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THE IMPACT OF ELEVATED HOMOCYSTEINE LEVELS ON THE DEVELOPMENT OF STRESS-ASSOCIATED ANXIETY AND DEPRESSIVE DISORDERS

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Methods. A prospective observational study included 131 adults (mean age 43.35 ± 16.37 years; 54.2 % women). Anxiety and depression were assessed using the GAD-7 and PHQ-9 scales. Homocysteine levels were quantified by LC-MS. Group comparisons and odds ratios (OR, 95 % CI) were calculated; $p < 0.05$ was considered statistically significant.

Results. Elevated homocysteine levels (≥ 10 μmol/L) were detected in 50.4 % of participants, while concentrations > 15 μmol/L were observed in 11.5 %. Homocysteine levels were approximately two-fold higher in individuals with clinically significant symptoms compared with those with subclinical manifestations (anxiety: 13.98 ± 4.50 vs 6.88 ± 2.08; depression: 13.92 ± 4.43 vs 6.87 ± 2.05; $p < 0.001$). Homocysteine ≥ 10 μmol/L was strongly associated with clinically significant anxiety (OR = 157.5; 95 % CI 33.4–741.6; $p < 0.001$) and depression (OR = 320.0; 95 % CI 40.0–2557.8; $p < 0.001$).

Conclusions. Hyperhomocysteinemia was common among individuals exposed to prolonged war-related stress and closely associated with the severity of anxiety and depression. Elevated homocysteine levels were identified in 50.4 % of the examined participants with ADDs, indicating a high prevalence of disturbances in one-carbon metabolism. A dose-dependent relationship between homocysteine concentration and ADDs severity was observed. Increased homocysteine levels were associated with a higher probability of clinically significant anxiety (58 %) and depressive disorders (64 %). These findings support the pathogenetic role of hyperhomocysteinemia in stress-associated ADDs and justify the use of homocysteine as a biomarker of risk, severity, and prognosis of anxiety-phobic and affective disorders.

Keywords: homocysteine, stress-associated disorders, anxiety depression, methylation, one-carbon metabolism.

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ВПЛИВ ПІДВИЩЕНОГО РІВНЯ ГОМОЦИСТЕЇНУ НА РОЗВИТОК СТРЕС-АСОЦІЙОВАНИХ ТРИВОЖНИХ ТА ДЕПРЕСИВНИХ РОЗЛАДІВ

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У дослідженні виявлено високу поширеність порушень одновуглецевого метаболізму серед осіб, які тривалий час перебували в умовах воєнного психотравмувального стресу. Підвищений рівень гомоцистеїну (≥ 10 мкмоль/л) виявлено у 50,4 % обстежених, що свідчить про метаболічну вразливість до тривожно-депресивних розладів (ТДР). Встановлено дозозалежний зв'язок між концентрацією гомоцистеїну та вираженістю ТДР. у пацієнтів із клінічно значущими симптомами тривоги та депресії його рівень становив близько 14 мкмоль/л, що майже вдвічі перевищувало показники осіб із субклінічними проявами (6,9 мкмоль/л). Підвищений гомоцистеїн був пов'язаний зі зростанням ризику клінічно значущої тривоги та депресії, підтверджуючи його патогенетичну роль і доцільність використання як біомаркера ризику та тяжкості ТДР.

Ключові слова: гомоцистеїн, стрес-асоційовані розлади, тривожно-депресивні розлади, метилювання, одно-вуглецевий метаболізм.

Introduction

Anxiety-depressive disorders (ADDs) are among the most common mental disorders today and constitute one of the leading medical and social problems worldwide [1]. In Ukraine, the urgency of this problem has become particularly acute due to the full-scale war, which is accompanied by the prolonged impact of extreme stressors, including direct threats to life, the loss of loved ones, forced displacement, socioeconomic instability, and psychological uncertainty [2]. According to international epidemiological studies, in populations exposed to armed conflict, the prevalence of anxiety and depressive disorders increases by 2–3 times compared to peacetime conditions, and their course is often characterized by chronicity and reduced response to standard therapy [3].

