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Research Article

Anemia and Cholesterol Level are Independently Associated with Anxiety and Depression

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Abstract

Background: Previous studies consistently showed significant associations between depression and anemia, or depression and low cholesterol level.However, almost all studies in this field evaluated effects of only one of these blood components on depression severity. Few studies evaluated effects of either anemia or low cholesterol on anxiety severity.

Methods: In the present retrospective study we analyzed data from the database of Moscow Research and Clinical Center for Neuropsychiatry. Data of 1937 in-patients with non-psychotic psychiatric disorders were included into the analysis. Patients were evaluated using Beck Depression Inventory (BDI),Hamilton Depression Rating Scale (HDRS), and Spielberger State-Trait Anxiety Scaleat admission and after 3 – 5 weeks of treatment. Hemoglobin and total cholesterol measurements at 08:00 a.m. within 24 hours of hospital admission were analyzed.

Results: Anemia was significantly associated with higher anxiety level at admission and lower improvement of anxiety at discharge in females independently of cholesterol level. Negative effects of anemia on depression severity was found only in females with cholesterol > 5 mmol/L. Contrary to our expectations, subgroup of females with cholesterol ≤ 5 mmol/L showed the opposite trend, i.e. anemia was associated with lower HDRS at both assessments in comparison with controls. Moreover, in young females (age < 40 years; n=250) hemoglobin positively correlated with BDI, HDRS and state anxiety scores. Only 3.6% of males showed anemia, so the data were inconsistent. Low cholesterol was nearly significantly associated with more severe anxiety in three patient subgroups: females with normal hemoglobin, females with anemia, and males. Contrary to our expectations, decreased cholesterol was associated with better improvement of HDRS in males.

Conclusion: Anemia and cholesterol level are independently associated with the severity of negative affectivity. However, the direction of these associations may differ according to the age and, perhaps, length of the hyperactivation of stress response systems.

Keywords: Hemoglobin; Cholesterol; Mood Disorder; Serum Lipids; Stress

Introduction

Depression and anxiety are multifactorial neuropsychiatric conditions characterized by intensive negative emotionality along with autonomic and neuroendocrine dysfunction. Overall, depression and anxiety are characterized by hyperactivation of neural mechanisms of stress response [1,2]. A hallmark of the stress response is the activation of the autonomic nervous system and hypothalamo-pituitary-adrenal (HPA) axis [3-5]. Chronic hyperactivation of HPA axis is now recognized as the most important pathway of pathological consequences of prolonged depression and anxiety conditions [4-6].

Multiple studies demonstrated a range of neurochemical abnormalities in patients with depressive and anxiety disorders [3,7]. Both low hemoglobin and low cholesterol were consistently demonstrated to be associated with depression. The majority of studies in this field addressed only one of these blood components, and it is unclear if the same factors as undernutrition,malabsorption, hemodilution, inflammation, neurotrophic abnormalities, etc., underlie association between depression and anemia, and depression and low cholesterol. Indeed, we found only two studies, which reported both cholesterol and hemoglobin level in depressive patients [8,9]. The patient groups were characterized by lower total cholesterol and lower hematocrit/hemoglobin in comparison with controls in both studies. Multivariate analysis revealed independent effects of anemia and cholesterol on depression severity in the study of [9].

Significant association between anemia and depression was demonstrated in general populations [10-13] and medical patients [14-16]. Onder and colleagues [10] found the association between anemia and depression to be progressively increasing with increasing depression severity. Importantly, Steptoe and colleagues [13] found significant effect of anemia on both somatic and cognitive symptoms of depression. When the authors omitted fatigue item from the analysis, the Beck Depression Score was still significantly larger in anemic patients in comparison with controls.

Significant association between depression and low cholesterol was shown in multiple studies [8,17-21], nevertheless, negative findings in this field [17,22] were also reported. Moreover, elevated total cholesterol was found to be associated with severe depression and treatment-resistant depression in few studies [17,23,24]. Interestingly, antidepressant treatment increases cholesterol level in depressive patients [17-25].

Association between low cholesterol and depression was reported in males [18] and females [20,26]. Giltay and colleagues [20] reported for every increase in serum total cholesterol of 1 mmol/L there was a decrease of -0.61 in Zung Depression Scale index score.

Association between low cholesterol and suicide was consistently demonstrated [27-30]. In the study of Perez-Rodriguez and colleagues [27] the odds ratios in females were 1.8 and in males 2.0 in the hypothesized direction, i.e. low cholesterol was associated with high risk of suicide. Negative findings in this field, i.e. absence of significant associations between suicide and low cholesterol were reported as well [30,31].

