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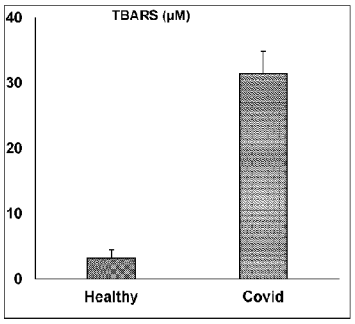
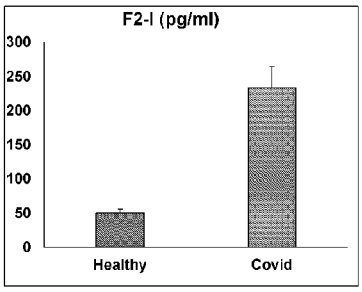
(54) Title: N-ACETYLCYSTEINE AND GLYCINE FOR TREATMENT OF COVID-19 AND POST COVID-19 SYMPTOMS

FIG. 1





(57) Abstract: The present disclosure concerns compositions and methods related to administering to an individual a composition comprising an effective amount of glycine or a functional derivative thereof and N-acetylcysteine or a functional derivative thereof, or precursors of glycine and cysteine including serine, methionine or derivatives thereof, wherein a viral infection is treated, prevented, delayed in onset, reduced in severity, or reduced in the postinfection effects in the individual. The compositions and methods further relate to treating, preventing, delaying onset of, or reducing in severity a viral infection caused by a respiratory virus, particularly a coronavirus, at least including SARS-CoV-2. The compositions and methods further relate to an individual having GSH deficiency, elevated Oxidative stress, inflammation, mitochondrial dysfunction, insulin resistance, immunosuppression, endothelial dysfunction, functional limitation, cognitive impairment, or a combination thereof.

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N-ACETYLCYSTEINE AND GLYCINE FOR TREATMENT OF COVID-19 AND POST COVID-19 SYMPTOMS

[0001] This application claims priority to U.S. Provisional Patent Application Serial No. 63/022,453, filed May 9, 2020, and also to U.S. Provisional Patent Application Serial No. 63/164,499, filed March 22, 2021, both of which applications are incorporated by reference herein in their entirety.

TECHNICAL FIELD

[0002] The present disclosure is directed at least to the fields of virology, biochemistry, cell biology, chemistry, molecular biology, immunology, and medicine.

BACKGROUND

[0003] The world is currently in the grip of a global pandemic caused by the novel Coronavirus SARS-CoV-2 and resulting viral pneumonia, COVID-19. As of May 10, 2021 over 158 million patients are currently identified to have COVID-19 globally with over 32.4 million patients in the USA, with a very high mortality ranging which is approaching 600,000 in the USA and has exceeded 3.3 million worldwide. Particularly affected are COVID-19 patients with significantly elevated risk of mortality such as elderly, immunosuppressed, and diabetic patients. The dynamic changes of COVID-19 with second and possibly third infection waves, limited availability of effective medications and very slow availability and rollout of vaccines have led to 'shelter in place' advisories in many countries as the lone available defense to protect people from getting infected by the Coronavirus. Most recently, the explosive 2nd wave in India has resulted in over 400,000 cases being diagnosed every day, with a skyrocketing mortality rate. Interestingly, the Indian COVID crisis appears to be even affecting vaccinated patients. There are no available interventions or therapies which have been proven to be successful in eliminating COVID-19, and multiple clinical trials are under way globally. To add to these serious concerns surrounding acute COVID infection is the emerging evidence documenting that about 35% of patients who have recovered from COVID (referred to as 'long-Covid' patients) are developing abnormalities in multiple organ functions with the most prominently reported defects being neurocognitive impairment and fatigability.

[0004] Although COVID-19 is mild and asymptomatic in most patients, emerging evidence from multiple published studies in hospitalized COVID-19 patients have shown that

these patients have severely elevated inflammation, suppressed immune function, and viral pneumonia. For example, elevated inflammatory cytokines such as IL-6 and C-reactive protein (CRP) correlated negatively with CD4+ T-Cells, CD8+T-Cells, B-cells and NK cells of the immune system in these patients, suggesting that elevated inflammation is linked to immunosuppression (Wang *et al.*, 2020; Shou *et al.*, 2020). As COVID-19 progresses, there is oxygen desaturation requiring mechanical oxygenated ventilation to save lives. Infections such as pneumonias are associated with severe and harmful oxidative stress, and an imbalance between free radicals and antioxidants in the body (Trefler *et al.*, 2014; Khomich *et al.*, 2018). Increased oxidative stress has been shown to adversely vascular endothelial function and impair red-blood function and oxygen delivery to tissues (Mohanty *et al.*, 2014). Under normal conditions cells protect themselves from the ravages of oxidative stress by synthesizing glutathione (GSH). Indeed, GSH is the most abundant natural intracellular antioxidant protein which combats and eliminates excess cellular oxidative stress. Acute viral infections such as influenza have been shown to result in GSH deficiency (Sies, 1999), and cell-culture studies have shown that increasing GSH levels can have a viricidal effect (for example, by inhibiting replication of the influenza virus (Amatore *et al.*, 2019)). In some embodiments related to the disclosure, the combination of GSH deficiency, elevated oxidative stress, endothelial dysfunction, inflammation, and/or immunosuppression combine to contribute to the severely elevated mortality due to COVID-19. In some embodiments related to the disclosure, oxidative stress (, as evaluated through as plasma levels of TBARS (a marker of oxidative stress), oxidant damage (measured as plasma levels of F2-isoprostanes) and intracellular glutathione concentrations were measured in 32 was found to be about 12-fold higher in 9 hospitalized COVID patients and found to be significantly abnormal when compared to than 2759 uninfected humans. Oxidative stress and oxidant damage were higher in all age groups in COVID patients, but the highest levels were seen in older humans in the 60-80y age range. Similarly, glutathione levels were lower in all age groups but were lowest in the 60-80y age range.

[0005] Clinical studies of GSH deficiency and oxidative stress in elderly humans (Sekhar *et al.*, 2011 Sept.; Sekhar *et al.*, 2018 Nov.; Sekhar *et al.*, 2019 Nov.), immunosuppressed HIV-patients (Nguyen *et al.*, 2014; Sekhar, 2019), diabetic patients (Sekhar *et al.*, 2011 Jan.), and aged mice (Nguyen *et al.*, 2013) have shown that these conditions (aging, HIV-infection and diabetes) have significant GSH deficiency and elevated oxidative stress. These studies found that older humans and HIV patients also have severely elevated inflammation, and this is also well

