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HYPERHOMOCYSTEINEMIA AND INFLAMMATORY PROCESSES: A PROGNOSTIC MARKER FOR COPD, CARDIOVASCULAR AND NEURODEGENERATIVE DISEASES

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Abstract: *The article analyzes the clinical and prognostic significance of homocysteine in chronic obstructive pulmonary disease (COPD), as well as its role in other inflammatory and systemic diseases. Homocysteine is considered a key biomarker of metabolic imbalance, oxidative stress, and endothelial dysfunction. Current data on its involvement in the pathogenesis of cardiovascular, neurological, psychiatric, autoimmune, and oncological diseases are presented. Special attention is given to the role of homocysteine in COPD, where its elevated levels are associated with the severity of systemic inflammation, decreased lung function, increased frequency of exacerbations, risk of cardiovascular complications, and poor prognosis. The mechanisms of the relationship between homocysteine and hydrogen sulfide (H2S) levels as a potentially more sensitive indicator of vascular risk are discussed. The material is based on an analysis of recent studies demonstrating the importance of homocysteine as a universal prognostic marker for a wide range of chronic diseases. The findings confirm the need for further investigation of this biomarker to improve diagnostics, predict disease progression, and personalize patient therapy.*

Keywords: *homocysteine, hyperhomocysteinemia, chronic obstructive pulmonary disease (COPD), systemic inflammation, oxidative stress, endothelial dysfunction, biomarkers; cardiovascular diseases, neurodegenerative disorders, atherosclerosis, metabolic imbalance.*

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Гипергомоцистеинемия и воспалительные процессы: как прогностический маркер при ХОБЛ, сердечно-сосудистых и нейродегенеративных заболеваниях

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Аннотация: *Статья посвящена анализу клинического и прогностического значения гомоцистеина при хронической обструктивной болезни лёгких (ХОБЛ), а также его роли при других воспалительных и системных заболеваниях. Гомоцистеин рассматривается как ключевой биомаркер метаболического дисбаланса, оксидативного стресса и эндотелиальной дисфункции. Представлены современные данные о его участии в патогенезе сердечно-сосудистых, неврологических, психических, аутоиммунных и онкологических заболеваний. Особое внимание уделено роли гомоцистеина при ХОБЛ, где его повышенный уровень ассоциируется с выраженностью системного воспаления, снижением лёгочной функции, повышением частоты обострений, риском сердечно-сосудистых осложнений и неблагоприятным прогнозом. Обсуждаются механизмы взаимосвязи гомоцистеина с уровнем водородного сульфида (H_2S) как потенциально более чувствительным показателем сосудистого риска. Материал основан на анализе современных исследований, демонстрирующих важность гомоцистеина как универсального прогностического маркера при широком спектре хронических заболеваний. Полученные данные подтверждают необходимость дальнейшего изучения данного биомаркера для совершенствования диагностики, прогнозирования течения и индивидуализации терапии пациентов.*

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Ключевые слова: *гомоцистеин, гипергомоцистеинемия, хроническая обструктивная болезнь лёгких (ХОБЛ), системное воспаление, оксидативный стресс, эндотелиальная дисфункция, биомаркеры; сердечно-сосудистые заболевания, нейродегенеративные расстройства, атеросклероз, метаболический дисбаланс.*

Over the past few decades, imbalances in methyl groups and homocysteine (Hcy) have become independent risk factors for a number of pathological conditions, including neurodegenerative diseases, cardiovascular disorders, cancer development, autoimmune diseases, and kidney diseases. (Behera J, 2017) The correlation between elevated plasma homocysteine levels and the risk of cardiovascular diseases was first observed in patients with cystathionine synthase deficiency or absence (Mudd et al., 1964), (Balashova O. A., 2018) and subsequent studies confirmed this relationship (Boushey et al., 1995; Nygård et al., 1997). The proposed mechanisms linking elevated plasma homocysteine levels and cardiovascular diseases include endothelial dysfunction, increased levels of oxidized LDL, vascular smooth muscle cell proliferation, and impaired coagulation processes. (Aghayan SS, 2020)

Several researchers have identified a significant link between elevated plasma homocysteine levels and depression, predicting that more than half of patients with depression will exhibit elevated plasma homocysteine levels (Bottiglieri et al., 2000; Reif et al., 2003; Tiemeier et al., 2002). (Machado S. et al., 2018)

