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Endogenous deficiency of glutathione as the most likely cause of serious manifestations and death from novel coronavirus infection (COVID-19): a hypothesis based on literature data and own observations

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Glutathione is a tripeptide consisting of cysteine, glycine, and glutamate, the most abundant antioxidant preventing oxidative damage of cells from reactive oxygen species (ROS) [1]. Maintenance of highest (millimolar) concentrations of reduced glutathione (GSH) in most cell types highlights its vital and multifunctional roles in the control of various biological processes such as detoxification of foreign and endogenous compounds, protein folding, regeneration of vitamins C and E, antiviral action, mitochondrial function, regulation of cellular proliferation, apoptosis and immune response [1,2]. Considering higher rates of serious illness and death from novel coronavirus SARS-CoV-2 infection (COVID-19) among older people and those with comorbidity leading to severe pressure on health services, there is an urgent need to identify effective drugs for disease prevention and treatment [3]. Despite a number of publications reporting beneficial effects of glutathione on human health including antiviral defense, the key role of this powerful antioxidant in human physiology and pathology and also a wide spectrum its clinical application remain underestimated.

Literature data analysis

In order to obtain scientific information regarding a possible link between glutathione deficiency and viral infections, including novel coronavirus SARS-CoV-2 infection, its risk factors, mechanisms

and clinical manifestations, a literature search was performed across Pubmed and Google Scholar publications (on April 15, 2020). Over a hundred original articles and reviews have been found and analyzed. As expected, numerous studies reported that endogenous glutathione deficiency attributed to its decreased biosynthesis and/or increased depletion, represents a significant contributor to the pathogenesis of a wide range of human disorders through the mechanisms involving oxidative stress and inflammation. Figure summarizes the most illustrative evidences from biomedical literature indicating that glutathione deficiency is the most likely explanation for epidemiological findings on COVID-19 infection regarding the groups at higher risk for severe illness and death, and the restoration of this deficiency can ameliorate clinical manifestations and prognosis significantly in such patients, as it has been clearly demonstrated in other acute respiratory viral infections and pulmonary diseases. In particular, strong evidence from human and animal studies points out the levels of endogenous glutathione are progressively declined with aging making the cells in elderly more susceptible to oxidative damage caused by different environmental factors including viral infections than in the young. The primary deficiency in endogenous glutathione, found in many chronic diseases such as type 2 diabetes, obesity, cancer, cardiovascular, respiratory and liver diseases, may shift per se redox homeostasis in COVID-19 patients towards oxidative stress, thereby exacerbating inflammation in the lung and airways that may lead to acute respiratory distress syndrome (ARDS), multiorgan failure and death. Numerious studies demonstrated that the levels of reduced glutathione in males are lower than in females. This may be a reason why males are more susceptible to oxidative stress and have often poor outcomes from COVID-19 infection than females. Cigarette smoke is known deplete cellular glutathione pool in the airways, thereby exacerbating oxidative damage and inflammation in the lung, more likely requiring intensive medical interventions. Importantly, glutathione is known to protect host immune cells through its antioxidant mechanism and provide the optimal functioning of cells of the immune system. Notably, there are evidences that glutathione inhibits replication of various viruses at different stages of the viral life cycle, thereby decreasing viral load and probably preventing the massive release of inflammatory cells into the lung (“cytokine storm”). Antiviral efficiency of such treatment has been demonstrated by a study of Flora with co-workers [4]

showed that six-month preventive administration of N-acetylcysteine (NAC, precursor of glutathione), significantly reduced the incidence of clinically apparent influenza and influenza-like episodes, especially in elderly high-risk individuals. In addition, pathophysiological conditions such as lung cell injury and inflammation found in patients with severe ARDS represents the targets for effective treatment by NAC (Figure).

Own observations of COVID-19 cases

Our research team from Kursk State Medical University is involved in the project on genetics of redox homeostasis in type 2 diabetes mellitus (T2D) since December, 2016 [5].In April 2020, four patients from the control group, examined in February 2020, contacted with persons with COVID-19 confirmed diagnosis (3 patients were quarantined at home and 1 patient was hospitalized in Kursk infectious hospital).Blood samples have been collected from the patients and used to measure total plasma ROS and GSH levels immediately after blood sampling).All four cases were females, non-smokers, without chronic diseases and with confirmed positive PCR-test for COVID-19.Description of the cases is presented below.

