The Effects of Homocysteine Level in the Critically Ill Patient. A Review

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ABSTRACT

Increased levels of homocysteine (HCYS) represent a risk factor for a series of physiopathological conditions: mental retardation, cardiovascular and neurodegenerative diseases, Parkinson's and Alzheimer's disease, depression, osteoporosis, endothelial dysfunction and inhibition of cell proliferation. This paper aims to present the pathophysiological implications of HCYS and the correlation of hyperhomocysteinemia (H-HCYS) with critical condition in the intensive care unit (ICU). Hypovitaminosis B and folate deficiency is directly involved in the inhibition of HCYS metabolism and the accumulation of HCYS in the plasma and tissues. Critically ill patients are more prone to H-HCYS due to hypermetabolism and accelerated synthesis produced by reactive oxygen species (ROS). In conclusion it can be affirmed that the determination and monitoring of HCYS plasma levels may be of interest in optimizing the therapy for critically ill patients. Moreover, by controlling HCYS levels, and implicitly the essential cofactors that intervene in the specific biochemical pathways, such as vitamin B6, vitamin B12 and folic acid can provide a diversified and personalized treatment for each patient.

Keywords: homocysteine, hypovitaminosis, oxidative stress, intensive care unit

INTRODUCTION

Homocysteine (HCYS) is a non-essential amino acid resulted from the breakdown of methionine. In the remethylation reaction of HCYS are involved a series of cofactors, such as pteroylglutamic acid (folic acid), cobalamin (vitamin B12) and pyridoxine (vitamin B6). HCYS normal plasma concentration is 5–14 µmol/L. Therefore, low cofactor concentration leads to the inhibition of the metabolic cycle. HCYS accumulation in the body (hyperhomocysteinemia, H-HCYS) entails multi-organ pathologies: neurological diseases — mental retardation, cerebral atrophy, seizures, depression, Alzheimer's disease, Parkinson's disease, ophthalmic abnormalities, bone disease, and cardiovascular disease. This paper presents an update on the biochemical mechanisms and the pathophys-
ological implications of H-HCYS in patients with certain diseases, including polytrauma patients.

**BIOCHEMICAL PROPERTIES OF HCYS**

**Structural aspects**

From a chemical point of view, HCYS is a non-proteinogenic amino acid. Its structure differs from cysteine by a methylene group. According to the International Union of Pure and Applied Chemistry (IUPAC), HCYS is defined as 2-amino-4-sulfanylbutanoic acid, with the molecular formula C₄H₉NO₂S (Figure 1).

**HCYS metabolism**

HCYS is biosynthesized only in cells, from methionine. Methionine is an essential amino acid, while cysteine is biosynthesized by transferring a sulfur atom from methionine to the hydroxyl group of serine. Through the action of methionine-adenosyl-transferase on methionine, S-adenosyl methionine is produced, which through the intervention of methyl-transferase produces S-adenosyl-HCYS and a free methyl group (CH₃). Finally, adenosyl-homocysteinase converts S-adenosyl-HCYS to HCYS, releasing a molecule of adenosine. Methionine thus formed is successively activated by the action of methylcobalamin/betaine. The methyl group is generated by the active form of folic acid (5-methyltetrahydrofolate) or by S-adenosylmethionine. After remethylation, methionine can be reused for the production of S-adenosylmethionine, which plays an important role in several biochemical reactions: DNA methylation, synthesis of carnitine, coenzyme A and melatonin synthesis. HCYS remethylation uses two enzymes: methionine-synthase and betaine-homocysteine-S-methyl-transferase. The action of these enzymes is regulated by two factors: vitamin B12, cofactor for methionine-synthase, and betaine, cofactor for betaine-homocysteine-S-methyl-transferase. Methionine thus formed is successively activated by the action of adenosine triphosphate (ATP) and adenosyltransferase, forming S-adenosylmethionine. The latter, through a transmethylation reaction, generates a methyl group, and through the action of S-adenosylmethionine-decarboxylase it is decarboxylated contributing to polyamine synthesis. On the transsulfuration pathway HCYS is converted to cysteine and taurine by the action of the following enzymes: cystathione-β-synthase and cystathione-γ-lyase. These enzymes have as cofactor the active form of vitamin B6 (pyridoxal-5-phosphate). The decarboxylation reaction of cysteine produces cysteamine. Cysteamine is a precursor in the biosynthesis of coenzyme A or taurine (Figure 2).