Homocysteine is a sulfur-containing amino acid formed during methionine metabolism and is a key component of one-carbon metabolism [4]. Its remethylation to methionine occurs with the participation of the enzyme methylenetetrahydrofolate reductase (MTHFR) and depends on an adequate supply of folic acid and vitamin B_{12} [5]. Impaired remethylation, as well as common MTHFR genetic polymorphisms, are associated with elevated homocysteine levels [6]. Homocysteine accumulation is considered a potentially neurotoxic factor and is associated with the development of a range of neurological and psychiatric disorders, including depression, anxiety, schizophrenia, cognitive impairments, and neurodegenerative diseases [7].

In addition, homocysteine can disrupt the biosynthesis of neurotransmitters. In the 5-methyltetrahydrofolate cycle, S-adenosylmethionine (SAM) – which is a methyl group donor and a precursor for the synthesis of serotonin, melatonin, norepinephrine, and dopamine – is demethylated to S-adenosylhomocysteine (SAH), and further to homocysteine, which is normally converted back to SAM [8].

Research findings also confirm the link between homocysteine and depression. It has been shown that low folate levels are a predictor of poor response to antidepressant therapy, as well as an increased risk of depression relapse [9]. The use of folic acid and/or vitamin B_{12} in patients with elevated homocysteine levels, compared to a placebo in healthy elderly individuals, resulted in a statistically significant reduction in serum homocysteine concentrations [10], but was not accompanied by an improvement in cognitive function [11] or a reduction in depressive symptoms [9].

At the same time, in clinical studies involving patients with depression, the use of folic acid and/or vitamin B_{12}, including as adjunctive therapy to antidepressants, has been associated in several studies with a reduction in the severity of depressive symptoms [12; 13]. A more pronounced reduction in symptoms was observed in patients with depression who had MTHFR gene polymorphisms [14]. In one study, the addition of folates and/or vitamin B_{12} to antidepressant therapy after remission was associated with a reduced risk of depression recurrence [15].

Despite the availability of a significant amount of data indicating a link between hyperhomocysteinemia and depression, research findings in this area remain inconsistent [16; 17]. Such variability in results may be due to differences in dietary habits, use of vitamin supplements, folate levels, as well as genetic, socioeconomic, and family factors that can modify homocysteine concentration and mental status.

Therefore, studying homocysteine levels in patients with ADDs under conditions of psychoemotional distress caused by the war in Ukraine is of particular relevance. Assessing homocysteine levels not only deepens our understanding of the biological mechanisms underlying stress-related disorders but also helps identify biochemical markers of ADDs severity and the risk of relapse. In addition, measuring homocysteine levels may have important prognostic significance regarding sensitivity to antidepressant therapy for ADDs, opening up prospects for a personalized approach to treatment.

Aim of the study. To determine the role of elevated homocysteine levels in the development of stress-associated ADDs and to assess the severity of these disorders in patients experiencing prolonged war-related psychological trauma.

Materials and Methods

This prospective observational study was conducted at the Saint Damian Healer Clinic in Kyiv and the Department of Psychiatry, Psychotherapy, Addiction Medicine, and Medical Psychology at Donetsk National Medical University (DNMU).

The study was conducted in accordance with the principles of bioethics and in compliance with the provisions of the Declaration of Helsinki ("Ethical Principles for Medical Research Involving Human Subjects"), as well as the UNESCO Universal Declaration on Bioethics and Human Rights. Prior to the start of the study, approval was obtained from the DNMU Ethics Committee (Protocol No. 3 dated March 5, 2025). All participants provided written informed consent to participate in the study.

The study included 131 patients who were residents of Ukraine, of whom 71(54.2 %) were women and 60(45.8 %) were men. The mean age of the participants was 43.35 ± 16.37 years, the median was 44 years, with an age range from 18 to 75 years, indicating adequate age representativeness of the sample.

In cases where subclinical symptoms were identified that did not meet the diagnostic criteria for anxiety-phobic and affective disorders according to the International Classification of Diseases, 10th Revision (ICD-10), psychoemotional distress was coded using code Z73.3 (stress, not classified elsewhere). This group included 75 individuals, accounting for 56.4 % of the total number of examinees.