In a study by Stanger et al., which included 30 healthy individuals and 30 Parkinson's disease patients, it was found that the homocysteine concentration in the patient group was at a moderate level (>12 μmol/L and <30 μmol/L), while in the control group it was within normal limits (Stanger et al., 2004). (Kang S. S., 2018) Related studies have previously reported a correlation between homocysteine concentration and anxiety levels (Pitsavos et al., 2006), (Glaus J. et al., 2018) as well as an association between elevated homocysteine levels and psychological disorders such as stress and anxiety (Atmaca et al., 2005). (Yan S. et al., 2022)

Tiemeier et al. (2002) (Esnafoglu E., 2020) demonstrated that individuals with depression have higher blood levels of homocysteine. Furthermore, Chen et al. (2010) (Soni R. M. et al. 2019) reported increased plasma homocysteine concentration in elderly individuals with severe depression. Additionally, Bjelland et al. (2003) (Bender A., 2017) showed that people with depression have higher blood homocysteine levels compared to healthy individuals. They also noted that the severity of depression is directly related to homocysteine concentration (Bjelland et al., 2003). (Bender A., 2017) Another study examining homocysteine concentration in individuals with bipolar disorder also reported elevated homocysteine levels (Dittmann et al., 2008). (Zhao M. et al.2022.)

Researchers have also demonstrated that elevated homocysteine levels cause damage and thickening of the vascular wall (Meier et al., 2010). (Di Lorenzo R. et al. 2015) It has been suggested that elevated levels of homocysteine can affect endothelial cells and induce a prothrombotic state with platelet activation (Hamzekolaei et al., 2020; Pasterkamp et al., 2002). (Naghipour Hamzekolaei M. et al. 2023) Elevated homocysteine levels also cause inflammation, the impact of which on atherosclerosis has been previously reported (Pasterkamp et al., 2002). (Aghayan SS, Farajzadeh A, 2020)

Over the past decade, several prognostic models have been developed to assess the risk of hepatocellular carcinoma (HCC) recurrence after transplantation in recipients, with the aim of optimizing the Milan criteria (MC) (Grat M., Stypulkowski J., 2020). In Yang et al.'s study, a correlation was observed between Hcy levels and the overall frequency of HCC recurrence after liver transplantation. One of the possible reasons for this is that liver transplant recipients are generally more susceptible to metabolic disorders that contribute to HCC recurrence. They suggested (Yang M, 2020) that, as a potential biomarker of SAM metabolism, an abnormal increase in Hcy levels reflects an increase in Hcy remethylation activity, leading to stimulation of methionine synthesis and a decrease in SAM levels. This, in turn, increases the risk of HCC, triggering several pathways that contribute to tumor development. Previous research showed that the production of S-

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adenosylmethionine (SAM), which is a biological methyl group donor necessary for extensive reactions within the cell, largely depends on the regulation of methionine adenosyltransferases (MATs) (Murray B. Barbier-Torres L., 2019). It has been shown that Hcy can be associated as an independent risk factor for heart, kidney, and brain diseases (Lominadze et al., 2006; Sen et al., 2009). (Lominadze D. et al., 2017)

Dryer et al. (Dryer S. E., 2015) investigated whether bone cells express N-methyl-D-aspartate (NMDA) receptors, specifically the subunit I of the ionotropic NMDA receptor (NMDARI). They also characterized the importance of these receptors for osteoclast activity using immunocytochemical analysis of rat bone sections. It has been shown that homocysteine (Hcy) increases oxidative stress-mediated generation of reactive oxygen species (ROS) by activating NMDA receptors, followed by intracellular calcium (Ca^{+2}) overload. This increase in ROS further activates matrix metalloproteinases (MMPs). MMP activation can play an important role in matrix degradation.

