DERLEME / REVIEW

Biochemical Relationship Between Glucose-6-Phosphate Dehydrogenase Deficiency and COVID-19 And Effects Of Glutathione Supplements

Glukoz-6-Fosfat Dehidrojenaz Yetersizliği ile COVID-19 Arasındaki Biyokimyasal İlişki ve Glutatyonun Etkileri

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Abstract

Glucose-6-phosphate dehydrogenase (G6PD) is an enzyme in the pentose phosphate pathway involved in the production of the reduced form of nicotinamide adenine dinucleotide phosphate (NADPH). One of the most common inherited enzyme abnormalities is G6PD deficiency. G6PD enzyme deficiency facilitates human coronavirus infection due to glutathione (GSH) depletion. Depletion of glutathione due to blockage of the pentose phosphate pathway can hardly preserve the oxidative and anti-oxidative balance. GSH protects the body from the harmful effects of oxidative damage from excess reactive oxygen radicals. Levels of GSH, the key antioxidant protector in all tissues, could be critical in quenching the exacerbated inflammation that triggers organ failure in the new coronavirus disease (COVID-19). Since several amino acids intersect with the GSH pathway, changing the concentrations of these amino acids directly or indirectly can alter cellular GSH homeostasis. Supplementation of amino acids and as well as the implementation of diet strategies offer safe and non-invasive strategies for improving GSH status and protect the body from oxidative stress in various diseases and conditions. The purpose of this review is to examine the biochemical relationship between G6PD deficiency and COVID-19 and the effect of GSH on this disease.

Anahtar Kelimeler: COVID-19, Glutathione, Glucose-6-phosphate dehydrogenase.

Öz

Glikoz-6-fosfat dehidrojenaz (G6PD), indirgenmiş nikotinamid adenin dinükleotid fosfat (NADPH) formunun üretiminde yer alan pentoz fosfat yolağındaki enzimdir. G6PD eksikliği, en yaygın kalıtsal enzim anormalliklerinden biridir. G6PD enzim eksikliği, glutatyon tükenmesine bağlı insan koronavirüs enfeksiyonunu kolaylaştırır. Pentoz fosfat yolunun blokajı nedeniyle glutatyonun (GSH) tükenmesi, oksidatif ve anti-oksidatif dengeyi zorlukla koruyabilir. GSH, vücudu aşırı reaktif oksijen radikallerinden kaynaklanan oksidatif hasarın zararlı etkilerinden korur. Tüm dokulardaki temel antioksidan koruyucu olan GSH seviyeleri, yeni koronavirüs hastalığında (COVID-19) organ yetmezliğini tetikleyen alevlenen inflamasyonu söndürmede kritik olabilir. Birkaç amino asit GSH yolağı ile kesiştiğinden, bu amino asitlerin konsantrasyonlarını doğrudan veya dolaylı olarak değiştirmek hücresel GSH homeostazını değiştirebilir. Amino asitlerin takviyesi ve diyet stratejilerinin uygulanması, çeşitli hastalık ve koşullarda GSH durumunu iyileştirmek ve vücudu oksidatif stresten korumak için güvenli ve invazif olmayan stratejiler sunar. Bu derlemenin amacı, G6PD eksikliği ile COVID-19 arasındaki biyokimyasal ilişkiyi ve GSH'ın bu hastalık üzerindeki etkisini incelemektir.

Keywords: COVID-19, Glutatyon, Glukoz-6-fosfat dehidrogenaz.

1. Giriş

COVID-19 is rapidly spreading and has become a global pandemic (1). COVID-19 patients show common cold symptoms such as fever, cough, and myalgia or fatigue at the onset of the disease (2). It is reported that these symptoms could vary from mild to severe. While exposure to COVID-19 is asymptomatic or mild in most affected at a younger age, those at the highest risk for disease have been found as having certain risk factors. These factors include older age and a smoking history (3), male gender (4), race (5) as well as prior medical problems including hypertension, cardiac disease, obesity, haemorrhagic or ischemic stroke, underlying respiratory illness (asthma, emphysema), cancer, immunosuppression, secondary infections as well as chronic kidney and liver