Clinically significant anxiety disorders meeting the diagnostic criteria for mental disorders according to ICD-10 were identified in 56(43.6 %) of the examined individuals. Generalized anxiety disorder (F41.1) was identified in 13 patients (22.8 %), mixed anxiety-depressive disorder (F41.2) in 19 patients (37.3 %), adjustment disorder with anxiety-depressive symptoms (F43.2) in 17 patients (29.8 %), a moderate depressive episode (F32.1) in 5 individuals (10.5 %), and dysthymia (F34.1) in 2 patients (3.5 %).

The study employed a comprehensive approach that included clinical-psychopathological, psychometric, and biochemical-molecular methods, as well as statistical analysis of the obtained data.

Anxiety and depression symptoms were identified using screening psychometric instruments, specifically the Generalized Anxiety Disorder Scale (GAD-7) [18] and the Patient Health Questionnaire (PHQ-9) [19].

The GAD-7 scale was used to quantitatively assess the severity of anxiety symptoms. Each of the 7 items was rated on a 4-point scale with a total score ranging from 0 to 21. A total GAD-7 score of ≥ 10 points was considered a criterion for clinically significant anxiety.

The PHQ-9 mental health questionnaire was used to assess depression. Each of the 9 items was rated on a similar 4-point scale (0–3 points), with a total score ranging from 0 to 27. A total PHQ-9 score of ≥ 10 points was defined as the threshold criterion for clinically significant depressive symptoms.

In the presence of clinically significant indicators of anxiety and depression, the results of the psychometric assessment were used as an auxiliary tool to confirm the nosological classification of mental disorders in combination with a clinical-psychopathological examination method. To confirm anxiety-phobic and affective disorders, the Structured Clinical Interview for DSM-5 Disorders (SCID-5) was used to establish a mental diagnosis in accordance with ICD-10 criteria.

Within the scope of this study, a comprehensive assessment of biochemical markers of one-carbon metabolism was conducted, reflecting the functional state of homocysteine methylation and remethylation processes. The analysis included the determination of several interrelated groups of indicators that characterize the metabolic and epigenetic mechanisms involved in the regulation of neurobiological processes.

Biological samples were collected via blood draw, followed by plasma analysis at accredited laboratory (Genova Diagnostics, USA). Methylation metabolite concentrations were determined using liquid chromatography-mass spectrometry (LC-MS). To assess the efficiency of methylation, homocysteine levels were measured, as homocysteine is considered a key biomarker of one-carbon metabolism disorders and a potential factor in the development of stress-associated ADDs.

Mathematical and statistical analysis was performed using Microsoft Excel 2019 software. Quantitative mathematical changes are presented as the mean (M) and standard deviation (SD). Linear regression analysis was used to analyze independent variables associated with homocysteine levels and indicators of anxiety and depression. To assess the risk of clinically significant anxiety and depression depending on homocysteine levels, odds ratios (OR) were calculated with a 95 % confidence interval (95 % CI). Quantitative indicators were compared between two independent groups using the nonparametric Mann–Whitney U test. A p-value of <0.05 was considered statistically significant.

Research results and their discussion

To comprehensively assess the state of one-carbon metabolism, an analysis of the distribution of serum homocysteine levels was performed. Table 1 presents the main descriptive statistics reflecting the distribution of homocysteine concentrations, the frequency of elevated levels, the prevalence of clinically significant hyperhomocysteinemia among the study participants, as well as the mean homocysteine level in patients with subclinical and clinical anxiety-depressive symptoms.

