavior; cholesterol; hypocholesterolemia

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1. Introduction

Globally, mental disorders have experienced exponential growth in recent decades. The World Health Organization [1] estimates that depression affects more than 280 million people. Additionally, up to 60% of individuals with major depressive disorder experience concurrent anxiety [2]. These conditions can be determinants for suicide [3,4]. Suicide rates vary among age groups, but the tendency is to increase in older age groups; older adolescents and young adults tend to commit suicide more often than young adolescents and children [4,5].

While it has been hypothesized that mental disorders are phenomena rooted in social and cultural factors, in recent years, they have been linked to genetic, neurophysiological, and biochemical factors, such as depression [6,7] or suicidal behavior [8,9]. Among these factors is the concentration of lipids in both serum and brain tissue, especially hypocholesterolemia [10–12]. Additionally, pandemics are related to long-term increases in the frequency of mental disorders worldwide [13] and augmenting risk factors for suicide [14] such as alcohol consumption [15].

The link between low cholesterol levels and the risk of suicide has attracted considerable attention in scientific research. Several studies have explored the potential link between hypocholesterolemia and psychological vulnerability [10–12,16–18].

Over the decades, a substantial body of research has supported this intricate relationship, suggesting that serum cholesterol concentration not only plays a fundamental role in cardiovascular health but may also have significant implications for mental well-being [19,20].

Some studies have examined the frequency of hypocholesterolemia in individuals exhibiting a history of suicidal ideation or suicide attempts [3,16]. Despite the intricate nature of this association not being fully elucidated, accumulating evidence suggests a plausible connection between low cholesterol levels and an increased risk of suicidal manifestations [21,22]. Understanding this relationship holds the potential not only for the early identification of populations at risk but also for the formulation of more effective intervention and prevention strategies within the domain of mental health.

Several theories and potential explanations have been proposed in the scientific literature regarding the biological basis of cholesterol and mental health. The first explanation is that cholesterol is indispensable for the integrity and function of cell membranes, including those of the nervous system [23,24]. The second explanation is that cholesterol may play a role in serotonin synthesis, a neurotransmitter linked to mood and emotional regulation [25–27]. Another explanation says that low cholesterol levels may be associated with increased inflammation and oxidative stress, biological processes linked to mental health [28–31]. A fourth hypothesis is centered in mitochondrial biogenesis, the process that ensures the removal of old defective mitochondria by mitophagy, and the replacement by new one, a process that involves cellular functionality [32]. Other studies have found differences in HDL levels [17,18,21] and hypercholesterolemia [16,33], while some report no differences in total cholesterol, HDL, and LDL [18,34]. Finally, reduced cholesterol levels interact with other risk factors for mental health [35].

Enhancing our comprehension of the biological factors contributing to symptoms and personality traits in individuals at risk of suicide may pave the way for more effective preventive and therapeutic approaches. In the present study, we, therefore, compare the serum lipid levels and depressive symptoms in individuals with and without symptoms. Also, in an exploratory manner, we examined within the case group the associations between lipids and anxiety severity and suicidal risk.

2. Materials and Methods

2.1. Participants

All subjects gave written informed consent to participate. We recruited forty-two participants with depressive symptoms as cases (BDI-II score > 10 points) and eighty-four participants without psychiatric or neurological antecedents as controls (n = 126, 94 women); participants signed written informed consent. All participants came from the Los Altos Sur region of Jalisco, Mexico, and were native and residents of the area. Cases were matched with controls based on age, gender, and body mass index. Individuals using statins or

those with conditions affecting lipid concentrations, such as diabetes mellitus, metabolic syndrome, cardiovascular disease, hypertension, or liver damage, were excluded.

2.2. Psychometric Assessments

All participants underwent a comprehensive medical history, anthropometry, laboratory tests, and psychometric assessments (including Beck Depression Inventory II [BDI-II], Beck Anxiety Inventory [BAI], Beck Hopelessness Scale [BHS], and Plutchik Suicide Risk Scale [SRS]).

2.3. Lipid Profile Assay

After a night of fasting, venous blood samples from the antecubital vein were collected at 8:00 a.m. in tubes containing EDTA. The samples were immediately placed on ice and centrifuged at 3000 *g* for 10 min to separate plasma from cellular components within 1 h of collection. Plasma levels of total cholesterol (TC), triglycerides (TG), and high-density lipoprotein cholesterol (HDL) were determined directly using enzymatic methods from Biosystems (Barcelona, Spain) and processed on the automated clinical chemistry analyzer Flexor EL 200 (Holliston, MA, USA). Low-density lipoprotein cholesterol (LDL) was calculated using the Friedewald equation, while very-low-density lipoprotein (VLDL) values were obtained by dividing triglyceride values by 5. It was considered that the cholesterol level was low when it was below 150 mg/dL and high when it was above 200 mg/dL.