Most of the above cited publications concerning association anemia/depression or cholesterol/depression did not evaluate anxiety symptoms. Papakostas and colleagues [17] in their review summarized the results of eight studies of anxiety effects on cholesterol published since 1989 to 2002. The authors concluded that all studies in this field found higher cholesterol in patients with anxiety disorder in comparison with controls. At the same time, Jendricko and colleagues [32] did not find significant differences in lipid profile between patients with posttraumatic stress disorder and controls. Pistorio et al. [33] reported significantly higher triglycerides, but not cholesterol levels in patients with pure anxiety disorders, whereas patients with anxious-depressive disorder were characterized by lower cholesterol and higher triglycerides in comparison with controls.

In the present retrospective study we analyzed the data from the database of Moscow Research and Clinical Center for Neuropsychiatry of the Healthcare Department, which included psychiatric scales and blood samples of in-patients admitted since January 2012 till July 2013. The aim of the study was to evaluate effects of moderate anemia (Hb >100 g/L) and cholesterol level on treatment outcomes in patients with depression or anxiety disorders. In order to determine if the effects of two blood components are interrelated or independent, we analyzed patients with anemia and low cholesterol separately from patient population with normal hemoglobin and elevated cholesterol level. Both threshold and linear relationships were analyzed.

Methods

The Sample and Settings

Moscow Research and Clinical Center for Neuropsychiatry of the Healthcare Department (formerly the Clinic of Neuroses named after Z.P. Solovyov) includes in-patient units for treatment of non-psychotic psychiatric conditions. The vast majority of patients are admitted due to depressive episodes, maladaptive anxiety, prominent asthenia or grief reactions. Absence of severe somatic disturbances are important criteria for hospitalization to the psychiatric center as no caregiver services or intensive care utilities are available. Treatment options include attendance of psychiatrist, psychotropic medications (antidepressants, anxiolytics, hypnotics, neuroleptics); nootropic and vasoactive drugs, psychological consulting and psychotherapy, kinesiothera-

-py, a range of physical therapy options (contrast bath, electrophoresis, reflexotherapy, etc.).

At admission and before discharge all patients are interviewed by the psychiatrist with a rating on the Hamilton Depression Rating Scale. At the same time points patients are asked to fulfill the Beck Depression Inventory and Spielberger State-Trait Anxiety Scale. In addition, all patients undergo basic medical examination which includes physical and neurologic examination, full blood count test, and electrocardiography. Routine blood tests, evaluating total cholesterol, liver and kidney functions, glucose level, etc., are conducted in about one third of patients. Elderly patients and patients with somatic and neurological complain undergo medical examinations, including x-Ray and ultrasound examination, hormonal profile, and other tests.

The data concerning patient psychiatric and medical examinations are registered in electronic database. Here we present analysis of the data derived from this electronic database.

Psychiatric Assessment

The diagnostics of diseases in Russian Federation is based on the 10-th revision of the International Statistical Classification of Diseases and Related Health Problems (ICD-10). Therefore, diagnoses of patients with depressive episode included 9 diagnostic categories (F31.3, F31.4, F32.0, F32.1, F32.2, F32.3, F33.1, F33.2, and F06.3), and diagnoses of patients with pure anxiety disorders included 5 diagnostic categories (F40.8, F40.9, F41.0, F41.1, F06.4) with predominance of panic disorder and generalized anxiety disorder in our patient population. Other common diagnoses in our patient sample were mixed anxiety and depressive disorder (F41.2) and somatoform disorder (F45.0 – F45.4) with predominance of hypochondrial disorder (F45.2). Finally, patients with several different non-psychotic psychiatric conditions (F06.5, F06.6, F07.0, F21, F31.6, F42, F43, F50, F60) constituted about 10% of our patient population. Many patients in this subgroup were characterized by high depression and anxiety scores on psychiatric scales at admission, and therefore we included this subgroup into the analysis.

Overall, the diagnostic classification was quite complex in our patient sample. Moreover, many patients had several diagnoses (e.g., depressive episode and somatoform disorder), however, only the first of these diagnoses was available in our electronic database. This situation could underlie some distortions in the distribution of diagnostic categories in our patient population (e.g., high prevalence of somatoform disorder in male population in comparison with females, as the latter were more probable to have both depressive episode and somatoform disorder diagnoses). Absence of patients with bipolar disorder in our patient population is typical for Russia, where this diagnosis is made quite rarely due to under diagnosis of manic episodes and perhaps real low frequency of mania (possible reasons: northern climate and highly stressful lifestyle). Therefore, we preferred to analyze anemia and cholesterol effects on quantitative scores on psychiatric scales rather than follow diagnostic categories.

Depression was evaluated by 21-item Hamilton Depression Rating Scale (HDRS) and self-reported Beck Depression Inventory (BDI), and anxiety was assessed by Spielberger State-Trait Anxiety Scale. Russian versions of these scales were derived from Belova and Shepetova [34]. All four scales were fulfilled twice, i.e. at admission and at discharge.

Blood Measurements

Venous blood samples were drawn from the antecubital vein at 08:00 a.m. after an overnight fast and within 24 hours of hospital admission. Hemoglobin and cells blood count were determined using LH-500 electronic counter (Beckman Coulter, USA). Total cholesterol measurements were carried out enzymatically with Random Access Automatic analyzer A-25 (BioSystems, Spain).

