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Review Article

Worse Course and Bad Prognosis of COVID-19 in Hyper-Homocysteinemia: Role of Some B-Group Vitamins and of Other Compounds

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Abstract

Background: Increased homocysteine serum levels (HHcy) induce Endothelium Dysfunction (ED), responsible of the activation of some pro-inflammatory agents ("cytokine storm"), the imbalance between vasodilation and vasoconstriction with vasoconstrictive prevalence, increased oxidative stress and hyper-coagulability.

Methods: All these events can worsen the course of COVID-19 in HHcy- patients, favoring the evolution towards vasculitis, thromboembolic complications, multi-organ dysfunction until acute respiratory distress and failure.

Results: Therefore, Severe Acute Respiratory Syndrome-Coronavirus 2 (SARS-CoV-2) also called COVID-19, elapses more dangerously in patients affected by HHcy and can easily complicate with thromboembolic events. But, some vitamins of B-group and other substances could positively affect both high Hcy levels and thrombotic complications of SARS-CoV-2 happening in lungs and other districts.

Conclusions: COVID-19 can have a dangerous evolution and a bad prognosis in patients with HHcy. Concerning this, some compounds seem to exert beneficial effects on HHcy, inflammatory and coagulopathic complications.

Keywords: Homocysteine; COVID-19; Endothelial dysfunction; Thrombotic-lungs complications; B-group vitamins; Vitamin D; Magnesium; N-Acetyl-Cysteine

Abbreviations

Hcy: Homocysteine; Met: Methionine; MTHFR: Methylene-Tetra-Hydro-Folate Reductase; MAT: Methionine; Adenosyl Transferase; ROS: Reactive Oxygen Species; TMG: Tri-Methyl-Glycine; HHcy: Hyper Homocysteine; CβS: Cystationine-Beta-Synthase; CGL: Cystationine-Gamma-Lyase; COVID-19: Corona-Virus Disease 2019; HRCT: High Resolution Computed Tomography; IL: Inter-Leukin; ED: Endothelial Dysfunction; NO: Nitric Oxide; ADMA: Asymmetric-Di-Methyl Arginine; DDAH: Dimethylarginine-Dimethyl-Amino Hydrolase; VCAM: Vascular Adeshion Molecule; SARS-CoV-2: Severe Acute Respiratory Syndrome-Coronavirus-2; ACE: Angiotensin Converting Enzyme; PE: Pulmonary Embolism; NAC: N-Acetyl-Cysteine

Introduction

Homocysteine

Homocysteine (Hcy) is an intermediate, sulfur amino acid produced by the Methionine (Met) demethylation. This amino-acid (Met) is present in meat, fish, eggs, grains and dairy diet products and plays a critical role in DNA methylation [1]. Hcy metabolization happens via two major pathways: re-methylation and trans-sulfuration [2]. About 50% of Hcy is re-converted back to Met *via* two enzymes: Methylene-Tetra-Hydrofolate Reductase (MTHFR) and Methionine-Adenosyl-Transferase (MAT) respectively having folate (vit.B9) and vit. B12 as cofactors. In trans-sulfuration pathway, Hcy condenses with serine to form Cystathionine. Afterwards, this is synthesized in Cysteine that rises to Glutathione, a powerful antioxidant of the body, able to prevent damage induced by Reactive Oxygen Species (ROS) (Figure 1). In this pathway, vit.B6 acts as a cofactor for the enzymes employed [3]. The enzymes coming in this pathway are respectively: Cystathionine-beta-Synthase (CβS) and Cystathionine-Gamma-Lyase (CGL). A third route for the conversion back of Hcy to Met happens in the liver and kidney involving Trimethylglicine (TMG) or betaine as a methyl donor *via* trimethyltransferase [3].

Normal serum concentration of Hcy is about 5-10μmol/L. An increase >15μmol/L is defined as Hyper-Homocysteinemia (HHcy) [4]. According to the HHcy serum levels, it is classified as mild (between 15 and 30μmol/L), moderate (between 30 and 100 μmol/L) and severe (>100μmol/L). Although severe HHcy is rare, mild and moderate HHcy occur in 5-10 % of the population. Usually, HHcy is of genetic origin and derives from the polymorphisms of MTHFR, MAT, CβS and CGL. But, HHcy can be also induced by acquired risk factors that include low thyroid hormone levels, kidney disease, reduced vitamins B intake, psoriasis, certain medications and other conditions [5].