2.4. Statistics

All statistical analyses were conducted using SPSS statistical software version 23.0. Student *t*-test was used for groupwise comparisons on parametric data. Non-parametric data were analyzed through Mann–Whitney test for groupwise comparisons and Spearman correlation test. All statistical analyses were tested for a two-tailed hypothesis. The alpha-level of significance was set at $p < 0.05$. To determine the strength of the association of risk and protective factors, chi-square with *odds ratio* was employed.

Some analyses were performed only for cases that relate to exploring variables related to depressive symptoms and suicidal risk. Criteria for case comparison were determined for each variable out of our selection criteria as follows: BDI-II score: minimal or low symptoms, equal to or less than 19 points, *versus* moderate or high symptoms, more than 19 points. BAI score: minimal or low symptoms, equal to or less than 15 points, *versus* moderate or high symptoms, more than 15 points. BHS score: normal or asymptomatic and low symptoms, equal to or less than 8 points, *versus* moderate or high symptoms, more than 8 points. SRS score: without suicidal risk, equal to or less than 6 points *versus* with suicidal risk, more than 6 points.

3. Results

3.1. Participant Demographic Characteristics

The sample consisted of 126 individuals (96 participants were female, ranging from 15 to 77 years old). None of the participants had comorbidities that could affect serum lipid levels. Among them, only 42 participants met the criteria for cases as they exhibited symptoms of depression based on BDI-II scores (>10 points). Additionally, 84 participants without psychiatric or neurological antecedents, matched by age and sex, were selected as controls. Table 1 shows the demographic characteristics of the population sample of Los Altos of Jalisco, examined in this study.

Table 1. Demographic characteristics of participants (case and controls) (n = 126).

Characteristic	$\bar{X}$ (SD)	Percentage %
Age (years)	38.24 (15.008)	------
Weight (Kg)	69.21 (15.612)	------
Height (m)	1.63 (0.095)	------
BMI (Kg/m^2)	25.86 (5.355)	------
Waist (cm)	82.72 (15.347)	------
Hip (cm)	100.38 (10.459)	------
Waist-hip Index	0.82 (0.112)	------
TC (mg/dL)	169.53 (41.209)	------
TG (mg/dL)	113.53 (68.455)	------
HDL (mg/dL)	59.03 (13.557)	------
LDL (mg/dL)	87.71 (37.312)	------
VLDL (mg/dL)	22.7 (13.691)	------
Alcohol consumption	------	27.8
Cigarette consumption	------	27.8
Sedentarism	------	41.3
Non-economically active people	------	42.9

BMI = body mass index, TC = total cholesterol, TG = triglycerides, HDL = high-density lipoprotein cholesterol, LDL = low-density lipoprotein cholesterol, and VLDL = very low-density lipoprotein cholesterol.

Lifestyle characteristics, antecedents, psychometric classification, and serum lipid levels by study group were summarized in Table 2. It is observed that cases had more familiar antecedents of mental illness, higher tobacco consumption, less-frequent physical activity, a lower presence of hypercholesterolemia, and higher levels of hypocholesterolemia compared with controls. It is noteworthy that controls showed an absence of anxiety symptoms and suicidal risk indicators, while these were prevalent in the case group.

Table 2. Lifestyle characteristics, antecedents, and serum levels by study group.

Characteristic	Cases (n = 42)	Controls (n = 84)
Alcohol consumption	23.8%	29.8%
Tobacco consumption	33.3%	25%
Frequent physical activity	40.5%	67.9%
Actually works	54.8%	58.3%
Familiar antecedents of mental illness condition	66.7%	63.1%
Familiar antecedents of suicide	7.1%	14.3%
Presence of hypercholesterolemia	11.9%	20.2%
Presence of hypocholesterolemia	54.8%	21.4%
Presence of anxiety symptoms	90.5%	0%
Presence of suicidal risk (by BHS and SRS scores)	54.8%	0%

3.2. Psychometric Assessment and Serum Lipid Levels

As expected, due to selection criteria, significant differences were observed between the case and control groups for BDI-II, also for BAI, BHS, and SRS scores (Table 3). It is important to emphasize that the effect size for all comparisons was larger, indicating statistically significant differences (all $p < 0.05$).

Table 3. Psychometric assessment scores for BDI-II, BAI, BHS, and SRS between case and control groups.