Only patients with hemoglobin > 100 g/L were included into the study in order to exclude cases with undiagnosed cancer or other severe somatic diseases, which could contribute to depression symptoms. Anemia was defined according to the World Health Organization criteria with hemoglobin (Hb) threshold of less than 120 g/L (<7.5 mmol/L) for women and less than 130 g/L (<8.1 mmol/L) for men [35].

As no conventional definition of hypocholesterolemia exist, we tested threshold of cholesterol to be less than 3, 4 or 5 mmol/L. No significant differences in depression and anxiety levels were found between patient groups "cholesterol < 3 mmol/L", "cholesterol 3.1-4.0 mmol/L" and "cholesterol 4.1-5.0 mmol/L". At the same time, females with cholesterol < 5 mmol/L and males with cholesterol < 4 mmol/L differed significantly on anxiety scores from patients with higher total cholesterol (see 'Results' section). Therefore, we have chosen 5 mmol/L for females and 4 mmol/L for males as thresholds for hypocholesterolemia in the present analysis.

Statistical Analysis

Analysis of the data was performed using SPSS software for windows (SPSS 17.0, Chicago, IL, USA). We conducted both parametric and nonparametric analyses of intergroup differences in psychiatric characteristics. Repeated measures ANCOVAs with anemia or cholesterol status as a fixed factor and age as a covariate were used for evaluation of dynamics of psychiatric variables in different patient subpopulations. In addition, Mann-Whitney test was conducted for confirmation of ANCOVAs findings by non-

parametric method. Linear associations were evaluated by Spearman's correlation tests.

Results

Patient Characteristics and Treatment Outcomes

Demographic and baseline clinical patient characteristics are summarized in table 1. Overall, data of 1937 patients were included into the analysis. Female population (n=1411) was in average 6 years older, and was characterized by significantly higher frequency and larger severity of depressive disorder in comparison with males (n=526). In addition, hemoglobin was significantly lower and cholesterol was significantly higher in female population in comparison with males. Therefore, we analyzed data of female and male populations separately.

Middle-aged patients constituted the majority of our patient population, however, the age varied considerably (females: 18 – 84 years; males: 17 – 85 years). In females, age significantly and positively correlated with BDI, HDRS and state anxiety at discharge (Rs=0.08–0.13, ps<0.01),

Table 1. Demographic and clinical characteristics of female and male patients

Demographic and clinical characteristics	Females	Males
Number of patients	1411	526
Age, years	**53.9±14.4 ****	**48.1±16.3**
Social status, number (%) of patients		
Employed	**407 (28.8%) ****	**200 (38.0%)**
Unemployed	**291 (20.6%)**	**142 (27.0%)**
Retired	**539 (38.2%)**	**114 (21.7%)**
Student	**25 (1.8%)**	**29 (5.5%)**
No information	**149 (10.6%)**	**37 (7.0%)**
Marital status, number (%) of patients		
Divorced, widowed	**587 (41.6%) ****	**295 (56.1%)**
Married	**381 (27.0%)**	**113 (21.5%)**
Single	**281 (19.9%)**	**78 (14.8%)**
No information	**162 (11.5%)**	**40 (7.6%)**
Primary diagnosis		
Depressive episode	**520 (36.9%) ****	**156 (29.7%)**
Mixed anxiety and depressive disorder	**507 (35.9%)**	**112 (21.3%)**
Anxiety disorder	**121 (8.6%)**	**63 (12.0%)**
Somatoform disorder	**137 (9.7%)**	**127 (24.1%)**
Other psychiatric condition	**126 (8.9%)**	**68 (12.9%)**
Psychiatric scales		
Hamilton Depression Scale	**17.6±5.3 ***	**17.1±5.5**
Beck Depression Scale	**20.2±8.8 ****	**18.5±9.6**
Spielberger Trait Anxiety	**53.0±9.4 ***	**52.0±9.6**
Spielberger State Anxiety	54.5±10.5	54.0±11.0
Blood tests		
Hemoglobin level, g/L	**135.4±10.3 ****	**152.3±12.3**
White blood cells, 10^3 per μL	**6.17±1.68 ****	**6.76±1.76**
Platelets, 10^3 per μL	**238±57 ****	**216±51**
Cholesterol level, mmol/L	**5.8±1.3 ****	**5.3±1.2**

*** t-test: p ≤ 0.05**

**** t-test or χ^2-test: p < 0.001**

hemoglobin (R=0.06, p=0.027) and cholesterol concentration (R=0.39, p<0.001). In males, age significantly and positively correlated only with cholesterol (R=0.27, p<0.001), whereas, significant correlation between age and hemoglobin (R=-0.26, p<0.001), and age and trait anxiety at admission (R=-0.09, p<0.05) were negative. Therefore, all analyses of associations between depression and blood variables included age as a covariate.