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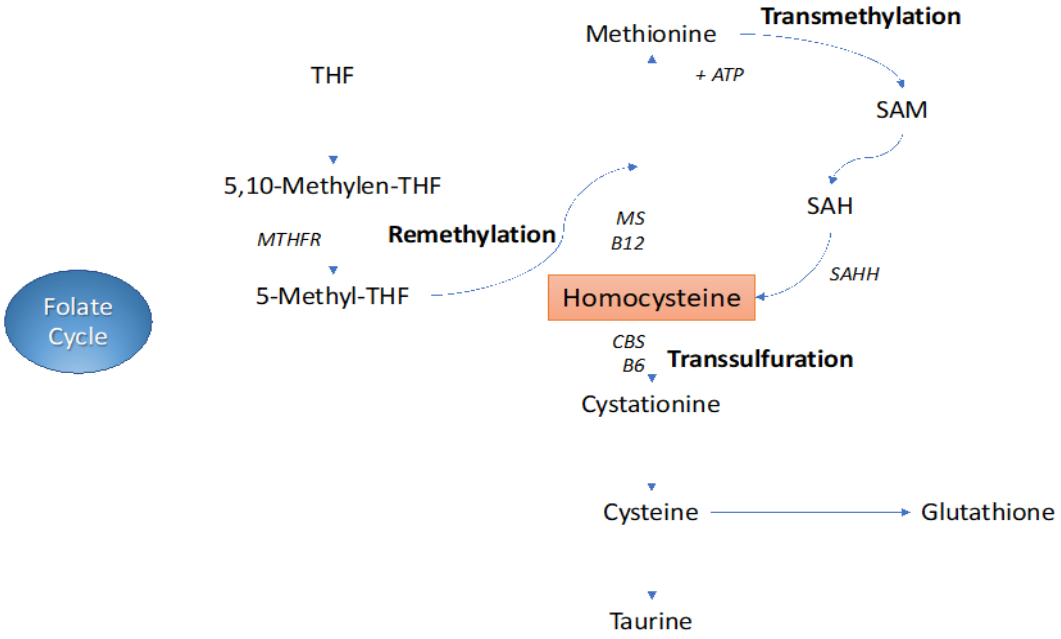

Figure 1: Homocysteine metabolism. Folate cycle, re-methylation, trans-methylation and trans-sulfuration pathways.

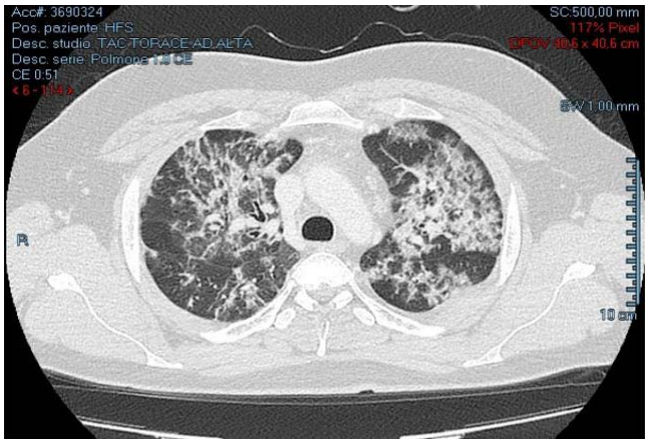

Figure 2: HRCT showing "ground-glass" opacities in a COVID-19 bilateral interstitial pneumonia.