Also, in the case of urgently required energy, the metabolism of HCYS can be transferred to the formation of α-keto-butyrate, and finally obtaining succinyl-CoA.

**PATHOPHYSIOLOGICAL EFFECTS OF HYPERHOMOCYSTEINEMIA (H-HCYS)**

**H-HCYS and neurological disorders**

Studies have shown that a high level of HCYS is associated with a high incidence of atherosclerosis. Cerebral small vessel disease is associated with a number of diseases: hypertension, macro- and microvascular disease, endothelial dysfunction and leakage of the blood-brain barrier. Kloppenborg et al. reported that patients with two or more atherosclerotic lesions have abnormal HCYS. Also, increased HCYS concentration is directly proportional to the degree of white matter lesions and lacunar infarcts. Other neurological disorders that present an increased HCYS plasmatic concentration are Alzheimer’s disease, Parkinson’s disease, dementia, cognitive decline, schizophrenia, depression and migraine. Another condition related to high levels of HCYS reported by many studies is ophthalmic vascular disease. Allam et
al. conducted a study on Egyptian patients diagnosed with Behcet’s disease which had high plasma levels of HCYS, that led to the conclusion that, in these patients, the accumulation of HCYS is directly implicated in eye injuries, such as retinal atrophy, vitreousum hemorrhage, retinal detachment and vasculopathic complications. 10

The main neurotoxic effects are caused by cytosolic calcium accumulation, which activates several neurodegenerative kinases, as a consequence to hydrogen peroxid production which can degrade DNA and potentiate neuronal beta-amyloid protein synthesis. 19 Vitamin B and folate deficiency, which are directly involved in the metabolism of methionine as cofactors, also have neurodegenerative effects. 19,27,28 Folate deficiency in neuroblastoma cells, 14 inducing free oxygen radicals simultaneously with H-HCYS, lead to memory loss up to 66%. 29 Patients with Alzheimer’s and Parkinson’s disease have high levels of HCYS together with folate deficiency and normal levels of vitamin B. 25,30

Neuronal death and neuronal DNA structural changes are caused by DNA hypomethylation, 31 due to the significant decrease of two enzymes: methyl-transferase and S-adenosyl-homocysteinase. 32 H-HCYS poses a risk for cerebral venous thrombosis, as it is an independent factor for atherothrombotic disease. 5,33,34 Numerous studies demonstrated that there is a direct proportionality between HCYS accumulation in the plasma, vitamin B deficiency and cerebral venous thrombosis. 35 Studies by Nagaraja et al. on Indian patients showed that the correlation between cerebral venous thrombosis and H-HCYS, as well as folate deficiency is statistically significant (OR = 10.8). 26

**H-HCYS and cardiovascular diseases**

HCYS accumulation in the plasma can be correlated with cardiovascular disease 36,37 caused by endothelial dysfunc-
tion, low density lipoprotein oxidation and monocyte adhesion.\textsuperscript{33} All these physiological and biochemical dysfunctions cause peripheral artery disease,\textsuperscript{38} myocardial infarction and coronary atherosclerotic disease.\textsuperscript{20} H-HCYS is associated with peripheral artery disease especially in men, as opposed to women, due to hormonal differences.\textsuperscript{33,39} In menopausal women, however, HCYS rises above the normal range and can reach or exceed the serum levels of male subjects.