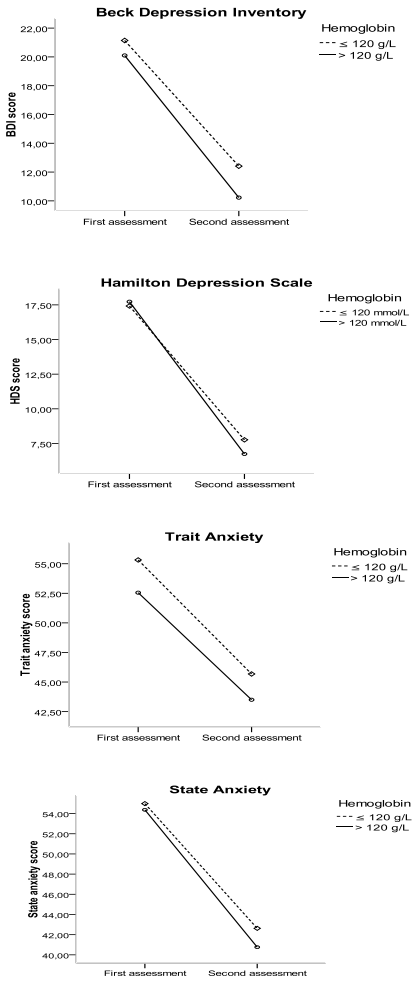
Both female and male populations showed prominent improvement at discharge in comparison with the primary assessment on all psychiatric scales, including trait anxiety scale (Fs=50 – 417, ps<0.001).

Hemoglobin Effects on Depression and Anxiety

Female patients

We analyzed effects of hemoglobin on the severity of depression and anxiety and treatment outcomes separately in female subgroup with cholesterol > 5 mmol/L (n=1016) and subgroup with cholesterol ≤ 5 mmol/L (n=395).

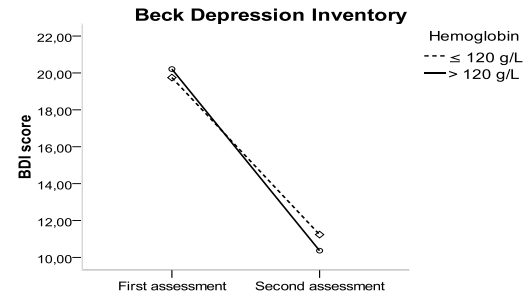
Figure 1: Effects of moderate anemia on depression and anxiety in female patients with high total cholesterol level (> 5 mmol/L). Anemic patients showed significantly higher trait anxiety at both assessments (F=5.36, p=0.021) with the similar trend for BDI score (F=3.35, p=0.068) in comparison with controls. The decrease of HDRS score at discharge was significantly smaller in anemic females compared to controls.

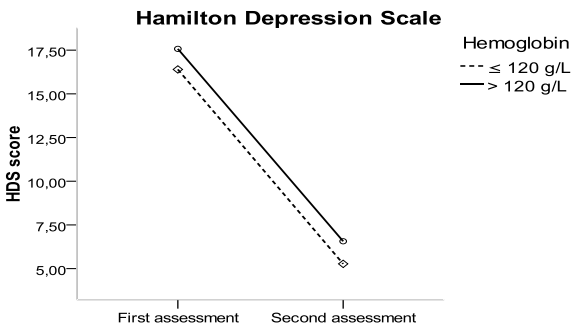


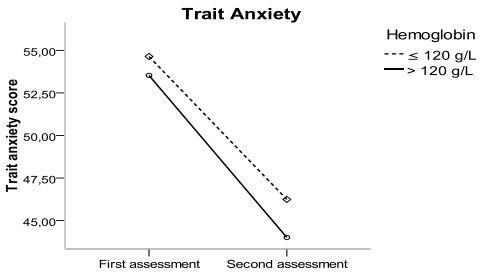
Seventy two (7%) females in high cholesterol subgroup were characterized by hemoglobin level ranging from 104 to 120 g/L (average hemoglobin: 114.3±4.8 g/L). The hemoglobin level in control group (n=944) varied from 121 to 173 g/L (average hemoglobin: 137.9±8.5 g/L).