Psychometric Assessment	Cases (n = 42) $\bar{X}$ (±DE)	Controls (n = 84) $\bar{X}$ (±DE)	*p* Value *	Effect Size
Beck Depression Inventory	22.24 (9.68)	4.06 (2.80)	$p = 0.000$	$r^2 = 0.815$
Beck Anxiety Inventory	22.98 (14.25)	4.12 (2.39)	$p = 0.000$	$r^2 = 0.755$
Beck Hopelessness Scale	6.93 (4.57)	2.17 (1.89)	$p = 0.000$	$r^2 = 0.534$
Plutchik Suicide Risk Scale	5.71 (3.01)	1.57 (1.35)	$p = 0.000$	$r^2 = 0.637$

* Mann–Whitney test, $p < 0.05$.

3.3. Exploration of Psychopathological Symptoms and Suicidal Behavior with Other Variables

Association between serum lipid levels and the presence of psychopathological symptoms was explored, finding a significant association between hypocholesterolemia and the presence of depressive symptoms (classification according to BDI-II score) ($\chi^2 = 15.402$, DF = 1, OR = 4.771, C.I. = 2.127–10.701, $p = 0.00008$). This suggests that, based on the *odds ratio*, the *odds* of depressive symptoms were 4.771 times higher if participants had low cholesterol levels.

No significant comparisons using the Mann–Whitney test on cases were found when grouped by BAI score (minimal or low symptoms *versus* moderate or high symptoms) and SRS (without suicidal risk *versus* with suicidal risk) for serum lipid levels. But for cases grouped by BDI-II, differences were observed for 'Normal or asymptomatic and low anxiety symptoms group' (*Mdn* = 53.55 mg/dL) *versus* 'Moderate or high anxiety symptoms group' (*Mdn* = 66.9 mg/dL) (U = 65, z = −2.378, $p = 0.017$, $r = -0.367$) for HDL. Also, for cases grouped by BHS, differences were observed on HDL for comparisons between 'Normal or asymptomatic and low anxiety symptoms group' (*Mdn* = 55 mg/dL) *versus* 'Moderate or high anxiety symptoms group' (*Mdn* = 70 mg/dL) (U = 109, z = −2.2, $p = 0.028$, $r = -0.339$).

A correlation analysis was conducted to examine the relationship between the age of case group and their scores on Beck Depression Inventory (BDI-II), Beck Anxiety Inventory (BAI), Beck Hopelessness Scale (BHS), and Plutchik Suicide Risk Scale (SRS). A correlation yielded significant results (Figure 1): a positive correlation with BHS score and age of cases was observed ($r = 0.327$, $p = 0.035$).

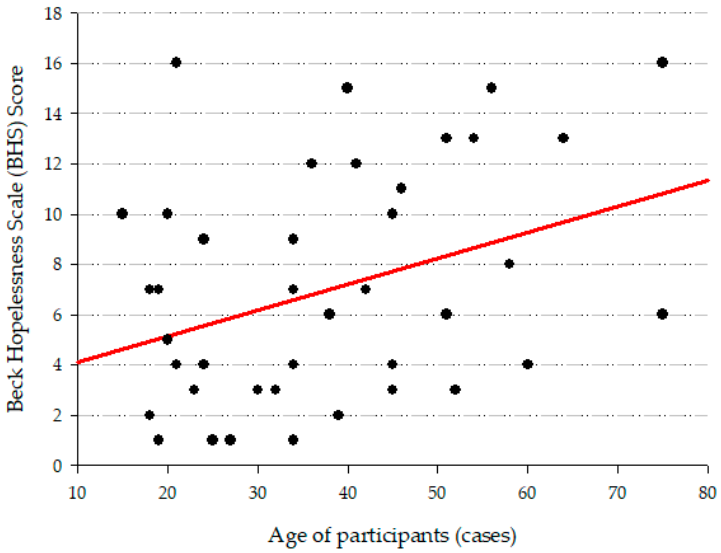


Figure 1. Graph that shows the correlation between the age of participants and BHS score.

Finally, additional associations were identified regarding protective factors against psychopathological symptoms; the analysis included data from both groups: cases and controls (Table 4). An association between depressive symptoms and frequent physical activity (χ^2 = 8.661, DF = 1), with the *odds ratio* for cohort engaging in frequent physical activity indicating a 0.596 decrease in the probability of experiencing depressive symptoms. Similarly, another association was found between anxiety symptoms and frequent physical activity (χ^2 = 6.204, DF = 1), with the *odds ratio* for cohort engaging in frequent physical activity indicating a 0.639 probability of experiencing anxiety symptoms.