disease. In addition to one health condition that could be increasing mortality risk in the COVID-19 infected people is G6PD enzyme deficiency, which is the most common enzyme deficiency worldwide affecting more than 400 million people and causes a variety of diseases (6). Wu et al. indicated, in vitro, that G6PD deficient cell lines are susceptible to coronavirus infection (7). G6PD catalyses the rate-limiting step in the pentose phosphate pathway that provides NADPH (8). NADPH catalyses the recycling of oxidized glutathione (GSSG) to GSH, a powerful physiological antioxidant. G6PD catalyses the formation of NADPH required to accelerate glutathione recycling (9). The depletion of GSH due to the blockage of the pentose phosphate pathway could barely sustain the oxidative and anti-oxidative balance in the body, thus failing in weakening oxidative damage caused by the invasion of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). Reducing oxidative stress by using GSH supplementation and glutathione include nutrients could be the best approach to protect the most vulnerable subjects from COVID-19. The purpose of this review is to examine biochemical the relationship between G6PD deficiency and COVID-19, the use of glutathione as supplementation and dietary strategies in the treatment and prevention of this disease.

1.1. G6PD Deficiency Induces GSH Depletion and Excess Oxidative Stress

The ubiquitous pentose phosphate pathway in all living organisms is one of the major metabolic pathways associated with glucose metabolism. The most important functions of this pathway comprise the production of reducing equivalents in the form of NADPH for reductive biosynthesis, and the production of ribose sugars for the biosynthesis of nucleotides, amino acids, and other macromolecules needed by all living cells (10). G6PD is the first limiting enzyme of the pentose phosphate pathway and is responsible for the production of NADPH which contains the balance of GSH/GSSG in both cytosol and mitochondria. GSH is considered the most abundant and vital endogenous antioxidant that protects cells against oxidative or nitrosative damage (8).

G6PD deficiency is the most prevalent X-linked inherited trait, affecting 7% of the global population, with a higher prevalance on the African continent, the Middle East, and Southeast Asia (11). These cohorts have been particularly affected by the COVID-19 pandemic (12).

Decreased G6PD levels cause increased levels of oxidative stress and disturb redox imbalance (13). Endothelial cells G6PD-deficient showed reduced expression of endothelial nitric oxide (NO) synthase and NO levels associated with reduced GSH (14). Decreased NO and increased oxidative stress impair endothelial and macrophage function and increases inflammatory cytokines, such as tumour necrosis factor (TNF) and monocyte chemoattractant protein-1 (MCP-1) in endothelial cells and monocytes (14,15).

Patients with G6PD deficiency may improve acute haemolytic anaemia after exposure to oxidative stress as the pentose phosphate pathway shunt is the only NADPH source. Since haemolysis can be triggered by bacterial or viral infections, certain foods, and certain drugs haemolytic anaemia may be life-threatening in G6PD-deficient patients (16). These factors can increase the levels of reactive oxygen species and causing red blood cells to disappear faster than the body can replace them. SARS-CoV infections and Avian influenza virus (H5N1) can induce acute lung injury and lead to acute respiratory distress syndrome (ARDS) by inducing the oxidative stress machinery, the innate immunity and toll-like receptor-4 signaling via activation of Nuclear Factor kappa B (NF-κB) (17,18). This induction causes cytokine storm or overproduction of the pro-inflammatory interleukins (19). All of these data assert that G6PD deficiency is in conjunction with oxidative stress and inflammatory response dysregulation and increases susceptibility to severe viral respiratory infections.

G6PD deficiency impairs the ability of cells to form NADPH and leads to GSH depletion (Figure 1). GSH (a tripeptide consisting of cysteine, glycine, and glutamate) is the most abundant antioxidant which plays an important role in antioxidant prevention against oxidative damage of cells from reactive oxygen species (ROS) and plays a role in regulating various metabolic pathways essential for the homeostasis, as well. Maintaining the highest (millimolar) concentrations of reduced glutathione in most cell types plays a vital role in the control of various biological processes such as detoxification of foreign and endogenous compounds, protein folding, regeneration of vitamins C and E, maintenance of mitochondrial function anti-viral defence, regulation of cellular proliferation, apoptosis and immune response (20,21). In addition, GSH is needed for the maintenance of vitamin D metabolism genes and circulating levels of 25-hydroxyvitamin D (25(OH)VD) (22).