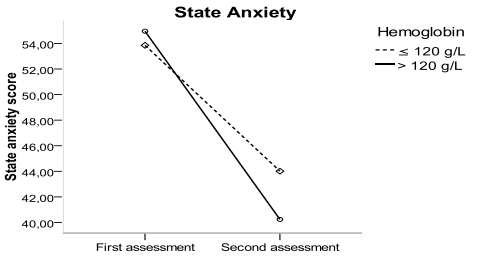
Females with anemia and high cholesterol tended to show higher BDI score at both assessments (Figure 1; F=3.35, p=0.068) in comparison with controls. Although, hemoglobin was not related to HDRS score before treatment, the positive dynamics of HDRS score after treatment was more prominent in patients with normal hemoglobin in comparison with anemic patients (F=3.90, p=0.049). Trait anxiety score was higher in anemic patients at both assessments (F=5.36, p=0.021), whereas no significant effects of anemia on state anxiety was found in patients with high cholesterol level. Non-parametric analysis confirmed significant intergroup difference in trait anxiety at first assessment (z=2.26, p=0.024); BDI score (z=2.64, p=0.008) at second assessment; and changes of BDI and HDRS scores (zs=2.46 and 2.30, ps=0.014 and 0.021, respectively). Forty three (10.9%) females with low cholesterol were characterized by moderate anemia (mean hemoglobin: 111.1±9.0 g/L versus 135.6±7.9 g/L in controls). There was a non-significant trend for patients with anemia to demonstrate less prominent dynamics of BDI score in comparison with the controls (F=1.17, p=0.28). Unexpectedly, patients with anemia demonstrated significantly lower depression level according to HDRS at both assessments (Figure 2; F=3.94, p=0.048).

Figure 2. Effects of moderate anemia on depression and anxiety in female patients with low total cholesterol level (≤ 5 mmol/L). Anemic patients showed significantly lower HDRS score at both assessments (F=3.94, p=0.048) and significantly less prominent improvement of state anxiety (F=6.48, p=0.011) in comparison with controls.





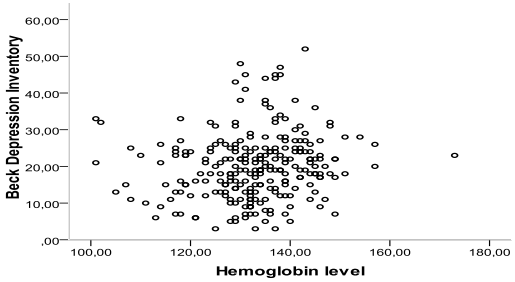


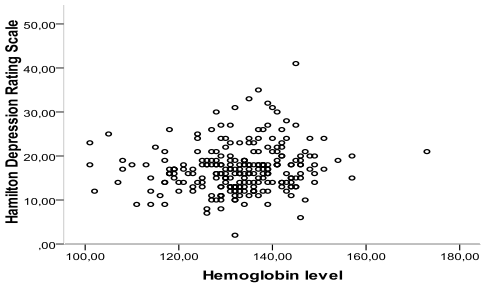


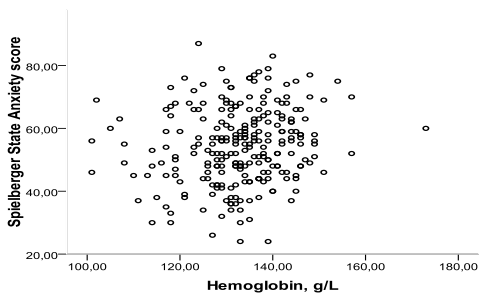
Non-parametric tests confirmed intergroup differences of HDRS at first and second assessments (zs=1.97 and 2.28, ps=0.048 and 0.023, respectively), and changes of state anxiety and HDRS score (zs=2.03 and 2.08, ps=0.042 and 0.038, respectively).

Post-hoc correlative analysis did not show any liner relationship between hemoglobin level and psychological scales in either subgroup of female patients.

Figure 3. Positive correlations between hemoglobin level and baseline (A) BDI (R=0.17, p=0.008), (B) HDRS (R=0.15, p=0.020) and (C) state anxiety (R=0.17, p=0.007) scores in young females (age<40 years old).







Interestingly, in young females (age < 40 years; n=250) hemoglobin significantly and positively correlated with BDI (R=0.17, p=0.008), HDRS (R=0.15, p=0.020) and state anxiety (R=0.17, p=0.007) scores (Figure 3).

Male patients

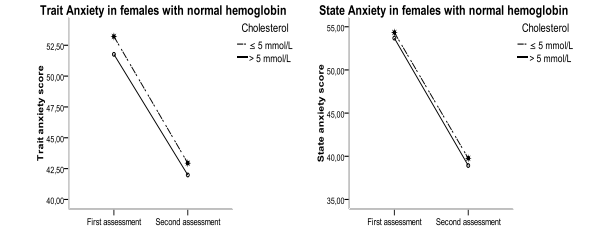
Only nineteen males (3.6%) were characterized by moderate anemia. No significant effects of anemia on either severity of emotional disturbances or treatment outcomes were found in male population. Non-parametric tests did not find significant intergroup differences in emotional variables according to hemoglobin level. No significant linear associations between psychiatric variables and hemoglobin level were found in any male patient subgroup.

Cholesterol Effects on Depression and Anxiety

Female patients

We analyzed effects of cholesterol on the severity of depression and anxiety and treatment outcomes separately in female subgroup with hemoglobin level > 120 g/L (n=1383) and subgroup with hemoglobin ≤ 120 g/L (n=136).