reported in diabetes. All 3 conditions are known to be associated with immunosuppression. Tracer studies demonstrated that the reason for elevated oxidative stress in all 3 conditions was severe deficiency of the endogenous antioxidant protein GSH, and the GSH deficiency occurs due to diminished availability of its precursor amino-acids glycine and cysteine. Supplementing glycine and N-acetylcysteine (a cysteine donor) – combination termed GlyNAC – successfully corrected deficiency of intracellular glycine and cysteine in elderly humans, HIV-patients and diabetic patients within 14-days (Sekhar *et al.*, 2011 Sept.; Nguyen *et al.*, 2014; Sekhar *et al.*, 2011 Jan.), and improved/corrected GSH deficiency and lowered oxidative stress in elderly humans, HIV-patients and diabetic patients within 14-days (Sekhar *et al.*, 2011 Sept.; *Sekhar et al* ., 2011 Jan.; Nguyen *et al.*, 2014). Results from these 3 clinical trials in elderly humans, HIV-patients and diabetic patients showed that GlyNAC supplementation improved/corrected intracellular GSH deficiency (synthesis and concentrations) together with a significant decrease in plasma oxidative stress. Additional studies in elderly humans (a 36-week open-label trial published 2021; and a 16-week randomized clinical trial) and in HIV-patients (a 20-week open label trial published Sept 2020) showed that compared to young controls (for elderly human trials) and non-HIV controls (for the HIV clinical trial), elderly humans and HIV patients had severely elevated inflammation (plasma IL-6, CRP and TNF-alpha), endothelial dysfunction (plasma sICAM1, sVCAM1 and E-selectin), insulin resistance, genomic damage, impaired autophagy, mitophagy and mitochondrial function and energy regulation, and with muscle weakness, poor exercise capacity and cognitive impairment. Supplementing GlyNAC in these studies led to significant improvement of these defects in elderly humans and HIV-patients with improvements in muscle strength, exercise capacity and cognition. (Sekhar *et al.*, 2019 Nov.) In some embodiments related to the disclosure, supplementing GlyNAC in patients infected, or that had previously been infected, with the SARS-CoV-2 virus can effectively treat or prevent or delay onset of or reduce severity of or reduce post-infection effects of COVID-19 by correcting GSH deficiency and lowering oxidative stress, inflammation, mitochondrial dysfunction, endothelial dysfunction and defective immune function, physical function (strength and exercise capacity) and cognitive function in patients with COVID-19. Thus, GlyNAC supplementation in patients with COVID-19, or who had COVID-19, could lead to significant decline in morbidity, mortality and healthcare expenditure, and result in clinical improvement, accelerated recovery and increased survival. Additional evidence to support this comes from measuring oxidative stress in hospitalized COVID patients, and available data from 9 patients show an extremely elevated level of plasma oxidative stress marker TBARS which is about 10-times higher than uninfected young healthy participants studied in previous trials.

Because GlyNAC effectively targets and lowers oxidative stress, this has the potential to do the same in patients with COVID-19.

[0006] Other and further objects, features, and advantages will be apparent from the following description of the presently disclosed embodiments of the disclosure, which are given for the purpose of disclosure.

SUMMARY

[0007] The present disclosure is directed to methods and compositions for treating, preventing, delaying the onset of, reducing severity of one or more symptoms of, and/or reducing or preventing the post-infection effects of a viral infection in an individual in need thereof, specifically a viral infection caused by a virus of the *Coronaviridae* family, including at least SARS-CoV-2. In specific embodiments, the *Coronaviridae* virus is a betacoronavirus. In other embodiments, the *Coronaviridae* virus is SARS-CoV-2 or SARS-CoV, including any strain or variant thereof.

[0008] In specific embodiments, the methods and compositions comprise targeting the virus itself and/or targeting the uptake of the virus into a host cell, including directly or indirectly targeting binding of a receptor on a host cell by the virus, such as for viral uptake. In specific embodiments, the methods and compositions comprise targeting the host cells, including targeting the cells such that the virus cannot be up taken by the cell. In specific embodiments, the methods and compositions comprise preventing the synthesis of viral RNA, inhibiting viral replication, blocking viral binding to cell receptors, and/or inhibiting viral self-assembly. In specific embodiments, the methods and compositions comprise inhibiting viral replication by inhibiting papain-like protease (PLpro). In specific embodiments, the methods and compositions comprise competitively binding to host cell angiotensin-converting enzyme 2 (ACE2) receptors. In specific embodiments, the methods comprise inducing gene expression signals in host cells that induce an unfavorable cellular environment for viral replication.

[0009] In specific embodiments, the methods comprise identifying or targeting the individual in need. In specific embodiments, the individual in need thereof is or is not at risk of being infected with the virus, has or has not been exposed to an individual infected with the virus, has or has not been tested for the viral infection, has or has not tested positive for the viral infection, or is or is not symptomatic of the viral infection. The individual may or may not have flu-like

symptoms and be suspected of having viral infection, including viral infection by a virus of the *Coronaviridae* family. The individual may or may not have had vaccination for a virus of the *Coronaviridae* family.

[0010] In specific embodiments, the individual has normal intracellular GSH levels. In specific embodiments, the individual has low intracellular GSH levels, elevated oxidative stress, inflammation, immunosuppression, endothelial dysfunction, mitochondrial dysfunction, genomic damage, impaired autophagy, impaired mitophagy, insulin resistance, cellular senescence, stem cell defects, stem cell fatigue, stem cell impairment, stem cell failure, epigenetic alterations, impaired cognition, functional limitation, tinnitus, physical limitations, decrease in exercise capacity or muscle strength or gait speed, fatigability, limitation in lung function or a combination thereof. In specific embodiments, the individual is an elderly individual, such as an individual greater in age than 70, 75, 80, 85, 90, or 95. In other embodiments, the individual is not elderly, such as younger in age than 70 including younger than 65, 60, 55, 50, 45, 40, 35, 30, 25, 20, 15, or 10. In specific embodiments, the individual is an individual with diabetes. In specific embodiments, the individual is an individual with pre-diabetes, such as an individual having a fasting glucose value between 100-125 mg/dl. In specific embodiments, the individual is an obese individual, such as an individual having a BMI of 30 or more. In specific embodiments, the individual is an immune-compromised individual. In certain embodiments of the disclosure, the individual is a mammal. In specific embodiments, the mammals can be of any kind and can include humans, dogs, cats, horses, pigs, sheep, and goats, for example.

[0011] In specific embodiments, the methods and compositions comprise administration of cysteine and glycine, or their various precursors (such as any of the precursor amino acids including, but not limited to, serine and methionine), derivatives, or other forms, to an individual in need thereof. In specific embodiments, the cysteine and glycine precursors, derivatives, or other forms include, but are not limited to, N-acetylcysteine (NAC), L-glycine, L-glycine ethyl ester, or dipeptide forms, such as cysteine and glycine dipeptide forms. In certain embodiments, cysteine and glycine dipeptide forms include cysteinylglycine or n-acetylcysteinylglycine. Certain embodiments concern compositions, and methods of administering, precursors of cysteine, n-acetylcysteine, and/or glycine. The precursors may include serine, methionine, and/or any other precursor including any composition in the one-carbon metabolism pathway (also known as the folate cycle) and/or the methionine cycle.

[0012] In specific embodiments, the methods and compositions comprise increasing the level of intracellular GSH in an individual in need thereof, including an individual infected by or at risk of being infected by a virus of the *Coronaviridae* family, by administration of an effective amount of cysteine and glycine, or their various precursors, derivatives, or other forms, to the individual. In specific embodiments, the effective amount is effective to increase the intracellular GSH levels of the individual. In specific embodiments, the methods and compositions further comprise increasing an intracellular GSH deficiency in an individual in need thereof by administration of cysteine and glycine, or their various precursors, derivatives, or other forms, to the individual. In specific embodiments, the effective amount is effective to increase the deficient intracellular GSH levels of the individual.