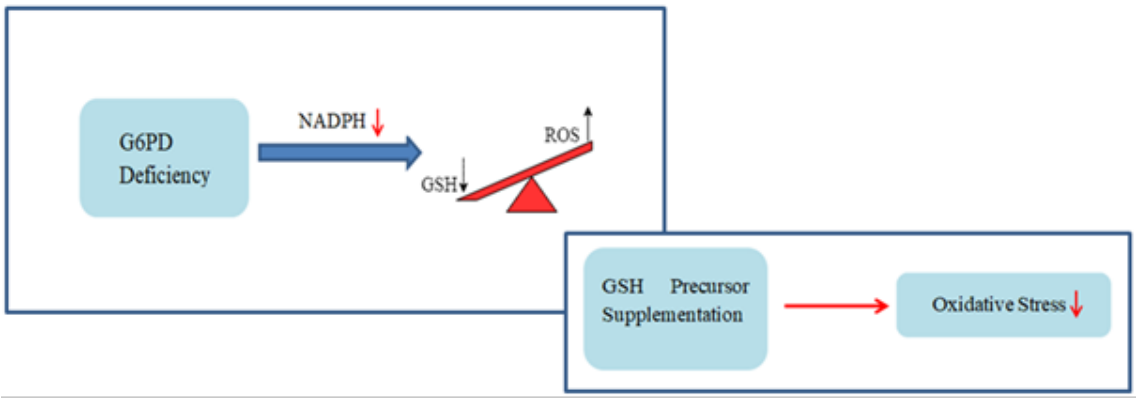

Fig 1. G6PD deficiency leads to decreased NADPH. In this case, while the recycling of GSH is decreasing, ROS increase, which induces oxidative stress. However, increased oxidative stress is frequently reversed by GSH or its precursors, such as glutamine, NAC, L-cysteine and serine

1.2. Supplements and Dietary Strategies Containing GSH

GSH is essential in the pathophysiology of human diseases (23). Chronic inflammation causes an increase in free radical production, and it promotes the production of proinflammatory cytokines. Therefore, it also leads to intracellular GSH depletion and increased free radical production (24). Therefore, it becomes important to maintain GSH homeostasis by dietary supplementation and nutrients.

Dairy products, bread, and cereals generally have low levels of GSH, whereas vegetables and fruits contain moderate to high GSH levels (25). In a study, the effect of garlic on glutathione S-transferase (GSTs) activity and the level of GSH in the mouse liver was investigated. Institute of Cancer Research (ICR) mice were intraperitoneally injected with a methanol extract of garlic and allyl sulfide, one of the possible active compounds in garlic. It has been shown that garlic increased the levels of GSH and the activity of GSTs (26).

In another study, primary rat hepatocyte cultures were exposed to cumene hydroperoxide or Tert-butyl hydroperoxide (t-BHP) to evaluate the protective and antioxidant properties of water-soluble extracts of artichoke leaves. In the study, it has been found that artichoke extracts reduced cellular leakage of GSSG and total GSH loss, but had no effect on cellular GSH levels. These findings indicate that artichoke extracts have apparent antioxidant and protective properties (27).

Wu and colleagues examined the effect of broccoli sprouts on GSH levels in a study. Rats were fed 200 mg of dried broccoli sprouts daily for 14 weeks. In the study, it has been found that heart, aortic, and kidney GSH levels did not change in healthy Sprague Dawley rats, but low GSH levels were almost entirely returned to normal in rats prone to stroke (28).

Supplementation of GSH component amino acids (glycine, cysteine, and glutamate) improves tissue GSH synthesis. Therefore, researchers have recommends individual GSH precursors supplementation to enhance GSH status. Several amino acids coincide with the GSH pathway. Thus, changing the concentrations of those amino acids can regulate cellular GSH homeostasis (29).