Table 1

Descriptive characteristics of homocysteine levels among the study participants (n = 131)

Indicator	Value
Mean homocysteine level, μmol/L (M ± SD)	9.89 ± 4.79
Median, μmol/L	10.0
Interquartile range (IQR), μmol/L	7.0–12.0
Minimum value, μmol/L	2.0
Maximum value, μmol/L	39.0
Patients with homocysteine levels < 10 μmol/L, n (%)	65(49.6 %)
Patients with homocysteine levels > 10 μmol/L, n (%)	66(50.4 %)
Patients with homocysteine levels > 15 μmol/L, n (%)	15(11.5 %)
Homocysteine in patients with clinical anxiety, μmol/L (M ± SD)	13.98 ± 4.50
Homocysteine in patients with subclinical anxiety, μmol/L (M ± SD)	6.88 ± 2.08
Homocysteine in patients with clinical depression, μmol/L (M ± SD)	13.92 ± 4.43
Homocysteine in patients with subclinical depression, μmol/L (M ± SD)	6.87 ± 2.05

Note: 0–5 μmol/L – low homocysteine level, 5–10 μmol/L – normal homocysteine level, 10–15 μmol/L – elevated homocysteine level, > 15 μmol/L – clinically significant hyperhomocysteinemia.

Analysis of homocysteine levels in the study sample revealed significant interindividual variability in this biochemical marker, reflecting the heterogeneity of one-carbon metabolism disorders. The mean homocysteine level was 9.89 ± 4.79 μmol/L. The observed range of values (from 2.0 to 39.0 μmol/L) indicates not only the presence of individuals with normal levels but also a significant proportion of patients with marked hyperhomocysteinemia.

In half of the examined patients (50.4 %), homocysteine levels exceeded the threshold value of 10 μmol/L, which is considered a clinically significant marker of methylation disorders and increased neurometabolic risk. In 15 patients (11.5 %), homocysteine concentration was greater than 15 μmol/L, corresponding to moderate and severe hyperhomocysteinemia and associated with neurotoxic, pro-inflammatory, and epigenetic abnormalities.

A comparative analysis of homocysteine levels according to the severity of anxiety symptoms revealed significant differences between the clinical groups. In patients with clinically significant anxiety, the mean homocysteine level was 13.98 ± 4.50 μmol/L, which was more than twice the corresponding value in the group with subclinical anxiety symptoms (6.88 ± 2.08 μmol/L, $p < 0.001$). The data obtained indicate a clear association between elevated homocysteine levels and more severe anxiety symptoms.

A similar pattern was observed regarding depressive symptoms. In patients with clinically significant depression, the mean homocysteine level was 13.92 ± 4.43 μmol/L, whereas in the group with subclinical depression it was nearly half as low – 6.87 ± 2.05 μmol/L ($p < 0.001$). The observed differences indicate a potential pathogenic role of hyperhomocysteinemia in the development of clinically significant ADDs.

The Spearman correlation analysis did not reveal any statistically significant associations between homocysteine levels and the age of the study participants ($\rho = -0.03$; $p = 0.71$), nor between homocysteine levels and gender ($\rho = 0.04$; $p = 0.62$). These results indicate that major demographic factors do not influence the variability of homocysteine concentration in the study sample. This suggests that elevated homocysteine levels in patients with ADDs are primarily driven by neurobiological mechanisms, specifically the effects of chronic psychoemotional distress and traumatic experiences, as well as disturbances in metabolic-epigenetic regulation associated with methylation processes.

To quantitatively assess the severity of anxiety symptoms in the study sample, a screening assessment was conducted using the GAD-7 scale. The results obtained allowed us to stratify patients by severity and characterize the distribution of clinically significant and subclinical anxiety in individuals who experienced prolonged distress under martial law. The analysis of the frequency distribution of GAD-7 scores is presented in Table 2.

A significant prevalence of anxiety of varying severity was observed in the study population. The lowest level of anxiety was recorded in only 24(18.3 %) patients. The largest group consisted of patients with mild anxiety, comprising 50 individuals (38.2 %).

Overall, in 57 patients (43.5 %), the level of anxiety reached a moderate or severe degree, indicating a high prevalence of clinically significant anxiety symptoms among individuals living under conditions of prolonged chronic stress.

The mean anxiety level on the GAD-7 scale among all study participants was 8.60±4.04 points, corresponding predominantly to mild-to-moderate anxiety.