[0013] In specific embodiments, the methods and compositions further comprise treating, preventing, delaying onset of, reducing severity of, and/or reducing or preventing one or more post-infection effects of a *Coronaviridae* family viral infection in an individual in need thereof by increasing intracellular GSH levels in the individual in need by administration of an effective amount of cysteine and glycine, or their various precursors, derivatives, or other forms, to the individual. In specific embodiments, the effective amount is effective to treat, prevent, delay onset of, reduce severity of, and/or reduce or prevent one or more post-infection effects of a *Coronaviridae* family viral infection in the individual. In specific embodiments, the methods and compositions further comprise increasing the survival rate of an individual infected with a *Coronaviridae* family virus. In specific embodiments, the methods and compositions further comprise reducing the recovery time of an individual infected with a *Coronaviridae* family virus. In specific embodiments, the methods and compositions further comprise treating, preventing, delaying onset of, reducing severity of, and/or reducing or preventing one or more post-infection effects of the symptoms of a *Coronaviridae* family viral infection in an individual. In specific embodiments, the methods and compositions further comprise treating, preventing, delaying onset of, reducing severity of, and/or reducing or preventing one or more post-infection effects of cellular, tissue, organ, or system damage caused by a *Coronaviridae* family viral infection in an individual.

[0014] In specific embodiments, the effective amount is effective to prevent the synthesis of viral RNA, inhibit viral replication, block viral binding to cell receptors, and/or inhibit viral self-assembly in the individual. In specific embodiments, the effective amount is effective to inhibit viral replication by inhibiting papain-like protease (PLpro) in the individual. In specific

embodiments, the effective amount is effective to competitively bind host cell angiotensin-converting enzyme 2 (ACE2) receptors in the individual. In specific embodiments, the effective amount is effective to inhibit virus associated gene expression in the individual. In specific embodiments, the effective amount is effective to inhibit virus associated gene expression of genes selected from the group consisting of: IFIH1, OAS2, DDX58, RTP4, TRIM21, CD86, CH25H, TDRD7, TIMELESS, FCGR2C, TANK, EDEM1, LCP2, and APOL6.

[0015] Low GSH levels further predispose an individual to increased oxidative stress, measured by plasma markers of oxidative stress, for example. In specific embodiments, the methods and compositions further comprise reducing and/or preventing oxidative stress in an individual in need thereof, such as one infected by or at risk of being infected by a virus from the *Coronaviridae* family, by administration of an effective amount of cysteine and glycine, or their various precursors, derivatives, or other forms, to the individual. In specific embodiments, the effective amount is effective to reduce and/or prevent oxidative stress in the individual of the individual. In specific embodiments, the methods and compositions further comprise reducing the plasma concentration of markers of oxidative stress and/or damage due to oxidative stress in the individual. In specific embodiments, the oxidative stress markers are thiobarbituric acid reactive substances (TBARS), malondialdehyde, lipid-peroxide, F2-isoprostane levels, F3-isoprostane, F2-isoprostane levels, neuroprostanes, F4-isoprostane levels, a hydroxynonenal or a combination thereof.

[0016] Increased oxidative stress levels further predispose an individual to adverse endothelial function. In specific embodiments, the methods and compositions further comprise reducing or preventing endothelial dysfunction in an individual in need thereof, such as one infected by or at risk of being infected by a virus from the *Coronaviridae* family, by administration of an effective amount of cysteine and glycine, or their various precursors, derivatives, or other forms, to the individual. In specific embodiments, the effective amount is effective to reduce or prevent endothelial dysfunction in the individual. In specific embodiments, the methods and compositions further comprise reducing endothelial dysfunction by reducing the plasma concentration of endothelial dysfunction markers in the individual. In some embodiments, the endothelial dysfunction markers are sICAM1, sVCAM1, E-selectin, EndoPAT, vascular reactivity, ultrasound flow mediated dilation, or a combination thereof.

[0017] Low GSH levels and oxidative stress further predispose an individual to elevated inflammation. In specific embodiments, the methods and compositions further comprise reducing or preventing inflammation in an individual in need thereof, such as one infected by or at risk of being infected by a virus from the *Coronaviridae* family, by administration of an effective amount of cysteine and glycine, or their various precursors, derivatives, or other forms, to the individual. In specific embodiments, the effective amount is effective to reduce or prevent inflammation in the individual. In specific embodiments, the methods and compositions further comprise reducing inflammation by reducing the plasma concentration of inflammatory markers (also known as biomarkers of inflammation) in the individual. In some embodiments, the markers of inflammatory response include but are not limited to IL-6, CRP, TNF-alpha, IL-10, MCP-1or a combination thereof.

[0018] Elevated inflammation is further correlated with immunosuppression. In specific embodiments, the methods and compositions further comprise reducing or preventing immunosuppression in an individual in need thereof, such as one infected by or at risk of being infected by a virus from the *Coronaviridae* family, by administration of an effective amount of cysteine and glycine, or their various precursors, derivatives, or other forms, to the individual. In specific embodiments, the effective amount is effective to reduce or prevent immunosuppression in the individual. In specific embodiments, the methods and compositions further comprise reducing immunosuppression by increasing the plasma concentration and improve or normalize the activity of cells of the immune system in the individual. In some embodiments, the immune cells include but are not limited to are CD4+ T-Cells, CD8+ T-Cells, B-cells, NK cells, antigen-presenting cells or a combination thereof.

[0019] Low GSH levels further predispose an individual to mitochondrial dysfunction. In specific embodiments, the methods and compositions comprise reducing or preventing mitochondrial dysfunction in an individual in need thereof, such as one infected by or at risk of being infected by a virus from the *Coronaviridae* family, by administration of an effective amount of cysteine and glycine, or their various precursors, derivatives, or other forms, to the individual. In specific embodiments, the effective amount is effective to reduce or prevent mitochondrial dysfunction in the individual. In specific embodiments, the effective amount is effective to increase fasted mitochondrial FA oxidation and to decrease fasted glucose oxidation in the individual. Mitrochondrial FA oxidation and glucose oxidation can be measured by calorimetry, molecular biology, respirometry, and other established methodologies.

[0020] Low GSH levels further predispose an individual to genomic damage. In specific embodiments, the methods and compositions further comprise reducing or preventing genomic damage in an individual in need thereof, such as one infected by or at risk of being infected by a virus from the *Coronaviridae* family, by administration of an effective amount of cysteine and glycine, or their various precursors, derivatives, or other forms, to the individual. In specific embodiments, the effective amount is effective to reduce or prevent genomic damage in the individual. Genomic damage can be measured by assays and molecular biology techniques.

[0021] Low GSH levels further predispose an individual to impaired autophagy, mitophagy, or a combination thereof. In specific embodiments, the methods and compositions further comprise reducing or preventing impaired autophagy, mitophagy, or a combination thereof, in an individual in need thereof, such as one infected by or at risk of being infected by a virus from the *Coronaviridae* family, by administration of an effective amount of cysteine and glycine, or their various precursors, derivatives, or other forms, to the individual. In specific embodiments, the effective amount is effective to reduce or prevent impaired autophagy, mitophagy, or a combination thereof, in the individual. Autophagy and mitophagy can be measured using molecular biology techniques.