Figure 4. Effects of low cholesterol on anxiety in three patient subpopulations: (A) females with normal hemoglobin (trait anxiety: F=3.71, p=0.054); (B) females with anemia (trait anxiety: F=4.21, p=0.042); and (C) males (state anxiety: F=3.81, p=0.051).



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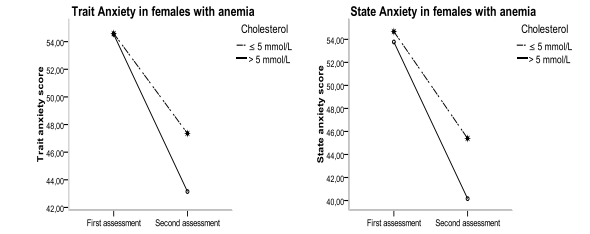

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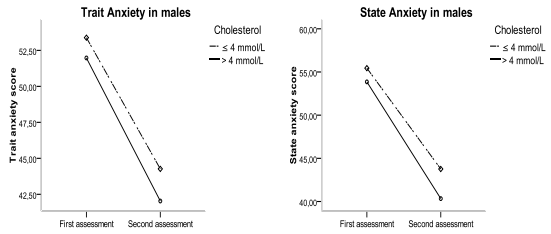


C.

Three hundred and seventy three (27%) female patients of normal hemoglobin subgroup were characterized by cholesterol level ranging from 2.8 to 5.0 mmol/L (average cholesterol: 4.41 ± 0.49 mmol/L). The cholesterol level in control group (n=1010) varied from 5.1 to 11.0 mmol/L (average cholesterol: 6.39 ± 0.99 g/L).

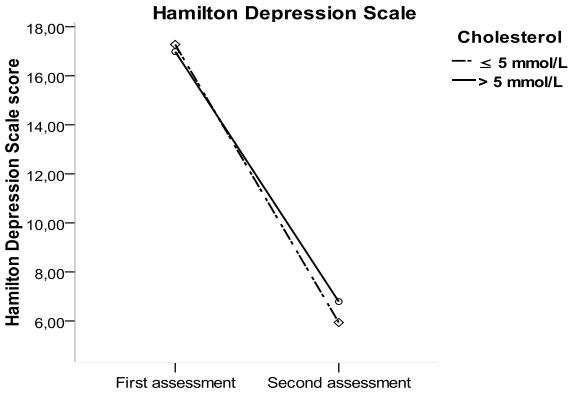
There was a near significant trend for association between low cholesterol level and high trait anxiety at both assessments in females with normal hemoglobin level (Figure 4A; F=3.71, p=0.054). Non-parametric tests confirmed intergroup differences on trait anxiety at first assessment with higher anxiety in low cholesterol group (z=2.25, p=0.024). No significant effects of cholesterol level on depression or state anxiety were found. No linear associations between cholesterol and psychological variables in females with high cholesterol and normal hemoglobin were found.

Fifty one (37.5%) females with anemia were characterized by low cholesterol level (mean cholesterol: 4.36±0.51 mmol/L versus 6.42±1.11 mmol/L in controls). This subgroup of female patients differed significantly from females with anemia and high cholesterol by significantly less prominent improvement of trait anxiety at the second assessment in comparison with anemic females with high cholesterol (Figure 4B; F=4.21, p=0.042). In addition, state anxiety tended to be significantly higher at both assessments (F=2.99, p=0.086) with the trend for less prominent improvement of state anxiety (F=3.25, p=0.073) in females with anemia and low cholesterol level in comparison with high cholesterol subgroup. Non-parametric tests did not confirm significant intergroup differences, there was only a non-significant trend for intergroup differences on the magnitude of decline of state anxiety (z=1.52, p=0.13).

Male patients

We excluded males with hemoglobin ≤ 130 g/L (n=19) from further analysis of cholesterol effects.

Figure 5. Males with lower cholesterol showed higher improvement on HDRS at discharge in comparison with the subgroup with higher cholesterol (F=5.11, p=0.024).



When males were divided into groups with cholesterol level threshold 5 mmol/L, 42.6% (n=214) of patients constituted 'low' cholesterol group (mean cholesterol – 4.27±0.57 mmol/L versus 6.11±0.85 mmol/L in controls). In this set of analyses no significant effects of cholesterol on BDI, trait and state anxiety were found (with a non-significant trend for higher trait anxiety in 'low' cholesterol group at both assessments: p=0.13). Contrary to our expectations, changes of depression according to HDRS was significantly more prominent in patients with 'low' cholesterol in comparison with the control group (F=5.11, p=0.024; Figure 5). Mann-Whitney tests confirmed significant intergroup differences in the HDRS score at the second assessment (z=2.03, p=0.043) and in decline on HDRS score (z=2.60, p=0.009) with a trend for higher trait anxiety at the second assessment in patients with 'low' cholesterol (z=1.95, p=0.051).