Table 2

Anxiety structure among study participants according to the GAD-7 scale

Anxiety Level	Scores	N	%
Minimum	0–4	24	18.3
Mild	5–9	50	38.2
Moderate	10–14	46	35.1
Severe	≥ 15	11	8.4
Total		131	100

The odds ratio analysis demonstrated a very strong association between elevated homocysteine levels and the likelihood of developing clinically significant anxiety symptoms. In particular, in patients with homocysteine levels ≥ 10 μmol/L, the probability of clinically significant anxiety (GAD-7 ≥ 10 points) was significantly higher compared to those with homocysteine levels < 10 μmol/L (OR = 157.5; 95 % CI: 33.4–741.6; $p < 0.001$).

Linear regression analysis demonstrated a clear positive correlation between homocysteine levels and the severity of anxiety as assessed by the GAD-7 scale (Figure 1).

Elevated serum homocysteine levels were associated with an increase in the total score on the GAD-7 scale, indicating a gradual worsening of anxiety symptoms as metabolic disturbances progressed. The obtained coefficient of determination ($R^2 = 0.584$) indicated that more than half (58 %) of the variability in anxiety scores on the GAD-7 scale was statistically explained by homocysteine levels and suggested a significant contribution of one-carbon metabolism disorders.

Our findings are consistent with some scientific studies in which hyperhomocysteinemia is considered a biomarker of anxiety disorders. In particular, a link between elevated homocysteine and generalized anxiety and panic disorders has been reported [4].

The identified association between elevated homocysteine levels and the severity of anxiety symptoms can be explained by disruptions in key neurobiological mechanisms involved in stress adaptation. Hyperhomocysteinemia is accompanied by a decrease in

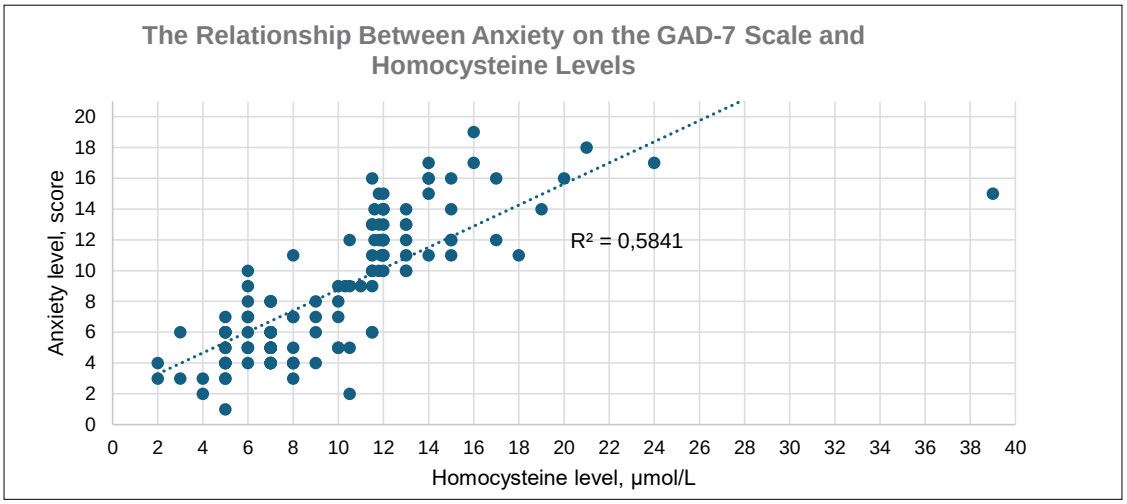

Fig. 1. Relationship between anxiety on the GAD-7 scale and homocysteine levels

cellular methylation capacity, leading to disruption of the epigenetic regulation of gene expression responsible for neuroplasticity, neurotransmission, and regulation of the hypothalamic-pituitary-adrenal (HPA) axis.