[0022] Low GSH levels further predispose an individual to insulin resistance (low insulin sensitivity). In specific embodiments, the methods and compositions further comprise reducing or preventing insulin resistance in an individual in need thereof, such as one infected by or at risk of being infected by a virus from the *Coronaviridae* family, by administration of an effective amount of cysteine and glycine, or their various precursors, derivatives, or other forms, to the individual. In specific embodiments, the effective amount is effective to reduce or prevent insulin resistance in the individual. Insulin sensitivity tests can be measured using the homeostatic modeling assessment (HOMA-IR), fasting glucose and insulin levels, and also by the clamp methods, such as the hyperglycemic clamp method and the hyperinsulinemic-euglycemic clamp method.

[0023] Low GSH levels further predispose an individual to impaired cognition. In specific embodiments, the methods and compositions further comprise reducing or preventing impaired cognition in an individual in need thereof, such as one infected by or at risk of being infected by a virus from the Coronaviridae family, by administration of an effective amount of cysteine and glycine, or their various precursors, derivatives, or other forms, to the individual. In

specific embodiments, the effective amount is effective to reduce or prevent cognitive impairment in the individual. In specific embodiments, the individual does not have detectable impairment of cognitive function. In specific embodiments, the individual has detectable impairment of cognitive function, including impairment for any reason. In specific embodiments, the methods and compositions allow a delay of the onset of cognitive impairment or the enhancement of normal cognitive function. In specific embodiments, cognitive function may be defined as the mental process of knowing, including aspects such as sensation, attention, memory, awareness, perception, reasoning, and judgment, including but not limited to that which comes to be known, as through perception, reasoning, or intuition, knowledge, problem-solving, decision making, motor coordination, language, thought and intelligence. In specific embodiments, the effective amount is effective to improve normal or impaired memory in the individual. Neuropsychological assessments for cognitive function are known in the art, including the Mini-Mental State Exam (MMSE) and Montreal cognitive assessment (MoCA) which are a widely used test of cognitive function among the elderly and tests orientation, attention, memory, language and visual-spatial skills.

[0024] Low levels of GSH are correlated with mitochondrial dysfunction, which further correlates to functional limitation, including at least declines in muscle strength and/or muscle mass, gait speed, and exercise capacity. In certain aspects, GSH-deficient COVID-19 patients have impaired fasted FA oxidation and higher fasted glucose oxidation, suggesting a mitochondrial defect. Because elevated glucose oxidation in the fasted state occurs either by increased gluconeogenesis mainly from muscle protein, or by direct utilization of muscle proteins for energy needs, both routes lead to muscle loss. In certain aspects, loss of muscle strength and/or mass, gait speed, 6-minute walk test and exercise capacity correlate to low levels of GSH associated with a *Coronaviridae* viral infection. In specific embodiments, the methods and compositions comprise reducing or preventing functional limitation in an individual in need thereof, such as one infected by or at risk of being infected by a virus from the *Coronaviridae* family, by administration of an effective amount of cysteine and glycine, or their various precursors, derivatives, or other forms, to the individual. In specific embodiments, the effective amount is effective to reduce or prevent functional limitation in the individual. In specific embodiments, the functional limitation is impaired muscle strength and/or muscle mass, gait speed, and exercise capacity. In specific embodiments, the functional limitation is loss of muscle strength. In specific, embodiments, the functional limitation is loss of skeletal muscle. In specific

embodiments, the functional limitation is cachexia. In specific embodiments, the effective amount is effective to prevent, slow, reduce, or reverse weight loss or fatigue in the individual, or a combination thereof. In specific embodiments, the functional limitation is loss of bone mass. In specific embodiments, the functional limitation is loss of bone strength, including osteopenia and osteoporosis. Physical assessments including body composition, muscle strength, and/or bone density assessments, are known in the art.

[0025] Low levels of GSH are correlated with functional limitation, including at least declines in muscle strength and/or muscle mass, gait speed, and exercise capacity. In certain aspects, because the process of breathing (respiration) requires adequate strength in the muscles of respiration, GSH deficient COVID-19 patients have decreased lung function as measured by standard clinical pulmonary function tests and oxygen saturation tests. In certain aspects, limitation in lung function correlates to low levels of GSH associated with a *Coronaviridae* viral infection. In certain aspects, the methods and compositions comprise reducing or preventing limitation in lung function in an individual in need thereof, such as one infected by or at risk of being infected by a virus from the *Coronaviridae* family, by administration of an effective amount of cysteine and glycine, or their various precursors, derivatives, or other forms, to the individual. In specific embodiments, the effective amount is effective to reduce or prevent limitation in lung function in the individual. In specific embodiments, the limitation in lung function is impaired pulmonary function and oxygen saturation. In specific embodiments, the limitation in lung function is impaired pulmonary function. In specific, embodiments, the functional limitation is impaired oxygen saturation. Assessments of pulmonary function and/or oxygen saturation are known in the art.

[0026] In specific embodiments, the methods and compositions comprise increasing the survival rate of an individual infected with a *Coronaviridae* family virus, by administration of an effective amount of cysteine and glycine, or their various precursors, derivatives, or other forms, to the individual. In specific embodiments, the effective amount is effective to increase the survival rate of an individual infected with a *Coronaviridae* family virus. In specific embodiments, the effective amount is effective to increase the survival rate of an individual infected with SARS-CoV-2. Standards for determining clinical survival and improvement rates are known (*e.g.*, the World Health Organization (WHO) 'Ordinal Scale' for assessing interventions for COVID-19).

[0027] In specific embodiments, the methods and compositions further comprise reducing the recovery time of an individual infected with a *Coronaviridae* family virus, by administration of an effective amount of cysteine and glycine, or their various precursors, derivatives, or other forms, to the individual. In specific embodiments, the effective amount is effective to reduce the recovery time of an individual infected with a *Coronaviridae* family virus. In specific embodiments, the effective amount is effective to reduce the recovery time of an individual infected with SARS-CoV-2. Standards for determining clinical survival and improvement rates are known (*e.g.*, the World Health Organization (WHO) 'Ordinal Scale' for assessing interventions for COVID-19).

[0028] In specific embodiments, the glycine or functional derivative thereof and the N-acetylcysteine or functional derivative thereof may be provided to the individual in the same composition or different compositions. In specific embodiments, the glycine or functional derivative thereof and the N-acetylcysteine or functional derivative may be provided orally to the individual. In specific embodiments, the cysteine and glycine, or their various precursors, derivatives, or forms, comprise comestibles, including at least dietary supplements, comprising glycine and n-acetylcysteine.