As we found the liner inverse correlation (R=-0.18, p=0.009) between cholesterol level and situational anxiety in patients with cholesterol ≤ 5 mmol/L, we reanalyzed the data with cholesterol level threshold – 4 mmol/L (low cholesterol group: n=66 [13%]; mean cholesterol – 3.57±0.58 mmol/L versus 5.59±1.02 mmol/L in controls). At this set of analyses, we did not observe significant effects of cholesterol level on either Hamilton Depression Scale score or BDI (ps>0.44). At the same time, there was a nearly significant trend for state anxiety to be significantly higher in patients with low cholesterol in comparison with high cholesterol group (Figure 4C; F=3.81, p=0.051) with the similar trend for trait anxiety (F=2.35, p=0.13).

Discussion

The present results evidence that anemia and cholesterol are independent predictors of treatment outcomes in patients with depression and anxiety. We confirmed the previous findings of association between anemia and higher depression in female patients. Moreover, patients with hemoglobin ≤ 100 g/L were not included into the present study, and moderate anemia was still associated with elevated depression and anxiety levels and less improvement at discharge in comparison with controls.

In contrast to the majority of previous studies, we found stronger effects of low cholesterol on anxiety than on depression in both female and male patients. The majority of intergroup differences were more prominent at discharge in comparison with baseline assessment.

Importantly, we found unexpected positive associations between depression/anxiety and hemoglobin or cholesterol level in young females and males. In the subgroup of young females positive linear association between hemoglobin and depression and state anxiety was observed. Males with higher cholesterol showed less prominent improvement on HDRS in comparison with controls, whereas opposite trend was observed for both anxiety scales.

This discrepancy may be explained by differences in the characteristics of patient populations. Overall, our patient sample was in average 20–25 years younger in comparison with patient populations in the majority of previous studies of hemoglobin effects on depression, as previous studies included only patients older than 65 years [10-13,20]. It may be suggested, that age may modulate association between hemoglobin and depression.

Depressive episodes in our patient population were moderate in 98% of cases, coded as F32 or F33 according to ICD-10, and therefore only small proportion of them might be designated as 'major depression' according to DSM-IV criteria. Hence, our patient population was younger, more anxious and less depressive in comparison with the most patient samples, reported in the previous publications.

Depression and anxiety are closely interrelated conditions, which are commorbid and recurrent in the majority of adult patients [6,36,37]. Anxiety disorder or depressive episode may manifest at any age, however, in pediatric and young adult populations anxiety is more prevalent in comparison with elderly samples [6,38]. Moreover, the spectrum and severity of anxiety symptoms is different in young and elderly populations [38] Commonly, pure anxiety disorder precedes depressive disorder in the same patient [6,36], whereas, inverse consequence, i.e. major depression preceding anxiety disorder, is less frequent [6,36].

Interpretation of the discrepancy between overall negative association between anemia/cholesterol and depression/anxiety in our general sample and positive correlation between these psychiatric and hematological variables in younger patient subgroups is possible in the framework of the concepts of stress response and allostatic load [3,5]. Hans Selye [3] proposed that stress response includes three stages: (1) alarm stage with dramatically increased activity of the hypothalamic-pituitary-adrenal (HPA) axis; (2) resistance stage with steady biological responses to the stressor and reduction or disappearance of overt symptoms of stress; (3) exhaustion stage with depletion of physiological defenses. Allostatic load conception states that exposure to stressors induces the new balance of system parameters, which are helpful in the short term, but may have negative long-term consequences for the organism [22]. When stress is repeated and chronic, allostatic load can occur through exhaustion of stress response systems. Overall, stress response is not static: rather it changes over time as a function of the life history of an individual [4,5].

It may be suggested that increased erythropoiesis and cholesterol synthesis are components of normal stress response, and therefore our young female patients demonstrated logical positive association between higher psychological distress symptoms and higher hemoglo-

demonstrated logical positive association between higher psychological distress symptoms and higher hemoglobin and cholesterol concentration. It should be noted that cholesterol and hemoglobin concentrations demonstrated positive correlations with age, and therefore our 'low cholesterol' female subgroup was younger in comparison with 'high cholesterol' subgroup. And contrary to our expectations, young females with low cholesterol and high hemoglobin showed higher depression in comparison with females with low cholesterol and low hemoglobin. In male sample, subjects with higher cholesterol showed higher HDRS in comparison with subjects with lower cholesterol as well.

Interpretation of our data in the context of the concepts of stress response and allostasis leads to the logical conclusion, that depletion of cholesterol level (? exhaustion of cholesterol synthesis system) happens earlier in comparison with exhaustion of erythropoiesis, as the former phenomenon was equally presented in three roups of patients with elevated anxiety, whereas association between anemia depression was characteristic predominantly for middle-aged and elderly females [38]. It should be noted, that previous studies reported significant association between anemia and depression predominantly in elderly populations [13-13,20], whereas depleted cholesterol was demonstrated in middle-aged depressive patients [40,42,58].