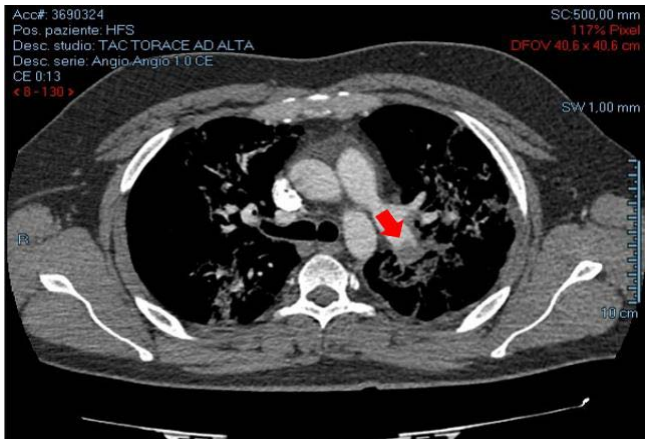

Figure 3: CT Pulmonary thromboembolism (red arrow) in a COVID-19 patient.

COVID-19

In December 2019, some cases of influence often complicated by acute pneumonia occurred in Wuhan (China). A new coronavirus, also called SARS-CoV2 (Severe Acute Respiratory Syndrome Coronavirus-2), was identified as responsible of the syndrome [6]. The clinical manifestations are numerous including fever, dry cough, asthenia, nasal obstruction, rhinorrhea, myalgia and diarrhea. Neurological symptoms can include anosmia, dysgeusia and mental confusion [7]. The respiratory difficulties (dyspnea with hypoxiemia) can progressively worse until respiratory distress and failure [8]. High Resolution Computed Tomography (HRCT) shows an interstitial pneumonia ("ground glass") (Figure 2) characterized by edema and inflammatory cell infiltrates in the interstitial spaces, due a high concentration of pro-inflammatory cytokines, such as Interleukin (IL)-6 ("cytokine storm") [9,10]. In turn, the inflammatory response induces a pro-coagulant effect and diffuse endothelial damage that predisposes to thrombotic vascular lesions and consequent pulmonary thrombotic vasculitis (microthrombi) [11] (Figure 3). The formation of arterial and vein thrombosis in Coronavirus Disease 19 (COVID-19) is summarized in Figure 4.

In this review, we evaluated the clinical conditions and the possible complications induced by the coexistence of COVID-19 and HHcy.

COVID-19 in HHcy

HHcy is caused by some congenital or acquired conditions, as genetic polymorphisms, renal failure or lifestyle behaviors. In individuals with HHcy, the infection of COVID-19 can elapse most severely than in the general population. The worse course that often ends with the death is due to several causes, such as Endothelial

Dysfunction (ED) HHcy-dependent; coexistence of systemic hypertension; diabetes mellitus; coronary artery disease; advanced age; obesity and others. But, the dangerous course of the illness and the possible vasculopathic complications happen via production of inflammatory cytokines reduced Nitric Oxide (NO) bioavailability and increased coagulation-tendency.

Endothelial Dysfunction

ED is the imbalance between vasodilator and vasoconstrictor factors, inflammation of the vessel walls, and prothrombotic state of the endothelial layer [12]. All these processes are characteristic of the early stages of atherosclerosis [13] and are due to impaired vasodilation; Pro-inflammatory state; Pro-thrombosis; Apoptosis of endothelial cells [14].

The reduction of NO bioavailability happens for increase of Asymmetric D-Methyl-Arginine (ADMA), an endogenous inhibitor of NOS. In turn, the increased ADMA concentration is due to the reduced activity of Dimethylarginine Di-methyl-Amino-Hydrolase (DDAH) related to HHcy [15,16]. Decreased NO bioavailability is likely a major mechanism of oxidative stress. That is defined as a disturbance in the balance between the production of Reactive Oxygen Species (ROS) and antioxidant defenses. Obviously, the ROS prevalence on the anti-oxidant defenses further aggravate ED [14].

Elevated Hcy concentration is also responsible for release of active cytokines and increase of Vascular Adhesion Molecule-1 (VCAM-1), recruitment of monocytes and T-lymphocytes, chemokines and growth factor including Interleukin-1 (IL-1), Interleukin-6 (IL-6), Interleukin-8 (IL-8) and macrophage chemo-attractant proteins [17]. These pro-inflammatory substances induce a prolonged but reversible ED, termed endothelial stunning.