[0029] In specific embodiments, the glycine derivative is selected from the group consisting of D-Allylglycine; N-[Bis(methylthio)methylene]glycine methyl ester; Boc-allyl-Gly-OH (dicyclohexylammonium) salt; Boc-D-Chg-OH; Boc-Chg-OH; (R)-N-Boc-(2′-chlorophenyl)glycine; Boc-L-cyclopropylglycine; Boc-L-cyclopropylglycine; (R)-N-Boc-4-fluorophenylglycine; Boc-D-propargylglycine; Boc-(S)-3-thienylglycine; Boc-(R)-3-thienylglycine; D-α-Cyclohexylglycine; L-α-Cyclopropylglycine; N-(2-fluorophenyl)-N-(methylsulfonyl) glycine; N-(4-fluorophenyl)-N-(methylsulfonyl)glycine; Fmoc-N-(2,4-dimethoxybenzyl)-Gly-OH; N-(2-Furoyl)glycine; L-α-Neopentylglycine; D-Propargylglycine; sarcosine; Z-α-Phosphonoglycine trimethyl ester, and a mixture thereof. The glycine and N-acetylcysteine may be comprised in a dipeptide, such as N-acetylcysteinylglycine or cysteinylglycine, for example.

[0030] In one embodiment of the disclosure, there is a composition consisting essentially of glycine and N-acetylcysteine. In another embodiment of the disclosure, there is a composition consisting of glycine and N-acetylcysteine. Methods of the disclosure include use of

either of these particular compositions for treatment or prevention of infection by a virus from the *Coronaviridae* family.

[0031] The foregoing has outlined rather broadly the features and technical advantages of the present disclosure in order that the detailed description of the disclosure that follows may be better understood. Additional features and advantages of the disclosure will be described hereinafter which form the subject of the claims of the disclosure. It should be appreciated that the conception and specific embodiment disclosed may be readily utilized as a basis for modifying or designing other structures for carrying out the same purposes of the present disclosure. It should also be realized that such equivalent constructions do not depart from the disclosure as set forth in the appended claims. The novel features which are believed to be characteristic of the disclosure, both as to its organization and method of operation, together with further objects and advantages will be better understood from the following description. It is to be expressly understood, however, that any description is provided for the purpose of illustration and description only and is not intended as a definition of the limits of the present disclosure.

BRIEF DESCRIPTION OF THE DRAWINGS

[0032] FIG. 1 shows oxidative stress, *via* Thiobarbituric acid reactive substances (TBARS) and F2-isoprostantes (I) measurements, in COVID-19 patients and healthy controls.

[0033] FIG. 2 shows correlation between RBC-GSH concentrations and increasing age.

[0034] FIG. 3 shows relation between older humans in the 60-80y age group when comparing those with COVID and without COVID.

[0035] FIG. 4 demonstrates relation between younger humans in the 21-60y age group when comparing those with COVID and without COVID.

[0036] FIG. 5 demonstrates correlation between oxidative stress and age.

[0037] FIG. 6 shows the relation between humans in the 60-80y age group when comparing those with COVID and without COVID for oxidative stress.

[0038] FIG. 7 provides the relation between younger humans in the 21-60y age group when comparing COVID-positive and COVID-negative humans.

[0039] FIG. 8 shows correlation between oxidant damage and age.

[0040] FIG. 9 shows relation between humans in the 60-80y age group when comparing those with COVID and without COVID for oxidant damage.

[0041] FIG. 10 demonstrates relation between COVID-positive and COVID-negative younger humans in the 21-60y age group.

DETAILED DESCRIPTION

I. Definitions

[0042] As used herein the specification, "a" or "an" may mean one or more. As used herein in the claim(s), when used in conjunction with the word "comprising", the words "a" or "an" may mean one or more than one. As used herein "another" may mean at least a second or more.

[0043] As used herein, the term “active infection” in specific embodiments refers to an infection, including any viral infection, in which a virus is actively replicating in an individual. Such an infection may be characterized by the spread of the virus to other cells, tissues, and/or organs in the individual, from the cells, tissues, and/or organs initially infected by the virus in the individual.

[0044] As used herein, the term “complications from diabetes” in specific embodiments refers to diabetic nephropathy, neuropathy, retinopathy, diabetic obesity, diabetic dyslipidemia, cardiometabolic syndrome, and combinations thereof, for example.

[0045] As used herein, the term “effective amount” refers to an amount of glycine and n-acetylcysteine (or functional derivatives thereof) that is required to improve at least one symptom of a medical condition in an individual; in specific embodiments, the medical condition exists in the individual directly or indirectly because of insufficient levels of glutathione. In specific embodiments, the effective amount refers to the amount of glycine and n-acetylcysteine that is utilized to increase glutathione levels in the individual.

[0046] As used herein, the term “elderly” refers to an individual over the age of at least 60, 65, 70, 75, 80, 85, 90, 95, or more years of age.

[0047] As used herein, the term "oxidative stress" refers to the state in an individual, or cell or tissue of an individual, of an imbalance between the production of reactive oxygen and the ability to detoxify the reactive intermediates or easily repair the resulting damage in a biological system. The natural reducing environment within cells is maintained by processes using a constant input of metabolic energy, and disturbances in this normal redox state can result in toxic effects through the production of, for example, free radicals and peroxides that damage cellular components, such as proteins, lipids, and/or DNA, for example.

[0048] As used herein, the term "post-infection effect", in specific embodiments, refers to one or more effects, such as one or more symptoms and/or syndromes that occur, or continue to occur, in an individual after the individual has cleared an active infection. In certain embodiments, a post-infection effect results from a chronic infection, including where one or more symptoms and/or syndromes occur, or continue to occur, in an individual after the individual has been said to have recovered from an infection. In some embodiments, a "post-infection effect" refers to one or more effects, including one or more symptoms and/or syndromes, that occur in an individual that has recovered from an infection.

II. General Embodiments

[0049] Embodiments of the disclosure include methods and compositions useful for treating, preventing, delaying onset of, reducing the severity of, or reducing post-infection effect(s) of a viral infection in an individual in need thereof. Particular embodiments of the disclosure include methods and compositions useful for treating, preventing, delaying onset of, or reducing severity of a *Coronaviridae* family viral infection in an individual in need thereof. In specific embodiments, the methods and compositions further comprise increasing blood levels of cysteine and glycine (*e.g.*, cysteinylglycine) to correct GSH deficiency, elevated oxidative stress, inflammation, immunosuppression, endothelial dysfunction, mitochondrial dysfunction, genomic damage, impaired autophagy, impaired mitophagy, insulin resistance, impaired cognition, functional limitation, or a combination thereof. In certain embodiments, the methods and compositions deliver to the individual at least glycine and N-acetylcysteine, in particular as precursor amino acids to facilitate raising GSH levels in the individual. One can measure red blood cell GSH, or a muscle biopsy to measure GSH levels intracellularly, for example. Intracellular GSH measuring assays are known in the art (Rahman et al., 2007).

[0050] In specific embodiments, an individual in need thereof is administered amounts of compositions as described herein that are effective to raise intracellular levels of GSH, cysteine, and/or glycine for the explicit purpose of treating, preventing, delaying onset of, or reducing severity of a viral infection in the individual, including a *Coronaviridae* family viral infection, including SARS-CoV-2. In specific cases, methods of the disclosure include the diagnosis of insufficient levels of intracellular GSH in an individual to treat, prevent, delay onset of, or reduce severity of a viral infection; the individual may or may not be subject to determination of insufficient levels of intracellular GSH upon onset of one or more viral infection symptoms, such as one or more flu-like symptoms.