Coronary artery disease has a high mortality all over the world, its incidence being affected by numerous endogenous and exogenous factors like: stress, nutrition, hormonal and metabolic dysfunction, xenobiotics, and not least genetic determinism. Some studies describe the relationship between hypovitaminosis B and folic acid deficiency related to H-HCYS and cardiovascular disease.\textsuperscript{3,40} Schaffer \textit{et al.} demonstrated in a prospective cohort study on 3,056 patients that the level of HCYS is proportional to the incidence of coronary artery disease.\textsuperscript{1} They confirmed the strong relationship between H-HCYS and coronary artery disease, the correlation between the two variables being statistically significant.\textsuperscript{3} H-HCYS is frequently associated with certain pathologies of the cardiovascular system such as endothelial dysfunction,\textsuperscript{3} reduction of nitric oxide (NO) bioactivity\textsuperscript{34} and pro-atherogenic mechanism within the blood vessel. Stoiser \textit{et al.} show that endothelial cell damage has been associated with the presence of laminin (high molecular weight glycoprotein). Through the action of HCYS on the fibronectin-fibrillin-1 complex structural and functional modifications of the cell are being produced.\textsuperscript{41} The population of interest was divided into three subgroups according to HCYS tertiles, subgroup 1 with a value lower than 13.3 nmol/mL, subgroup 2 with a value between 13.3 nmol/mL and 18.2 nmol/mL, and subgroup 3 with a value higher than 18.2 nmol/mL.\textsuperscript{3} Another cardiovascular disorder reported in the literature as being caused by H-HCYS is spontaneous cervical artery dissection with an incidence of 2.6 from 100,000 cases.\textsuperscript{42}

**H-HCYS and bone disease**

Numerous studies in the literature point out the risk of osteoporosis and bone fractures as a result of increased HCYS associated with oxidative stress, the production of free radicals and the inhibition of metabolic regeneration.\textsuperscript{43–45} It has been shown that H-HCYS inhibits the biosynthesis of bone tissue. This process relies on osteoclasts destroying old bone and osteoblasts participating in the biosynthesis of new tissue.\textsuperscript{43} The biomechanics are regulated by a number of factors — hormones, cytokines, inter-leukins, and are inhibited by free radicals, collagen linked to HCYS\textsuperscript{39} and the decrease of bone vasculature.\textsuperscript{46}

Tyagi \textit{et al.} reported in an experimental model a significant link between bone loss and H-HCYS.\textsuperscript{46} Kuyumcu \textit{et al.} conducted a cross-sectional study including a group of 2,190 patients\textsuperscript{13} regarding the implications of endogenous antioxidants and the implications of H-HCYS regarding bone density. Uric acid is blocking the action of free radicals through its antioxidant capacity. In the studied patients low serum level of uric acid were correlated with a low action of xanthine oxidase. Bilirubine is the main blocker of the lipoprotein oxidation redox cycle, also having a high immunomodulatory capacity. Albumin has an antioxidant role, mainly given by its capacity of forming a complex with free radicals, thus inactivating their action. These three endogenous antioxidants are associated with a low incidence of osteoporosis, most likely due to their capacity of equilibrating the redox status. In the opposite sense, high levels of HCYS are correlated with a decrease of bone mineral density, and implicitly with an elevated level of osteoporosis.\textsuperscript{43}

Herramann \textit{et al.} confirmed that osteoporosis and metabolic bone quality are negatively affected by the accumulation of HCYS.\textsuperscript{29} Also, Enneman \textit{et al.} confirm that arthritis is directly related to H-HCYS.\textsuperscript{31}