Table 4. Association between psychopathological symptoms and suicidal behavior with protective factors.

Parameter	*p* Value *	Odds Ratio (OR)	Confidence Interval Limits
Frequent physical activity–depressive symptoms	$p = 0.004$	0.322	0.149–0.694
Frequent physical activity–anxiety symptoms	$p = 0.018$	0.376	0.172–0.821

* Chi square test.

Analysis by the Mann–Whitney test, including only case group data, demonstrated no significant differences among the frequency of physical activity comparisons.

4. Discussion

The principal finding of this observational case-control study is that individuals with depressive symptoms from the Los Altos Sur region of Mexico exhibit a distinct serum lipid profile characterized by significantly lower levels of total cholesterol, LDL, and VLDL compared to matched controls without psychiatric antecedents. This finding aligns with a growing body of evidence linking hypocholesterolemia to major depressive disorder [11,12,36,37] and reinforces the notion that lipid metabolism may be a relevant biological factor in the pathophysiology of depression in this specific population. To our knowledge, this is the first report to describe such an association in this particular region of Mexico. This finding is especially relevant from a public health perspective, as this population experiences a suicide rate (13.97 per 100,000) [38] that is more than double the national average (6.8 per 100,000) in 2023 [39], highlighting the urgent need for novel approaches to understanding mental health risks in this population.

The biological mechanisms underlying the association between low cholesterol and depression may involve serotonergic neurotransmission and neuronal integrity. Cholesterol is a critical component of lipid rafts in neuronal membranes, which regulate the function of serotonin receptors, such as the 5-HT1A receptor [27]. Low cholesterol levels could disrupt this environment, leading to reduced serotonin signaling and subsequent depressive-like behavior, as demonstrated in animal models [27,37]. Furthermore, the observed hypocholesterolemia might also be a consequence of persistent inflammation and oxidative stress, which are established pathophysiological components of depression [31], and also activation of the HPA axis by chronic stress [31,40]. While our results support this hypothesis, it is important to acknowledge the heterogeneity in the literature, with some studies reporting higher lipid levels in depressed patients [10,11,18,21,41].

No clear explanations of these lipids-levels variances in different populations exist. Cholesterol processing varies due to genetic factors and is correlated with behavioral and mental health characteristics [16]. This suggests that genetic population differences may

explain the divergent findings across studies, highlighting the importance of genetics as a risk factor for depression [4,31], and the role of lipids on DNA methylation [42], due to the epigenetic modifications on genes related to stress and depression-like phenotypes [43].

Also, it is stated that a family history of major depression [44] and other disorders [45] is related to the development of depression. Equally, the consumption of tobacco and alcohol is related to depression and anxiety [45,46]. This demonstrates that mental disorders are multicausal, and no simple explanation could be offered.

Another relevant result is the psychometric assessment of depression, anxiety, hopelessness, and suicide risk symptoms, comparing cases and controls. The differences observed demonstrate a robust effect size on measures for depression, anxiety, hopelessness, and suicide risk. This reinforces the results showing hypocholesterolemia associated with depressive symptoms in the case control.

Our results were similar to Segoviano et al. [11] who found differences on cases and controls in TC, LDL, and VLDL. Also, differences between cases were observed, differing from our results; we found differences in only HDL levels when comparing cases by depression or hopelessness. Other studies have found that HDL and other inflammatory indicators are associated with depression [47]; these mechanisms could be characteristic of severe depressive conditions and not for low depressive symptoms.

Depression and anxiety are commonly comorbid disorders [2]. Our results confirm that cases with high scores for depressive symptoms also often exhibit anxiety symptoms. Depression with anxiety comorbidity and depression alone *versus* anxiety disorder alone show specific serum lipid profiles, with no alterations observed in anxiety disorders alone [41]. It is hypothesized that stress causes depression and anxiety [48], but no concluding studies exist [46]; also, brain circuits and neurotransmitters related to depression [31,49] and anxiety [50] differ, implying common factors for comorbidity [2,49]. Differences on etiology and brain mechanism could explain why cases grouped by BAI scores did not differ.

Hopelessness and suicide risk are related. Our results show differences between cases and controls in BHS and SRS scores, as well as in the presence of suicidal risk. This aligns with a meta-analysis indicating that severe hopelessness predicts the risk of committing suicide [51]. Due to mood and cognition changes by conditions as depression and anxiety, there is an increased risk of suicide attempt and ideation, as noted in other studies [52,53].