HHcy is linked to the thrombi formation via several mechanisms. These include: increased tissue-factor expression, attenuated anticoagulant processes, enhanced platelet reactivity, increase thrombin generation, augmented factor V activity, DNA hypomethylation, and impaired fibrinolytic potential [18]. These pro-coagulant activities prevail, for loss of protective molecules and expression of adhesive molecules, and favour ED.

Finally, an increase of Hcy can induce apoptosis of endoplasmic cells mediated by endoplasmic reticulum stress and unfolded proteins' response [19]. At present, we have limited knowledge of the cellular and molecular mechanisms responsible for Hcy-induced endothelial cells' apoptosis. That seems happen via activation of caspase-3 and expression of annexin V.

Other effects

In addition, a study by Lord and Ruwart sustained that Hcy favors the entry of virus in the cells. For instance, it is known that Severe Acute Respiratory Syndrome-Virus 2 (SARS-CoV 2) enters cells through a spike protein that attack to the Angiotensin Converting Enzyme 2 (ACE-2) receptor. Hcy, in attacking to the enzyme, may liberate the receptor and allow more virus enter the cells [20,21].

Obviously, ED HHcy-related can often complicate the SARS-CoV-2 because of the significantly increase of the vascular damage both in small and large vessels [22-24].

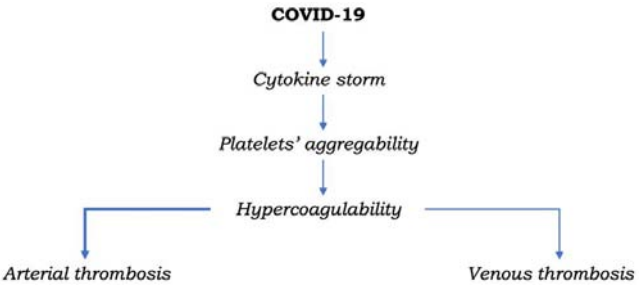

Figure 4: Succession of events causing arterial and venous thrombosis during COVID-19.

Anti-HHcy Therapy

A high frequence of Pulmonary Embolism (PE) was noted in patients suffering from HHcy and simultaneously affected by COVID-19. Apart the treatment with prophylactic antithrombotic drugs, some compounds containing vitamins of B group must be also employed [25,26]. Specifically, folate (vit.B9) is useful to lower the levels of HHcy [27]. Chung et al. found that dietary folate intake is a factor lowering the plasma levels of monocyte chemoattractant protein-1 and Interleukin-8 [28]. Most recently, Wiltshire et al. recommended treatment of the pulmonary hypertension in COVID-19 with high dose of folate [29]. Finally, in aged patients suffering from HHcy, a combination of vitamin D3, Magnesium, and vitamin B12 significantly reduced the need of oxygen therapy and the ICU support, in comparison with controls [30]. Referring to vitamin D, most recently Verdoia et al. evidenced an inverse relationship between vitamin D and Hcy levels, for the intervention of this (vitamin D) in the regulation of CβS, the enzyme involved in trans-sufuration pathway [31].

Conclusive Remarks

Referring to its frequent thrombotic complications, high plasma level of Hcy in persons infected by COVID-19 significantly increases the incidence of thrombo-embolic events, multi-organ dysfunction and vasculitis, not only on the lungs but also on cardiac, cerebral and vascular sites and on the blood pressure levels [20,21-32]. It is known that some B Vitamins-deficiency can reduce high Hcy levels [33]. Therefore, these compounds seem to be useful in to antagonize some dangerous events (thrombosis) happening during the infection of COVID-19. Particularly, Calder demonstrated that Vitamin B3 is able to negatively affect the "cytokine storm" [34]. Vitamin B6 downregulates the pulmonary inflammation by inhibiting macrophages' activation and reduced production of IL-1B, IL-6 and tumor necrosis factor-α [35]. The folic acid may interfere with the cell entry of SARS-CoV-2 [36]. Furthermore, we demonstrated that N-Acetyl-Cysteine (NAC) supplementation lowers Hcy plasma levels and increases Glutathione synthesis, an antioxidant useful against oxidative stress. This compound also modulates cell proliferation, apoptosis, immune function and fibrogenesis [37]. Nevertheless, further studies are needed to confirm all these effects both on increased Hcy levels and on SARS-CoV-2 coagulopathic complications.

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