Under conditions of hyperhomocysteinemia, negative feedback mechanisms are disrupted, leading to persistent dysregulation of the cortisol response. This is accompanied by a decrease in the sensitivity of glucocorticoid receptors (FKBP5), disruption of the circadian rhythm of cortisol secretion, and a reduction in the body's adaptive reserve due to decreased expression of oxytocin receptor (OXTR) genes. This leads to hyperactivation of the amygdala, which plays a leading role in the formation of fear and anxiety, as well as to a reduction in the regulatory function of the prefrontal cortex.

Elevated homocysteine levels are accompanied by reduced expression of serotonin transporter (SLC6A) and serotonin type 1A receptor (HTR1A) genes, which significantly disrupts serotonergic neurotransmission and negatively affects the regulation of mood and behavior. At the same time, relative hyperactivation of the noradrenergic system is observed, which clinically manifests as increased vigilance, internal tension, and somato-vegetative symptoms of anxiety. Additionally, the balance between excitatory and inhibitory neurotransmitters is disrupted, particularly between glutamate and γ-aminobutyric acid (GABA), which contributes to the development of a state of neuronal hyperexcitability.

Hyperfunction of NMDA receptors leads to the activation of oxidative stress and mitochondrial dysfunction cascades, which damage neurons in the hippocampus and prefrontal cortex – structures involved in the regulation of mood, cognitive functions, and the emotional response to stress.

Our data are of particular scientific value in the context of war-related psychoemotional distress, as they are consistent with the findings of previous studies. In particular, the study by Lushchak O. et al. (2023) showed that patients with post-traumatic stress disorder (PTSD) have elevated homocysteine levels, and the duration of the disorder may serve as a predictor of the degree of its increase. The results obtained indicate the cumulative effect of chronic psychotraumatic stress on disturbances in one-carbon metabolism and methylation processes, which is of fundamental importance for understanding the biological mechanisms underlying the development of stress-associated disorders [20].

To assess the prevalence and severity of depressive symptoms in the study cohort, a screening survey was conducted using the PHQ-9 questionnaire. The results were stratified according to the generally accepted cutoff scores of the scale, which allowed for a quantitative characterization of the distribution of depression by severity level (Table 3).

Table 3

Structure of depression among study participants based on the PHQ-9 mental health questionnaire

Level of depression	Scores	n	%
Minimum	0–4	41	31.3
Mild	5–9	34	26.0
Moderate	10–14	18	13.7
Moderately severe	15–19	35	26.7
Severe	≥ 20	3	2.3
Total		131	100

Analysis of the PHQ-9 questionnaire data demonstrated significant heterogeneity in the clinical manifestations of depressive symptoms among the study participants. In 41 patients (31.3 %), the scores corresponded to the minimal level of depression, indicating the absence of or clinically insignificant manifestations. At the same time, 34 individuals (26.0 %) were found to have mild depressive symptoms. Overall, 75(57.3 %) patients exhibited subclinical manifestations of depression that did not meet the diagnostic criteria for affective disorders according to the ICD-10.

Clinically significant depressive symptoms (PHQ-9 ≥ 10 points) were observed in 56 patients, accounting for 42.7 % of those examined. Specifically, in 18 individuals (13.7 %), symptoms corresponded to a moderate level of depression; in 35 patients (26.7 %), to a moderate-to-severe level; and in 3 individuals (2.3 %), a severe level of depression was recorded. This distribution indicates a significant prevalence of affective disorders among the study population and a high level of wartime psychoemotional distress.

The mean depression score on the PHQ-9 scale among all participants was 9.10 ± 5.86 points, which corresponds to the boundary between mild and moderate depression. The interquartile range of 4–15 points indicates an asymmetric distribution of scores with a shift toward higher values, reflecting the presence of a significant proportion of patients with clinically significant depressive symptoms.

It is worth noting that an extremely high odds ratio for the development of clinically significant depression (PHQ-9 ≥ 10 points) was found in patients with elevated homocysteine levels (OR = 320.0; 95 % CI: 40.0–2557.8; $p < 0.001$), indicating a strong association between hyperhomocysteinemia and the development of depressive disorders.

Figure 2 shows the relationship between the severity of depression on the PHQ-9 scale and serum homocysteine levels in patients who experienced prolonged psychoemotional stress under martial law conditions.