[0051] The present disclosure encompasses treatment or prevention of infection of any virus in the *Coronaviridae* family. In certain embodiments, the disclosure encompasses treatment or prevention of infection of any virus in the subfamily Coronavirinae and including the four genera, Alpha-, Beta-, Gamma-, and Deltacoronavirus. In specific embodiments, the disclosure encompasses treatment or prevention of infection of any virus in the genus of Betacoronavirus, including the subgenus Sarbecovirus and including the species of severe acute respiratory syndrome-related coronavirus. In specific embodiments, the disclosure encompasses treatment or prevention of infection of any virus in the species of severe acute respiratory syndrome-related coronavirus, including the strains severe acute respiratory syndrome coronavirus (SARS-CoV) and severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2, the virus that causes COVID-19). The disclosure encompasses treatment or prevention of infection any isolate, strain, type (including Type A, Type B and Type C; Forster *et al.*, 2020, PNAS, https://doi.org/10.1073/pnas.2004999117), cluster, or sub-cluster of the species of severe acute respiratory syndrome-related coronavirus, including at least SARS-CoV-2. In specific embodiments, the virus being treated with methods and compositions of the disclosure is not SARS-CoV and is not MERS-CoV. In specific embodiments, the virus being treated with methods and compositions of the disclosure is SARS-CoV or is MERS-CoV. In specific embodiments, the virus has a genome length between about 29000 to about 30000, between about 29100 and 29900, between about 29200 and 29900, between about 29300 and 29900, between about 29400 and 29900, between about 29500 and 29900, between about 29600 and 29900, between about 29700 and 29900, between about 29800 and 29900, or between about 29780 and 29900 base pairs in length.

[0052] Examples of specific SARS-CoV-2 viruses include the following listed in the NCBI GenBank® Database, and these GenBank® Accession sequences are incorporated by reference herein in their entirety: (a) LC534419 and LC534418 and LC528233 and LC529905 (examples of different strains from Japan); (b) MT281577 and MT226610 and NC_045512 and MN996531 and MN908947 (examples of different strains from China); (c) MT281530 (Iran); (d) MT126808 (Brazil); (e) MT020781 (Finland); (f) MT093571 (Sweden); (g) MT263074 (Peru); (h) MT292582 and MT292581 and MT292580 and MT292579 (examples of different strains from Spain); (i) examples from the United States, such as MT276331 (TX); MT276330 (FL); MT276328 (OR) MT276327 (GA); MT276325 (WA); MT276324 (CA); MT276323 (RI); MT188341 (MN); and (j) MT276598 (Israel). In particular embodiments, the disclosure encompasses treatment or prevention of infection of any of these or similar viruses, including viruses whose genome has at least 80, 81, 82, 83, 84, 85, 86, 87, 88, 89, 90, 91, 92, 93, 94, 95, 96, 97, 98, 99, 99.1, 99.2, 99.3, 99.4, 99.5, 99.6, 99.7, 99.8, or 99.9% identity to any of these viruses. In particular embodiments, the disclosure encompasses treatment or prevention of infection of any of these or similar viruses, including viruses whose genome has its entire sequence that is greater than 80, 81, 82, 83, 84, 85, 86, 87, 88, 89, 90, 91, 92, 93, 94, 95, 96, 97, 98, 99, 99.1, 99.2, 99.3, 99.4, 99.5, 99.6, 99.7, 99.8, or 99.9% identity to any of these viruses. As one specific example, the present disclosure includes methods of treatment or prevention of infection of a virus having a genome sequence as represented by GenBank® Accession No. NC_045512 (origin Wuhan, China) and any virus having a genome sequence with at least 80, 81, 82, 83, 84, 85, 86, 87, 88, 89, 90, 91, 92, 93, 94, 95, 96, 97, 98, 99, 99.1, 99.2, 99.3, 99.4, 99.5, 99.6, 99.7, 99.8, or 99.9% identity to this virus. Infection with any strain of SARS-CoV-2 may be treated or prevented, including at least B.1.526, B.1.526.1, B.1.525, B.1.1.7, B.1.351, B.1.427, B.1.429, B.1.617, P.1, and P.2.

[0053] An individual in need thereof may be an individual having one or more symptoms of infection by a virus of the *Coronaviridae* family, such as SARS-CoV-2 or SARS-CoV. Common initial signs and symptoms of SARS-CoV-2 may include fever, cough, shortness of breath or difficulty breathing, tiredness, aches, chills, sore throat, loss of smell, loss of taste, headache, diarrhea, dizziness, and/or vomiting. As the viral infection progresses, the individual may develop pneumonia or acute respiratory distress syndrome (ARDS). In some embodiments, the virus is SARS-CoV-2, and in certain embodiments the virus is not SARS-CoV or MERS.

[0054] Certain embodiments encompass the prevention or reduction of one or more post-infection effects. In some embodiments, an individual having one or more post-infection

effects is administered any composition described herein. In some embodiments, an individual having one or more post-infection effects is administered compositions consisting of, consisting essentially of, or comprising glycine (or a functional derivative or precursor thereof) and N-acetylcysteine (or a functional derivative or precursor thereof). A post-infection effect may be a chronic syndrome, a chronic illness, a chronic disorder, and/or a chronic disease. In some embodiments, post-infection effects may result from a chronic infection. A post-infection effect may start during or after an active infection. In some embodiments, one or more post-infection effects last in an individual for 1, 2, 3, 4, 5, 6, 7 days; 1, 2, 3, 4 weeks; 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12 months, or 1, 2, 3, 4, 5, or more years after an active infection. In some embodiments, one or more post-infection effects comprise post-COVID-19 syndrome and/or long COVID-19. An individual suffering from at least one post-infection effect may be a COVID long hauler. In specific embodiments, any symptom referred to herein with respect to acute-Covid could also apply to long-Covid. An individual considered to be a COVID long hauler may be one that is recovered from the acute phase of the illness and no longer has live coronavirus in the body and that would test negative for the coronavirus, but they still have one or more symptoms. This individual may also be referred to as having post-acute sequelae of SARS-CoV-2, post-COVID syndrome, long COVID, or long-term COVID. Some of these individuals may have fatigue, shortness of breath, cough, joint pain, chest pain, cognitive problems, difficulty concentrating, depression, muscle pain, headache, rapid heartbeat, and/or intermittent fever. Generally, long haulers may have breathing issues, including from lung scarring; heart problems, including from inflammation of the heart muscle; kidney damage; lost or distorted senses of smell and/or taste; neurological problems, including brain fog, fatigue, headaches and/or dizziness; autonomic nervous system symptoms, including Postural orthostatic tachycardia syndrome, headache, fatigue, brain fog, difficulties in thinking or concentrating, and/or insomnia; mental health issues, including anxiety and/or depression; and/or development of type 2 diabetes.