**The relationship between H-HCYS and critically ill patients**

Patients with prolonged stay in the ICU frequently develop sepsis\textsuperscript{47} which may progress to septic shock and multiple organ failure (MODS). Ploder \textit{et al.} report high levels of HCYS in patients with multiple trauma or sepsis. Studies show that H-HCYS and thrombophilia are key factors in developing septic shock.\textsuperscript{48} HCYS influences clotting factors, partially inhibiting the coagulation cascade, particularly Factor V, and stimulates the excessive production of oxygen free radicals.\textsuperscript{49–51} Patients hospitalized in the ICU\textsuperscript{52} are more prone to the negative effect of H-HCYS due to organ dysfunction and nutritional deficiencies.\textsuperscript{9,31}

HCYS level becomes markedly increased after 4 days of hospitalization in the ICU (compared to day 0).\textsuperscript{47} This can be explained by the altered metabolic status and systemic inflammatory response syndrome (SIRS), sepsis and multiple organ dysfunction syndrome. Renal impairment also contributes to increasing levels of HCYS.\textsuperscript{53} Patients with multiple trauma often develop post-traumatic depression, which itself leads to increased plasma levels of HCYS,\textsuperscript{54} being frequently associated with reduced physiological and metabolic capacity. B vitamins and fo-
late are key substrates in different metabolic cycles — the synthesis of methionine, depression-related serotonin, dopamine and norepinephrine. The literature demonstrates that B hypovitaminosis and low folate induce clinical depression in most patients. Pascoe et al. demonstrated that patients with prolonged stay in the ICU develop malnutrition due to hypercatabolism, resulting in the inhibition of several metabolic cycles that lead to clinical depression. All these disorders, combined with high levels of HCYS and serious deficiencies of B vitamins and folate lead to decreased survival in patients with multiple trauma.

**H-HCYS control in critically ill patients**

At present, various pharmaceutical preparations that can reduce HCYS are being studied. Supplementation with B vitamins and folate is an important alternative, but it proved not to be sufficiently effective in reducing dysfunctions induced by H-HCYS. Recently a remarkable compound has been introduced that inhibits HCYS anethole dithiolethione. Another compound with promising effect is resveratrol (3,5,4′-trihydroxystilbene). Koz et al. highlighted a number of beneficial effects: it prevents apoptosis, has antioxidant properties and decreases inflammation by inhibiting nuclear factor-kappa B (NF-kB). The administration of resveratrol to laboratory mice decreased the level of HCYS and progressively improved tissue sections of the aorta. In addition, resveratrol is involved in complex biochemical mechanisms, stabilizing DNA replication and recombination, thereby preventing the neurodegenerative actions of H-HCYS. Ohashi et al. demonstrated the inhibitory action of ginsenoside Rb1 upon HCYS, a ginseng compound. This compound is preventing the oxidative consequences, tissue damage and neurodegenerative effects.

**CONCLUSIONS**

HCYS induces degenerative changes in many organs and systems. HCYS accumulation produces a series of dysfunctions that lead to impaired health status and quality of life. Degenerative cardiovascular diseases, the first cause of mortality in the world, are potentiated by H-HCYS. The main mechanisms are: increased concentration of the reactive oxygenated species, DNA damage, abnormal cell replication and impaired vascular endothelium. Cognitive diseases — Parkinson’s and Alzheimer’s disease, ischemic stroke and depression are also potentiated by H-HCYS. The survival rate of patients with multiple trauma is decreased further, due to increased levels of HCYS caused by malnutrition, SIRS, sepsis, MODS, which occur frequently in ICU patients.

Current research on H-HCYS recommends resveratrol, ginsenoside Rb1 and anethole dithiolethione as promising substances having anti-H-HCYS properties besides supplementing with vitamin B and folate. Research is ongoing and of great interest given the necessary social costs to treat degenerative diseases. In conclusion, H-HCYS studies are of great interest regarding the mechanisms of action, fighting therapies, as well as the introduction of a screening to determine HCYS in subjects with cognitive impairment and degenerative cardiovascular, bone and eye disorders, or those with genetic determinism for them.

**CONFLICT OF INTEREST**

The authors declare that they have no competing interest.

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