In another study, it was found that Hcy induces apoptosis through a ROS-mediated mitochondrial pathway in primary human bone marrow stromal cells and in the NF-kappa B-activated HS-5 cell line. This leads to the release of cytochrome-c and subsequent activation of caspases-3 and 9. This suggests that Hcy may exert similar apoptotic effects on osteoblasts, leading to osteoporosis due to decreased bone formation. This physiological disturbance can serve as evidence for Hcy's involvement in bone loss in osteoporosis (Kim et al., 2006). (Saito M., 2018)

In recent decades, molecular biomarkers of stroke in peripheral blood have become targets for diagnosis, prognosis, and treatment. The question of whether Hcy contributes to cerebrovascular changes, cognitive function, or both remains controversial; nevertheless, it appears that elevated Hcy levels are a risk factor for dementia in older adults, regardless of the mechanism. The relationship between Hcy levels and cognitive functions is contentious. Although some studies have shown negative results, indicating that Hcy levels are not associated with cognitive decline after stroke (Correini P. et al., 2017, Chaudhari T. S. et al., 2014), it is known that

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high Hcy levels are an independent risk factor for cerebrovascular events (Cao Y. et al., 2021, Ostrakhovitch E.A., 2019) and cognitive impairments (Luzzi S. et al., 2022; Price B.R., 2018; Zhou S., Chen J., 2021). Furthermore, a recent study has shown that patients with higher Hcy levels exhibited more pronounced cortical and hippocampal atrophy compared to patients with lower Hcy levels (Zuliani G. et al. 2024). Thus, Hcy levels may be a potential biomarker for post-stroke cognitive impairment (PSCI), and understanding their prognostic impact on PSCI can be clinically significant. (Kim KY, Shin KY, 2022)

Three other large-scale Mendelian randomization studies are noteworthy: first, a report on 31,400 subjects with coronary heart disease and 92,927 control individuals of European descent, which identified 18 polymorphisms affecting tHcy concentration (van Meurs JB, 2013). This study found no association between 18 polymorphisms in 13 loci affecting tHcy and the risk of coronary heart disease. This finding led the authors to conclude that the results "once again refute the causal relationship between moderately elevated tHcy concentrations and coronary heart disease in the white population." However, all these 18 genetic polymorphisms explained only 5.9% of the variability in tHcy levels. Moreover, as Lehmann and Cortina-Borja noted, 8 out of 18 polymorphisms were associated with lower tHcy levels, resulting in a total additive effect of 0.109 standard deviations of tHcy on the standard normal scale, which represents a small shift in the normalized distribution that would not have clinical significance. Therefore, we do not consider the conclusion of van Meurs et al. (van Meurs JB, 2013) to be justified.

Taking into account both the evidence of defective and increased production of H2S under conditions of hyperhomocysteinemia, as well as the interaction between homocysteine and H2S, a change in the H2S/homocysteine ratio may be more valuable than an absolute change in the concentration of $_{H2S}$ and homocysteine for describing the role of these metabolites in disease pathogenesis. Children with hypertension showed significantly lower plasma H2S/homocysteine ratios compared to normotensive children due to increased homocysteine concentration and decreased $_{H2S}$ levels. There was also a negative correlation between systolic

blood pressure and plasma H2S/homocysteine ratio (Momin M. et al. 2017). According to Sun L. et al., reduced $_{H2S}$ levels and elevated homocysteine levels have a significant negative correlation in congenital heart disease-associated pulmonary hypertension, which is explained by reduced MTHFR and CSE expression along with vitamin B12 deficiency (Sun L., Sun S., Li Y., et al.). He Y. and colleagues found that while patients with chronic obstructive pulmonary disease (COPD) and comorbid cardiovascular disease (CVD) had higher H2S and homocysteine levels $_{than}$ patients without CVD but with COPD, the serum H2S/homocysteine ratio in patients with COPD and CVD was significantly lower than in patients with COPD alone, and this ratio positively correlated with lung function (He Y., Liu S., Zhang Z., et al. 2017). These studies confirmed the idea of metabolic imbalance between homocysteine and H2S $_{in}$ cardiovascular pathologies, and compared to homocysteine or H2S individually, the H2S $_{to}$ homocysteine ratio may be a more reliable biomarker for predicting cardiovascular disease risk. (Yang Q, He GW. 2019)

Homocysteine is considered an important prognostic and diagnostic marker not only for cardiovascular diseases but also for many other pathologies. Hyperhomocysteinemia is associated with the acceleration of neurodegenerative processes in diseases of the central nervous system (Alzheimer's disease, dementia, post-stroke cognitive impairments). Additionally, elevated homocysteine levels in bone fractures, endocrine disorders, and certain oncological diseases serve as an additional indicator in assessing disease severity, risk of complications, and prognosis. Therefore, determining homocysteine levels is crucial for early diagnosis and developing individualized treatment strategies for a wide range of diseases.

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