[0055] Post-infection effects may include fatigue (including chronic fatigue syndrome), shortness of breath, cough, congestion, joint pain, chest pain, abdominal pain, difficulty with thinking and/or difficulty with concentration, brain fog, confusion, depression, muscle pain, headache, tinnitus, intermittent fever, fast-beating and/or pounding heart (also known as heart palpitations), diarrhea, nausea, cardiovascular issues (including heart inflammation), impairment of exercise capacity, pulmonary embolism, stroke, blot clots, immunological issues, respiratory issues (including lung function abnormalities), renal issues (including acute kidney

injury), dermatologic issues (including rash or hair loss), neurological issues (including smell and taste problems, sleep issues, post-traumatic stress disorder, or memory problems), psychiatric issues (including anxiety or changes in mood), or a combination thereof.

[0056] In some embodiments, a post-infection effect may occur in an individual that has recovered from an infection, including an active infection. In some embodiments, the determination of whether an individual has recovered from an infection, including an active infection, is done by a person skilled in the art. In some embodiments, an individual has recovered from an infection 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21 or more days after being diagnosed with the infection and/or after developing symptoms caused by or associated with the infection. In some embodiments, an individual has recovered when the individual is able to return to normal daily functions, such as returning to work or school. In some embodiments, an individual has recovered from an infection if at least 1, 2, 3, 4, 5 or more days have passed without the individual having a fever, including while the individual is not taking fever-reducing medication. In some embodiments, an individual has recovered from an infection if at least 1, 2, 3, 4, 5 or more days have passed without any active infection symptom, or any symptom has decreased in severity. In some embodiments, an individual has recovered from an infection when the individual has developed an adaptive immune response to the infection source, such as the virus comprising the infection. In some embodiments, an individual has recovered from an infection when the individual is no longer contagious to other individuals. In some embodiments, an individual has recovered from an infection if the individual tests negative for the infection at least once after having been diagnosed with, or testing positive for, the infection. The test for the infection may comprise any laboratory test, any swab test, any PCR test, any antibody test, any antigen test, any imaging test (such as a CT scan), or any other test capable of determining whether an individual has an infection.

III. Pharmaceutical Compositions

[0057] In specific embodiments, the present disclosure is directed to pharmaceutical compositions for use in treating, preventing, delaying onset of, or reducing severity of a viral infection in an individual, including at least in some cases a viral infection that is directly or indirectly related to reduced intracellular GSH levels. In specific embodiments, the compositions consist of, consisting essentially of, or comprise glycine (or a functional derivative thereof) and N-acetylcysteine (or a functional derivative thereof). A functional derivative of glycine is defined as a glycine derivative that is effective in an individual in by itself or in

conjunction with N-acetylcysteine (or a functional derivative thereof) to increase intracellular GSH levels. A functional derivative of N-acetylcysteine is defined as a N-acetylcysteine derivative that is effective in an individual in by itself or in conjunction with glycine (or a functional derivative thereof) to increase intracellular GSH levels. In specific embodiments, a "cysteine" derivative, *i.e.*, a functional derivative of cysteine that is effective in an individual in by itself or in conjunction with glycine, may be employed.

[0058] The glycine component and N-acetylcysteine component may be provided together or separately. The glycine component and N-acetylcysteine component may or may not be provided in the same formulation. In specific embodiments, the composition comprises N-acetylcysteinylglycine; cysteinylglycine and all its forms, *e.g.*, L-cysteinylglycine; and so forth. Examples of glycine derivatives includes at least D-Allylglycine; N-[Bis(methylthio)methylene]glycine methyl ester; Boc-allyl-Gly-OH (dicyclohexylammonium) salt; Boc-D-Chg-OH; Boc-Chg-OH; (R)-N-Boc-(2′-chlorophenyl)glycine; Boc-L-cyclopropylglycine; Boc-L-cyclopropylglycine; (R)-N-Boc-4-fluorophenylglycine; Boc-D-propargylglycine; Boc-(S)-3-thienylglycine; Boc-(R)-3-thienylglycine; D-α-Cyclohexylglycine; L-α-Cyclopropylglycine; N-(2-fluorophenyl)-N-(methylsulfonyl) glycine; N-(4-fluorophenyl)-N-(methylsulfonyl)glycine; Fmoc-N-(2,4-dimethoxybenzyl)-Gly-OH; N-(2-Furoyl)glycine; L-α-Neopentylglycine; D-Propargylglycine; sarcosine; Z-α-Phosphonoglycine trimethyl ester; serine (*e.g.*, as a precursor for glycine); and methionine (*e.g.*, as a precursor for cysteine; and so forth.

[0059] In specific embodiments, the pharmaceutical compositions comprise N-acetylcysteine (NAC), L-glycine, L-glycine ethyl ester, and/or dipeptide forms, *e.g.*, cysteinylglycine.

[0060] In specific embodiments, glycine is administered at 1-150 mg/kg/day and NAC is administered at 1-150 mg/kg/day for a particular period of time. The range of dose for either or both may be 1-150, 1-125, 1-100, 1-75, 1-50, 1-25, 1-20, 1-10, 1-5, 10-150, 10-125, 10-100, 10-75, 10-50, 10-25, 25-150, 25-125, 25-100, 25-75, 25-50, 50-150, 50-125, 50-100, 50-75, 75-150, 75-125, 75-100, 100-150, 100-125, or 125-150 mg/kg/day, for example. In specific embodiments, glycine is administered at 1.33 mmol/kg/d and NAC is administered at 0.83 mmol/kg/d for a particular period of time. Durations of treatment may last for one or more days, 1 week, 2 weeks, 3 weeks, one month, two months, three months, four months, five months, six months, one year, two years, five years, ten years, fifteen years, twenty years, twenty-five years,

thirty years, and so forth, for example. In specific embodiments, an individual with acute-Covid is treated from 1-30 days, including 1-25, 1-20, 1-15, 1-10, 1-5, 5-30, 5-25, 5-20, 5-15, 5-10, 10-30, 10-25, 10-20, 10-15, 15-30, 15-25, 15-20, 20-30, 20-25, 25-30, and so forth. In specific embodiments, an individual with long-Covid is treated from 3 months to lifelong, 3 months to 70 years (yrs), 3 months to 60 yrs, 3 months to 50 yrs, 3 months to 40yrs, 3 months to 30 yrs, 3 months to 20 yrs, 3 months to 10 yrs, 3 months to 5 yrs, 3 months to 1 yr, and any range derivable therein. In some cases the treatment lasts for the remaining life of the individual. In specific embodiments, the administration occurs until no detectable symptoms of the viral infection remain or until one or more symptoms have disappeared, such as ARDS, pneumonia, and/or fever, for example. In specific embodiments, the administration occurs until a detectable improvement of at least one symptom occurs and, in further cases, continues to remain ameliorated. The treatment may occur on individuals who are not hospitalized but are quarantining or recovering at home.

[0061] Where the disclosure is directed to treating with the compounds of the present disclosure, administration of the compounds of the disclosure with a suitable pharmaceutical excipient as necessary can be carried out *via* any of the accepted modes of administration. The compounds may be comprised in a pharmaceutically acceptable excipient, which may be considered as a molecular entity and/or composition that does not produce an adverse, allergic and/or other untoward reaction when administered to an animal, as appropriate. It includes any and/or all solvents, dispersion media, coatings, antibacterial and/or antifungal agents, isotonic and/or absorption delaying agents and/or the like. The use of such media and/or agents for pharmaceutical active substances is well known in the art. Except insofar as any conventional media and/or agent is incompatible with the active ingredient, its use in the therapeutic compositions is contemplated.