1. Patient-M. (age-34), BMI-23.8 kg/m^2. Symptoms (fever 38°C, mild myalgia) appeared on the 8th day after contact with a COVID-19 positive patient and disappeared on the 6th day of disease without treatment. GSH 0.712 μmol/L, ROS 2.075 μmol/L, ROS/GSH ratio 2.9.

2. Patient P. (age 47), BMI 21.0 kg/m^2. Symptoms (fever 37.3°C, mild fatigue) appeared on the 10th day after contact with a COVID-19 positive patient and disappeared on the 4th day of disease without treatment. GSH 0.933 μmol/L, ROS 1.143 μmol/L, ROS/GSH ratio 1.2.

3. Patient C. (age 44), BMI 22.5 kg/m^2, family history (FH) for diabetes. First symptoms such as fever 37.7°C and air hunger appeared on the 4th day after contact with a COVID-19 positive patient. Daily fever between 37.1 and 38.5°C, dry cough, hoarseness, significant myalgia and fatigue are persisting to date for 13 days. GSH 0.079 (!) μmol/L, ROS 2.73 μmol/L, ROS/GSH ratio 34.6 (!).

4. Patient-R. (age 56), BMI-33.0-kg/m^2, PH for diabetes. Symptoms (fever 39°C, severe dry cough, dyspnea, significant fatigue and tachycardia) appeared on the 7th day after contact with a

COVID-19 positive patient, and she was hospitalized with characteristic radiological signs of COVID-19 pneumonia. Clinical symptoms are persisting to date for 11 days. GSH 0.531 μmol/L, ROS 3.677 (!) μmol/L, ROS/GSH ratio 6.9 (!).

Conclusions

Based on the literature findings and own observations, a conclusion can be drawn that glutathione deficiency is the most plausible explanation of why people with established risk factors have severe clinical manifestations of COVID-19 infection and increased risk of death. Glutathione deficiency appears to be a common disorder attributed to both environmental and genetic factors including those determining an individual susceptibility to chronic diseases and possibly related with changes in age- and sex-dependent gene expression. Apparently, glutathione deficiency formation takes a long time and occurs predominantly in a winter-spring season associated with an insufficient consumption of fresh vegetables and fruits, natural sources of glutathione [6]. In this regard, a decreased consumption of fresh vegetables and fruits may explain established racial difference in the rate of severe manifestations and death from COVID-19 infection with lower rate among Japanese and Koreans consuming a lot of plant foods and higher rate among African Americans having a limited access to such healthy foods.

The antiviral effect of glutathione is clearly non-specific, since GSH is known to inhibit replication of various types of viruses, and therefore there is reason to believe that glutathione is also active against the novel coronavirus infection. Our observations demonstrate that patients with moderate to severe COVID-19 infection have lower levels of glutathione, higher ROS levels, and greater ROS/GSH ratio than patients with a mild illness suggesting that coronavirus SARS-CoV-2 cannot actively replicate at higher levels of cellular glutathione, and a lower viral load is manifested by milder clinical symptoms. This makes glutathione a promising drug for etiological treatment of various viral infections. Therefore, oral administration of N-acetylcysteine as a preventive measure against viral infections [6], as well as intravenous injection of NAC or reduced glutathione (GSH is highly bioavailable) in patients with serious illness may be effective options against novel coronavirus SARS-CoV-2 infection. However,

clinical trials are needed to objectively assess an efficacy of N-acetylcysteine and reduced glutathione for both the treatment and prevention of this novel viral infection.