Analysis of the results demonstrates a clear positive linear relationship between homocysteine levels and the severity of depression. As serum homocysteine concentrations increase, there is a consistent rise in PHQ-9 scores.

The coefficient of determination ($R^2 = 0.6372$) indicates that approximately 64 % of cases of depression depend on homocysteine levels. It is worth mentioning that at homocysteine concentrations < 10 μmol/L, low and moderate PHQ-9 scores predominate, whereas at levels ≥ 10 μmol/L, there is a significant increase in the proportion of patients with clinically significant depression. Individual cases with very high homocysteine levels (≥ 20 μmol/L) are accompanied by moderately severe and severe depressive symptoms, further emphasizing the dose-dependent effect.

The results obtained are consistent with current understanding of the key role of hyperhomocysteinemia in the pathogenesis of depressive disorders as a biochemical

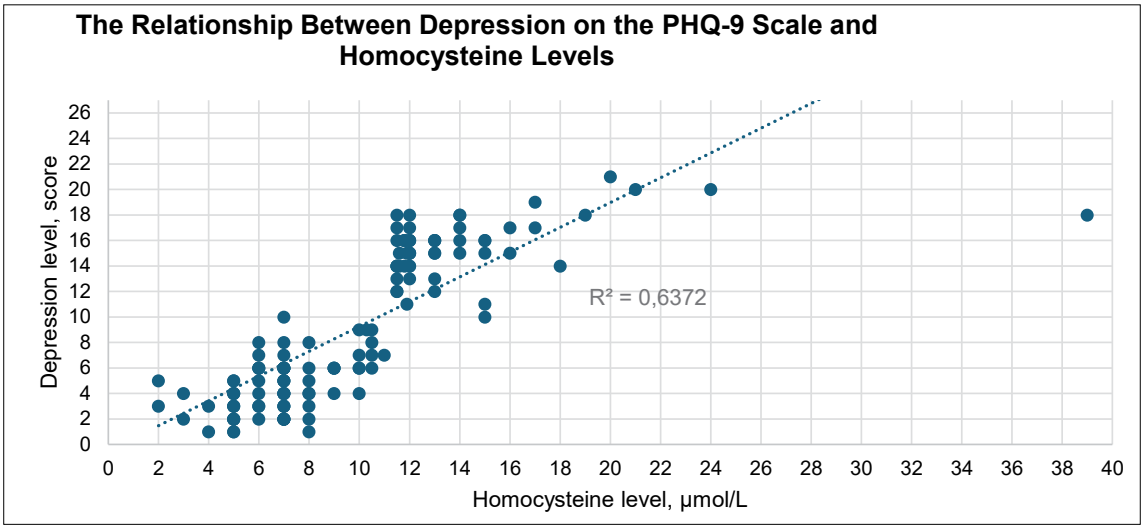

Fig. 2. Relationship between depression severity on the PHQ-9 scale and homocysteine levels

marker and a major pathogenic factor [6]. Elevated homocysteine levels reflect significant disturbances in one-carbon metabolism, leading to dysfunction in methylation processes, neuroplasticity, and neurotransmitter regulation.

Hyperhomocysteinemia leads to a shift in the balance of the methionine cycle toward the accumulation of SAH, which is a potent endogenous inhibitor of methyltransferases. This results in a functional decrease in the methylation index even at normal or subnormal SAM levels. Consequently, the methylation of DNA, RNA, proteins, and phospholipids is inhibited, which has direct epigenetic consequences.

Disruption of DNA methylation leads to dysregulation of gene expression responsible for neuroplasticity, neurogenesis, neurotransmitter regulation, and stress response, particularly genes encoding neurotrophic factors (BDNF), dopamine and serotonin receptors (COMT, DRD1, DRD2, DRD3, DRD4, HTR1A, SLC6A4), as well as enzymes involved in neurotransmitter metabolism (CACNA1C, ANK3, GSK3B, CHRNA3/CHRNA5, CNR1) and stress response genes (FKBP5, OXTR).

