# Homocysteine in SARS-CoV-2 Infection

Subjects: Integrative & Complementary Medicine

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Since December 2019, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has spread rapidly throughout the world causing health, social and economic instability. The severity and prognosis of patients with SARS-CoV-2 infection are associated with the presence of comorbidities such as cardiovascular disease, hypertension, chronic lung disease, cerebrovascular disease, diabetes, chronic kidney disease, and malignancy. Thrombosis is one of the most serious complications that can occur in patients with COVID-19. Homocysteine is a non-proteinogenic α-amino acid considered a potential marker of thrombotic diseases.

homocysteine SARS-CoV-2 thrombosis

## 1. Introduction

The World Health Organization (WHO) declared in early 2020 that severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection was a public health emergency of international concern. To date, considerable efforts have been made to both prevent and diagnose and treat SARS-CoV-2 infection. SARS-CoV-2 enters host cells via the angiotensin-converting enzyme 2 (ACE2) receptor and can infect the heart, vascular tissues, and circulating cells [1][2].

Pneumonia, multiorgan failure, or even death was highlighted in patients with SARS-CoV-2 infection. In order to manage and treat patients with Coronavirus disease 2019 (COVID-19), it is really important to know the risk factors (comorbidities) and specific biomarkers. Hypertension, cardiovascular diseases, diabetes, kidney diseases, lung diseases, and cancer were the comorbidities associated with the severity of COVID-19 [3][4][5][6]. Laboratory biomarkers of organ damage have an important role in the diagnosis and prognosis of patients infected with SARS-CoV-2 because the virus has been identified in endothelial, liver, kidney, lung and neuronal cells [7][8][9][10]. Proinflammatory cytokines, neuron-specific enolase, lactate dehydrogenase, aspartate transaminase, neutrophil count, neutrophil-lymphocyte ratio, troponins, creatine kinase, myoglobin, D-dimer, brain natriuretic peptide and its N-terminal prohormone are the most widely used biomarkers to predict disease severity [11][12][13].

Thrombosis is one of the most serious complications that can occur in patients infected with SARS-CoV-2 [14][15][16][17]. Helms et al. [18] evaluated the thrombotic risk in a number of 150 patients with COVID-19 and reported a percentage of 42% with thrombotic complications, mainly pulmonary embolisms. It is clear that patients with SARS-CoV-2 may have coagulation abnormalities leading to a hypercoagulability state.

Homocysteine is a non-proteogenic α-amino acid that is formed in the metabolism of methionine. The increase in serum homocysteine values can be caused either by the excessive intake of methionine, or most frequently, by the blocking of one of the metabolic pathways through dietary deficiency of folic acid, vitamin B12 and vitamin B6. Elevated serum homocysteine concentration is thought to be involved in many diseases, including neurological diseases [19][20][21], cardiovascular diseases [22][23][24], osteoporosis [25][26], and diabetes [27].

## 2. Homocysteine Metabolism

Homocysteine is a sulfated amino acid, formed during the metabolism of methionine, an essential amino acid present in proteins of animal origin [28]. Homocysteine is metabolized in two ways, namely: remethylation (through which methionine is regenerated) and transsulfuration (through which it degrades to cysteine). The serum level varies according to the two metabolic pathways.

Methionine is the body's main donor of methyl radicals in the form of S-adenosylmethionine (SAM) which is then converted into S-adenosylhomocysteine (SAH). Homocysteine is generated by the cleavage of SAH, the reaction catalyzed by S-adenosylhomocysteine hydrolase (SAHH; EC 3.3.1.1). Once synthesized, homocysteine quickly undergoes remethylation to methionine in a reaction catalyzed by methionine synthase (MS; EC 2.1.1.13) (which uses N5-methyltetrahydrofolate as a methyl donor and cobalamin as the cofactor). N5-methyltetrahydrofolate is formed by the reduction of N5,10-methylenetetrahydrofolate in a reaction catalyzed by N5,10-methylenetetrahydrofolate reductase (MTHFR; EC 1.5.1.20) [29][30][31].

Remethylation of homocysteine is also achieved via betaine (derived from choline) under the action of betaine-homocysteine S-methyl transferase (BHMT; EC 2.1.1.5), betaine being then converted to dimethylglycine. This last reaction occurs only in the liver and kidneys, while remethylation via methionine synthase is distributed in all tissues [32][33].

Methylcobalamin receives the methyl group from S-adenosylmethionine (SAM) or 5-methyltetrahydrofolate (5-methylTHF), the active form of folic acid. After remethylation, methionine can be reused to produce SAM, the body's "universal methyl group donor," which actively participates in numerous metabolic pathways that include myelin methylation, the synthesis of carnitine, coenzyme Q10, creatine, epinephrine, melatonin, methylcobalamin, and phosphatidylcholine [34][35][36].