In a case report study, it has been shown that the repeated use of both 2000 mg of oral administration and intravenous injection of GSH was effective in relieving the severe respiratory symptoms of COVID-19, demonstrating for the first time the efficacy of this antioxidant therapy for COVID-19 (30).

The inflammatory response can be traced to the viral entry pathway via its receptor Angiotensin-converting enzyme 2 (ACE2). ACE2 is a protease involved in the renin-angiotensin system (RAS) together with the accompanying angiotensin-converting enzyme (ACE). The downstream effects of the two enzymes are opposite: ACE activity results in vasoconstriction, oxidative stress, inflammation and apoptosis, while ACE2 leads to vasodilatation, angiogenesis and anti-inflammatory, anti-oxidative and anti-apoptotic effects (31).

SARS-CoV-2 binds to the ACE2 receptor and induces the downregulation of nuclear factor erythroid 2-related factor 2 (NRF2) causing inhibition of GSH release. This results in elevated inflammatory cytokines, high ROS, and recruitment of immune cells (32). NRF2 is associated with karyopherins known as importin α5 and importin β1 (33).

Coronavirus inhibits karyopherins, preventing NRF2 from translocation to the nucleus and reducing GSH production (34).

Glutamine is the precursor of glutathione and it is the widest amino acid in the body. It includes 60% of the total free amino acids pool. Adipose tissue, skeletal muscle and lungs are the main synthesis sources of glutamine, which circulates in plasma. (35). Glutamine regulates the expression of several genes of cell metabolism, cell defence, signal transduction proteins, and repair regulators. In addition, it activates intracellular signalling pathways by phosphorylation, such as c-Jun N-terminal kinases (JNKs) and mitogen-activated protein kinase (MAPKs) (36).

Cengiz et al pointed out that L-glutamine supplementation shortened hospital stay and led to less need for intensive care unit (ICU) in COVID-19 patients. Hence, it can be thought that glutamine has a role in the repair of COVID-19 and regulation of lung inflammation (35).

N-acetyl cysteine (NAC) has a free sulfhydryl group that lowers mucus viscosity by reducing disulfide bonds in the cross-linked mucus glycoprotein matrix. Therefore, it exhibits a mucolytic effect. Besides, NAC is a powerful antioxidant that affects directly certain types of oxidants. It is also a precursor of cysteine, and it is necessary for glutathione synthesis. It can renovate thiol pools, which regulates the redox state (37).

In ARDS patients, NAC therapy can improve patient outcomes by increasing total thiol molecule and antioxidant molecules (38). In vitro, NAC disrupts the NLRP3 inflammasome pathway in a dependent manner via effects on mRNA expression of NLRP3 and caspase-1 activation (39).

NAC restrains the downstream activities after TNF-α receptor activation and inhibits gene expression of TNF-α and interleukin-6 (IL-6) when under oxidative stress. In addition, NAC has been shown to reduce mucin production, interleukin-1ß (IL-1ß) and interleukin-18 (IL-18) (40,41).

NAC supplementation ensures that the cell is better equipped to combat oxidative stress, and the presence of a thiol group can block ACE2 activity, which would prevent SARS-CoV-2 from penetrating target cells (42,43).

Ibrahim et. al. pointed out that NAC administration led to reverse GSH depletion. A patient, who has COVID-19 infection and G6PD-deficiency, treated with hydroxychloroquine draw on intravenous (IV) NAC. NAC inhibited haemolysis and improved ferritin, liver enzymes (Alanine aminotransferase (ALT) and aspartate aminotransferase (AST)), and C-reactive protein (CRP) levels. Besides, it ensured the complete recovery of the G6PD-deficient patient. NAC was also applied to 9 additional respiratory device-dependent COVID-19 infected patients who were not G6PD deficient. NAC supported clinical improvement. Also, it reduced ferritin in 9/10 patients and CRP in all patients. In this context, NAC can be useful for blocking of viral infections (44).