Elevated total cholesterol was reported in the youngest patient cohorts with pure anxiety disorders [7,39]. In the study of Peter and colleagues [40] total cholesterol level was significantly higher in patients with anxiety disorder (mean age 35.4±9.6 years) in comparison with healthy controls. Igna and colleagues [41] found significant positive correlation between the Beck Depression Inventory score and high density lipoprotein cholesterol in healthy males aged 45–55 years. In the study of van Reedt Dortland and colleagues [42] young patients (average age 41.7 years) with atypical depression showed elevated total cholesterol as well.

Severity and length of anxiety and depressive disorder is an important factor as well. Two studies showed that patients with comorbid anxiety and depression were characterized by significantly lower cholesterol in comparison with patients with pure anxiety disorder [33,43]. Lehto and colleagues [44] observed decreased HDL cholesterol only in patients with major depression length > 3 years, whereas patients with shorter depression duration did not differ from controls. Van Reedt Dortland et al. [42] observed decreased HDL cholesterol only in patients with melancholic type of depression.

Alternative explanation of association between depression/anxiety and hemoglobin/cholesterol is nutritional deficits or malabsorption with direct depressive effects of anemia and hypocholesterolemia on brain. Indeed, iron deficiency and low vitamin B12 were consistently demonstrated in depressive patients in a range of studies [13,21,45-49]. Negative findings were reported as well [3,44]. Positive effects of iron and vitamin supplementation on depression symptoms were shown in several studies with the largest improvement of fatigue and vitality [13,50-52], however, systematic research in this field is absent.

Overall, homeostatic processes are disturbed in depressive patients, and improvement of iron and vitamin status in these patients appear to be of benefit. Nevertheless, our data may not be explained by malnutrition as a causal factor inducing depression in our patient population. Interestingly, Onder and colleagues [10] observed significant association between anemia and depression after exclusion patients with iron deficiency or vitamin B12 deficiency from the analysis (OR=1.96).

Three possible pathophysiological pathways of direct involvement of cholesterol into brain dysfunction are discussed in the publications concerning association between cholesterol level and depression. First, brain is the most cholesterol-rich organ, and cholesterol is an essential component of myelin and plasma membranes of neurons and astrocytes [53], therefore it may be hypothesized that decreased cholesterol concentration may adversely affect neurotrophic and neuroplastic processes in brain. Second, experimental studies showed that cholesterol was stabilizes signaling of GABA-A, serotoninergic [17] and mu-opioid receptors [54], and this is perhaps another pathway of altered GABA, serotoninergic and opioid activity in depressive subjects. Third, cholesterol is a source for synthesis of neuroactive steroid hormones, which are shown to be implicated into the pathophysiology of depression [55]. Further research is needed in order to determine if some treatment of hypocholesterolemia may be of benefit for patients with mood and anxiety disorders.

Our retrospective study had a range of limitations. First, the available clinical diagnoses of psychiatric disorders in our patient population were imperfect, and therefore we preferred to use the quantitative psychiatric scales. Although, the psychiatrists managing patients undertook special training for using these scales, it could be insufficient for optimal assessment of depression and anxiety in our patient population. This limitation is especially important for the Hamilton Depression Rating Scale, as this scale is a physician-rated one.

The second important limitation of the study was the absence of the data concerning iron and vitamin status in our patient cohort, because these laboratory probes are not undertaken routinely in our medical center. Including these data into the future studies would be important in order to differentiate stress and nutrition effects on the association between negative affectivity and anemia.

differentiate stress and nutrition effects on the association between negative affectivity and anemia.

The similar limitation concerns the cholesterol effects on negative affectivity. Cholesterol fractions were not evaluated in the present patient cohort, however, the previous studies showed differential effects of depression on high and low density cholesterol fractions with predominant decrease of high density cholesterol fraction and a trend for an increase of low density cholesterol fraction [42,44,46,50,55-62]. These discrepancies may explain opposite effects of the total cholesterol on the anxiety and depression in our male cohort. Future studies including cholesterol fractions are needed.

Conclusion

The present results showed that moderate anemia (hemoglobin 101-120g/L) and low cholesterol (total cholesterol ≤5mmol/L) predicted outcomes of treatment of depression and anxiety in females independently, i.e. treatment outcomes were overall better in females with normal hemoglobin and cholesterol. Contrary to our expectations, young females (≤40 years) showed positive linear correlation between hemoglobin and baseline depression/anxiety, i.e. severe depression/anxiety was associated with elevated hemoglobin. In males low cholesterol was associated with overall higher anxiety level and better depression dynamics at discharge. Our data may be explained using the concepts of stress response shifts in physiological functioning and allostatic load rather than some nutritional concept. It seems probable that younger subjects with depression and anxiety tend to mobilize erythropoiesis and cholesterol synthesis, whereas the same processes in older patients with depression and anxiety are exhausted.

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