Elevated homocysteine levels are considered not only a marker of one-carbon metabolism disorders but also an active pro-inflammatory marker capable of initiating and sustaining a cascade of immuno-inflammatory reactions. Homocysteine stimulates the expression of pro-inflammatory cytokines, including interleukin-1β (IL-1β), interleukin-6 (IL-6), and tumor necrosis factor-α (TNF-α), at both peripheral and central levels. Elevated concentrations of these cytokines lead to the activation of microglia, the brain's primary immune cells, which is a key step in the development of neuroinflammation.

Chronic neuroinflammation and reduced expression of BDNF and its associated signaling pathways contribute to dendritic atrophy, decreased synaptic plasticity, and functional disintegration of the limbic-prefrontal networks of the brain, which are characteristic neurobiological markers of depression.

In addition to epigenetic mechanisms, homocysteine possesses direct neurotoxic properties; its excess can activate NMDA receptors, leading to increased calcium influx into neurons, the activation of oxidative stress cascades, and the development of mitochondrial dysfunction. Additionally, hyperhomocysteinemia is associated with depletion of the transsulfuration pathway and reduced levels of glutathione, the primary intracellular antioxidant. Glutathione deficiency exacerbates oxidative and nitrosative (NO) stress, further contributes to microglial activation, and worsens the state of chronic neuroinflammation.

In situations of prolonged psychoemotional and traumatic stress caused by war, these metabolic disturbances take on particular clinical significance. Prolonged activation of the HPA axis leads to persistent hypercortisolism, which further inhibits methylation, disrupts homocysteine remethylation and neuroplasticity, exacerbates neuroinflammation and oxidative stress, and causes mitochondrial and neurotransmitter dysfunction. Thus, a vicious cycle forms in which chronic stress, hyperhomocysteinemia, and depressive symptoms potentiate one another.

Conclusions

1. A high prevalence of one-carbon metabolism disorders was observed among patients who had lived under prolonged conditions of war-related stress. Elevated homocysteine levels (≥ 10 μmol/L) were recorded in half of the study participants (50.4 %), indicating significant metabolic vulnerability.

2. Homocysteine levels are closely associated with the severity of anxiety and depression. In patients with clinically significant anxiety, the mean homocysteine concentration was 13.98 ± 4.50 μmol/L, which was nearly twice as high compared to patients with subclinical anxiety (6.88 ± 2.08 μmol/L). In patients with clinically significant depression, homocysteine levels reached 13.92 ± 4.43 μmol/L, whereas in the group with subclinical depression, they were 6.87 ± 2.05 μmol/L. These differences indicate a clear dose-dependent relationship between hyperhomocysteinemia and the severity of affective disorders and confirm its potential pathogenetic role in the development of stress-associated mood disorders.

3. Extremely high odds ratios for the development of clinically significant anxiety and depression were found in

the presence of elevated homocysteine levels (OR = 157.5; 95 % CI: 33.4–741.6; $p < 0.001$) for anxiety and depression (OR = 320.0; 95 % CI: 40.0–2557.8; $p < 0.001$), indicating the key role of hyperhomocysteinemia as a biomarker of ADDs.

4. The results of linear regression analysis indicate that elevated homocysteine levels are associated with a significant increase in the likelihood of clinically significant anxiety (58 %) and depressive symptoms (64 %) and confirm the role of homocysteine as a biomarker of risk and severity of ADDs.

5. The obtained results confirm the pathogenetic role of hyperhomocysteinemia in the development of stress-associated ADDs through disruptions in methylation processes, epigenetic regulation, neuroplasticity, oxidative, mitochondrial, and neurotransmitter dysfunction, and the activation of neuroinflammatory processes.

6. Under conditions of prolonged war-related traumatic stress, hyperhomocysteinemia can be considered not only as a biochemical marker but also as a key factor forming a pathological cycle between dysregulation of the HPA axis, metabolic disturbances, neuroplasticity, and affective symptoms.

7. Determining homocysteine levels in patients with stress-related disorders is of significant clinical importance for risk stratification, assessing the severity of ADDs, and potentially predicting response to treatment with antidepressants.

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