Research has shown that the accumulation of high amounts of homocysteine and adenosine at the cellular level causes all methylation reactions to be completely inhibited [37][38][39]. Homocysteine is converted to cysteine via cystathionine. Cystathionine β-synthase (CBS; EC 4.2.1.22) catalyzes the first step of transsulfuration and allows the condensation of homocysteine and serine to generate cystathionine. It uses vitamin B6 in its active form (pyridoxal 5-phosphate) as a co-factor. Cystathionine γ-lyase (CSE; EC 4.4.1.1) catalyzes the hydrolysis of cystathionine to form α-ketobutyrate and cysteine, and is also dependent on pyridoxal-5-phosphate [40][41].

The amino acids cysteine and taurine are important compounds at the cardiac level, and for liver detoxification, cholesterol excretion, bile salt formation and glutathione production [42][43]. Recent studies mention that 5-methylTHF, methylcobalamin, betaine, pyridoxal 5-phosphate, and N-acetylcysteine significantly lower elevated homocysteine levels [44][45][46].

## 3. Homocysteine: A Closer Look at the Correlation with SARS-CoV-2 Infection

To date, there are few studies on the involvement of homocysteine in the COVID-19 disease.

The first prospective single-center cohort study on this subject is presented by Yang et al. [47]. The authors investigated different parameters such as homocysteine and predictors of imaging progression on lung computed tomography scans in the case of patients infected with SARS-CoV-2. Their results indicate that homocysteine levels were correlated with the severity of lung lesions (assessed by chest CT scans) [47]. Until now, few studies have been presented in the literature regarding the correlation of homocysteine with pulmonary imaging progression in patients with SARS-CoV-2 infection. Ponti et al., [48] in a study conducted on Italian-nationality patients hospitalized with COVID-19 investigated the role of homocysteine in this disease. In agreement with the obtained results, they propose plasma HCY levels and MTHFR gene sequencing as markers for the clinical management of SARS-CoV-2 infection [48]. Although several studies report homocysteine as a strong predictive marker for the severity of SARS-CoV-2 infection, the results of the study by Khalid et al. [49] reported that it is a moderate predictive marker for the disease.

The renin-angiotensin-aldosterone system is central to circulatory blood volume and peripheral vascular resistance regulation; its main components are ACE, angiotensin II/angiotensin II receptors, types AT1 and AT2. ACE's main role is converting angiotensin I to angiotensin II which binds to type I Ang II receptors thus triggering an intracellular pathway leading to a plethora of potentially detrimental vascular effects (sodium and water retention, vasoconstriction, inflammation, oxidative stress, apoptosis) [50][51]. Conversely, the ACE2 enzyme is involved in angiotensin II proteolysis; the resulting Ang (1–7) peptide coupled to Mas receptors has opposite biological effects to angiotensin II. SARS-CoV and SARS-CoV-2 spike proteins have an affinity for ACE2 which acts as a receptor and mediates membrane fusion and cell entry [52][53]. Cell entry, aside from viral ACE2 binding, alters the balance between angiotensin II and Ang (1–7) effects leading to pro-inflammatory events and triggering cytokine cascade activation [54][55]. A possible correlation between HHCY and SARS-CoV-2 infection may be explained by the direct involvement of homocysteine angiotensin II type I receptor activation, contributing to the severity of vascular/endothelial lesions [56]. There are multiple mechanisms accounting for AT1 activation—homocysteine-triggered upregulation of AT1 transcription has been described but also direct interaction between homocysteine and the AT1 receptor with intracellular conformational changes and subsequent activation [56]. There are three biological active forms of homocysteine (free, oxidized and reduced) [57][58][59]. There are no clear data on the differences between them in terms of intensity of interaction with AT1 and cardiovascular effects. Considering these interactions, it would be useful to find out if patients with comorbidities associated with high plasma homocysteine levels (such as megaloblastic anemia) have worse SARS-CoV-2 infection outcomes. Should this be the case

therapeutic approaches may be developed although reducing homocysteine plasma levels by vitamin B supplementation seemed not to alleviate cardiovascular risk in renal transplant patients [60].

Another possible correlation between HHCY and the severity of SARS-CoV-2 infection may be related to the presence of the C677T point mutation in the gene encoding MTHFR [61]. Herrera et al. [62] performed a retrospective study on 334 patients having had coronary, pulmonary, or other location arterial thrombosis to investigate the relationship between the C677T polymorphism, homocysteine concentration and prothrombotic biomarkers. Their results indicate the correlation of HHCY in the presence of the T allele in the C677T gene with pulmonary embolism and acute myocardial ischemia [62]. The study by Ponti et al. [63] showed, in the Latino population, a strong correlation between the C677 T variant and death due to SARS-CoV-2 infection.

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