NAC given at per os (PO) doses ranging from 1200 to 2400 mg/day has been shown to reduce the inflammatory response, increase intracellular GSH, and ameliorate acute respiratory distress syndrome in patients with community-acquired pneumonia (45).

L-Cysteine is present mostly in the extracellular space in the L-cystine form. Via a transport system, extracellular L-cystine crosses the plasma membrane. It is reduced to L-cysteine within cells by reduced GSH and thioredoxin. Intracellular L-cysteine, which is a precursor for GSH production, plays a substantial role in cellular homeostasis (46).

Cysteine is a necessary metabolic precursor for taurine synthesis (47). A study was conducted by Yıldırım et. al. to evaluate the effects of taurine on GSH, malondialdehyde (MDA), thioredoxin reductase (TR), glutathione peroxidase (GPx), and endothelial nitric oxide synthase (eNOS) in middle aged and young rat liver. When compared to the control group, liver GSH levels, TR and GPx activities were importantly higher in the taurine group of middle aged rats. In young rats, liver GPx activity and GSH levels did not statistically differ between taurine and control groups. Thus, it can be considered that exogenous taurine can play a role in reducing oxidative stress by increasing liver GSH levels, GPx and TR activities (48).

An critical molecule S-Adenosyl-L-methionine (SAM) is found in all alive organisms. Since SAM converts to cysteine via the transsulfuration pathway, it is a precursor for GSH (49). Serine, which is a non-essential amino acid, is required for cellular proliferation. Serine promotes one-carbon metabolism, which is a complex network of metabolic pathways that involve the synthesis of SAM, nucleotides, GSH, and NADPH (50,51).

In a study by Sim et. al. in which the effects of L-serine on alcoholic fatty liver and homocysteine metabolism were evaluated, L-serine supplementation was found to increase SAM levels (without affecting the S-adenosylhomocysteine (SAH) concentration) and GSH by 30.6% and 94%, respectively. It has also been found that L-serine supplementation inhibits the increase in intracellular homocysteine levels. Thus, it can be considered that L-serine heals alcoholic fatty liver disease by affecting homocysteine metabolism (52). Overall, supplementing GSH precursors may be an effective option at raising GSH concentrations.

2. Conclusion and Recommendations

There is an association between G6PD deficiency and oxidative stress with the severity of COVID-19. G6PD activity is crucial for the adequate functioning of both the pro-oxidant and anti-antioxidant components of the innate immune response to counter immune dysregulation induced by COVID-19. Given the potential for coronavirus to trigger oxidative stress, G6PD deficiency which is not recognised in the presence of the COVID-19 viral infection, may cause haemolytic crisis and worse outcomes in affected individuals. G6PD deficiency induces GSH depletion, so the defence system of the body is not effective. This leads to oxidative stress with the accumulation of reactive oxygen species.

Consumption of GSH supplements and ingredients with high antioxidant capacity including might be beneficial in COVID-19 patients due to providing and maintenance of a redox environment and reducing the susceptibility of the host cell to COVID-19 infection consequences. In light of the studies, we believe that supplementation using the GSH precursor amino acids could potentially improve GSH status. A randomized, controlled study of GSH and its precursors with inflammatory/oxidative stress markers should be conducted in the future to determine the effect of GSH and antioxidants on the clinical course of COVID-19 pneumonia and ARDS.

3. Contribution to the Field

COVID-19, which has an effect all over the world, have caused many deaths and permanent damage to people. It is essential to keep the immune system strong to get out of the disease caused by the coronavirus with the least damage and loss. GSH, which plays an important role in strengthening the immune system, is thought to be beneficial for studies in COVID-19. For this reason, it is anticipated that our article will contribute to the literature.

Conflict of Interest

This article did not receive any financial fund. There is no conflict of interest regarding any person and/or institution.

Authorship Contribution

Consept: EO; **Desing:** EO, AC; **Supervision:** EO, AC; **Funding:** EO, AC; **Materials:** EO, AC; **Data Collection/Processing:** EO, AC; **Analysis/Interpretation:** EO, AC; **Literature Review:** EO, AC; **Manuscript Writing:** EO; **Critical Review:** AC.

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