Age and hopelessness were positively correlated to the age of cases. Some studies report lower mental health condition symptoms in adults compared to adolescents [54,55]. However, another study in Mexican population did not find an association between age and depressive symptoms [56] as we found. The association between age and hopelessness may be explained by a decrease in cognitive and physical resources along with challenging life events [57,58].

Our study also reinforces the role of frequent physical activity as a protective factor against depressive and anxiety symptoms in the entire sample. Frequent physical activity appears to reduce the risk of significant depressive and anxiety symptoms. Physical activity [59] and physical health [29] are documented protective factors against depression. Some studies explain that factors like BDNF [32,60,61] and kynurenine [61] are promoted by physical activity and exercise. Also, physical activity and exercise promote cortisol (a hormone related to stress response) [62] as inflammatory response regulation [63,64] and also promote mitochondrial biogenesis regulators, influencing buffering of ROS in the brain [32].

Finally, our study had limitations, including a small sample size due to the inclusion criteria for cases and controls. Another limitation was the lack of clinical depression diagnosis in cases like Segoviano et al. [11], which could have provided more robust associations between serum lipid levels and symptoms of depression, anxiety, and suicidal

risk. BDI-II, BAI, and BHS discriminate well between clinical and non-clinical samples, but they are detection instruments [65].

These limitations suggest directions for future studies in the general population without stringent filters, as well as larger sample sizes with the same criteria. Studies involving clinical conditions of depression and anxiety or previous suicide attempt could help specifically characterize serum lipid profiles in the Mexican population. Detailed exploration of scale items for better characterization of symptoms related to serum lipid levels is also recommended. Future studies should consider cultural adaptations of BDI-II [66,67] and BAI [67].

Also, it is plausible that exercise-induced adaptations could counteract some of the proposed mechanisms linking low cholesterol and depression, such as inflammation and impaired neurogenesis [32,60], although this interaction needs direct investigation in future studies.

Another important limitation was considering suicide attempts as a single profile. Distinct suicide profiles to attempts and risk have been documented [68]. Future studies could partially address this by using detailed items and categories from the Beck Hopelessness Scale (BHS) and the Plutchik Suicide Risk Scale (SRS).

5. Conclusions

Our results demonstrate that hypocholesterolemia is prevalent among individuals with depressive symptoms in the population from the Los Altos Sur region of Mexico. We established that LDL levels are significantly lower in cases than in controls. Between cases, HDL differs in the severity of depressive symptoms and hopelessness. Anxiety symptoms and suicidal risk were also highly prevalent among cases. Physical activity was identified as a protective factor against depression, potentially due to its role in promoting optimal cellular function, such as through anti-inflammatory effects of mitochondrial biogenesis. Future studies should involve larger, population-based samples and focus on individuals with clinically diagnosed depression to confirm and extend these findings. Overall, this investigation highlights the potential benefits on early detection and intervention for people with depression through serum lipid profile while also contributing to the identification of underlying cellular and molecular pathophysiological mechanisms.

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Institutional Review Board Statement: This study was conducted in accordance with the guidelines of the Declaration of Helsinki. It was approved by the Research Ethics Committee from Los Altos University Center, University of Guadalajara (approval code: CUA/CEI/DIVBIO-03/2021, approval date 12 July 2021).

Informed Consent Statement: Written informed consent was obtained from all participants prior to their inclusion in the study, ensuring the confidentiality of their personal data, minimizing risks, and prioritizing their well-being at all times.

Data Availability Statement: The datasets generated and analyzed for this study are not publicly available because they contain sensitive personal information from the participants; this confidentiality is protected by the Mexican Federal Law on Protection of Personal Data. However, the data are available to qualified researchers who meet the access criteria for the ethical handling of information, upon reasonable request to the corresponding author and provided that the use of the data is limited to the purposes of the request. The data will be anonymized to guarantee the participants' privacy.

Conflicts of Interest: The authors declare no conflicts of interest. The funders had no role in the design of the study; in the collection, analyses, or interpretation of data; in the writing of the manuscript; or in the decision to publish the results.

Abbreviations

The following abbreviations are used in this manuscript:

BAI	Beck Anxiety Inventory
BDI-II	Beck Depression Inventory II
BHS	Beck Hopelessness Scale
BMI	Body Mass Index
HDL	High-Density Lipoprotein cholesterol
LDL	Low-Density Lipoprotein cholesterol
SRS	Plutchik Suicide Risk Scale
TC	Total Cholesterol
TG	Triglycerides
VLDL	Very-Low-Density Lipoprotein cholesterol

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