Conflict of interests: not declared

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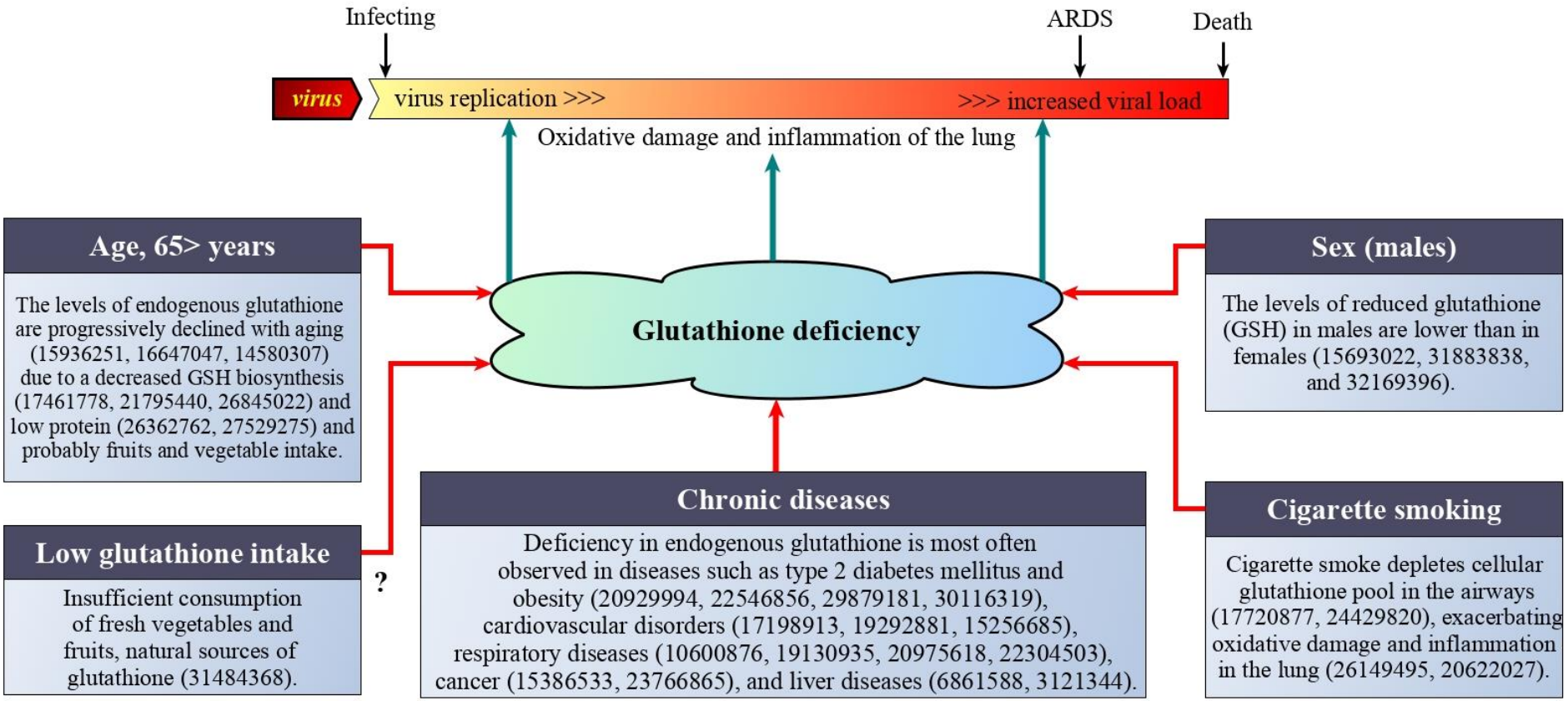

Figure illustrates that glutathione deficiency is the most likely cause of serious manifestations and death.
The bottom of the figure shows that all established risk factors for COVID-19 infection are known to be associated with depletion of intracellular glutathione. The upper part of the figure shows possible mechanisms by which glutathione deficiency can be related to clinical manifestations of the disease. In particular, glutathione is known to inhibit replication of various viruses such as influenza (12594179, 12654482, and 32123833), HIV (1520537, 8911579) and some other RNA viruses. Deficiency of reduced glutathione in the alveolar fluid in ARDS patients may enhance lung cell injury by ROS/oxidative stress (1935300, 8239150, and 10638663) and inflammation (11565956, 21403800) and these pathological conditions can be effectively prevented and treated by NAC (9228372, 8549180,17984140). Numbers in brackets indicate PubMed references (PMID).

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