[0062] Thus, administration can be, for example, intravenous, topical, subcutaneous, transcutaneous, intramuscular, oral, intra-joint, parenteral, peritoneal, intranasal, intravesical or by inhalation. Suitable sites of administration thus include, but are not limited to, skin, bronchial, gastrointestinal, anal, vaginal, eye, bladder, and ear. The formulations may take the form of solid, semi-solid, lyophilized powder, or liquid dosage forms, such as, for example, tablets, pills, capsules, powders, solutions, suspensions, emulsions, suppositories, retention enemas, creams, ointments, lotions, aerosols or the like, *e.g.,* in unit dosage forms suitable for simple administration of precise dosages.

[0063] The compositions typically include a conventional pharmaceutical carrier or excipient and may additionally include other medicinal agents, carriers, adjuvants, and the like. In specific embodiments, the composition will be about 5% to 75% by weight of a compound or compounds of the disclosure, with the remainder consisting of suitable pharmaceutical excipients. Appropriate excipients can be tailored to the particular composition and route of administration by methods well known in the art, *e.g.*, REMINGTON'S PHARMACEUTICAL SCIENCES, 18TH ED., Mack Publishing Co., Easton, Pa. (1990).

[0064] For oral administration, such excipients include pharmaceutical grades of mannitol, lactose, starch, magnesium stearate, sodium saccharine, talcum, cellulose, glucose, gelatin, sucrose, magnesium carbonate, and the like. The composition may take the form of a solution, suspension, tablet, pill, capsule, powder, sustained-release formulation, and the like.

[0065] In some embodiments, the pharmaceutical compositions take the form of a pill, tablet or capsule, and thus, the composition can contain, along with the biologically active conjugate, any of the following: a diluent such as lactose, sucrose, dicalcium phosphate, and the like; a disintegrant such as starch or derivatives thereof; a lubricant such as magnesium stearate and the like; and a binder such a starch, gum acacia, polyvinylpyrrolidone, gelatin, cellulose and derivatives thereof.

[0066] The active compounds of the formulas may be formulated into a suppository comprising, for example, about 0.5% to about 50% of a compound of the disclosure, disposed in a polyethylene glycol (PEG) carrier (*e.g.*, PEG 1000 [96%] and PEG 4000 [4%]).

[0067] Liquid compositions can be prepared by dissolving or dispersing compound (about 0.5% to about 20%), and optional pharmaceutical adjuvants in a carrier, such as, for example, aqueous saline (*e.g.*, 0.9% w/v sodium chloride), aqueous dextrose, glycerol, ethanol and the like, to form a solution or suspension, *e.g.*, for intravenous administration. The active compounds may also be formulated into a retention enema.

[0068] If desired, the composition to be administered may also contain minor amounts of non-toxic auxiliary substances such as wetting or emulsifying agents, pH buffering agents, such as, for example, sodium acetate, sorbitan monolaurate, or triethanolamine oleate.

[0069] For topical administration, the composition is administered in any suitable format, such as a lotion or a transdermal patch. For delivery by inhalation, the composition can be delivered as a dry powder (*e.g.*, Inhale Therapeutics) or in liquid form *via* a nebulizer.

[0070] Methods for preparing such dosage forms are known or will be apparent to those skilled in the art; for example, see Remington's Pharmaceutical Sciences, supra., and similar publications. The composition to be administered will, in any event, contain a quantity of the pro-drug and/or active compound(s) in a pharmaceutically effective amount for relief of the condition being treated when administered in accordance with the teachings of this disclosure.

[0071] Generally, the compounds of the disclosure are administered in a therapeutically effective amount, *i.e.*, a dosage sufficient to effect treatment, which will vary depending on the individual and condition being treated. Typically, a therapeutically effective daily dose is from 0.1 to 100 mg/kg of body weight per day of drug. Most conditions respond to administration of a total dosage of between about 1 and about 30 mg/kg of body weight per day, or between about 70 mg and 2100 mg per day for a 70 kg person.

[0072] Stability of the conjugate can be further controlled by chemical alterations, including D amino acid residues in the polypeptide chain as well as other peptidomimetic moieties. Furthermore, stability of the conjugates could also be enhanced by unnatural carbohydrate residues.

[0073] The glycine and N-acetylcysteine components may be formulated in a particular ratio, whether or not they are present in the same formulation. In certain embodiments, the components are provided to the individual in the following exemplary ratios (including in specific cases in the same formulation): 1:1, 1:2, 1:3, 1:4, 1:5, 1:6, 1:7, 1:8, 1:9, 1:10, 1:12, 1:15, 1:20, 1:25, 1:30, 1:35, 1:40, 1:45, 1:50, 1:55, 1:60, 1:65, 1:70, 1:75, 1:80, 1:85, 1:90, 1:95, 1:100, 1:150, 1:200, 1:300, 1:400, 1:500, 1:600, 1:750, 1:1000, 1:10,000, and so forth, for example. In specific embodiments, the formulation may comprise the components in the following percentages by formulation (either the same or different percentages for each): 1%, 2%, 3%, 4%, 5%, 6%, 7%, 8%, 9%, 10%, 12%, 15%, 20%, 25%, 30%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, 97%, or 99%, for example.

[0074] Glycine (or a functional derivative) and N-acetylcysteine (or a functional derivative) may be delivered in the same composition or in different compositions. In

embodiments wherein glycine (or a functional derivative) and N-acetylcysteine (or a functional derivative) are provided separately, the regimen for their separate delivery may be of any suitable kind. In specific embodiments, the glycine is provided to the individual prior to the N-acetylcysteine, at the same time as N-acetylcysteine, or subsequent to N-acetylcysteine. Separate deliveries may encompass the same route of administration but at different times or may be different routes of administration.

IV. Combination Treatments

[0075] In specific embodiments, an additional viral therapy or preventative may be provided in combination with the disclosed treatment. In specific embodiments, the additional viral therapy or preventative is for a *Coronaviridae* family infection (including SARS-CoV-2) selected from the group consisting of Azithromycin, AC-55541, Apicidin, AZ3451, AZ8838, Bafilomycin A1, CCT 365623, Daunorubicin, E-52862, Entacapone, GB110, H-89, Haloperidol, Indomethacin, JQ1, Loratadine, Merimepodib, Metformin, Midostaurin, Migalastat, Mycophenolic acid, PB28, PD-144418, Ponatinib, Ribavirin, RS-PPCC, Ruxolitinib, RVX-208, S-verapamil, Silmitasertib , TMCB, UCPH-101, Valproic Acid, XL413, ZINC1775962367, ZINC4326719, ZINC4511851, ZINC95559591, 4E2RCat, ABBV-744, Camostat, Captopril, CB5083, Chloramphenicol, Chloroquine (and/or Hydroxychloroquine), CPI-0610, Dabrafenib, DBeQ, dBET6, IHVR-19029, Linezolid, Lisinopril, Minoxidil, ML240, MZ1, Nafamostat, Pevonedistat, PS3061, Rapamycin (Sirolimus), Sanglifehrin A, Sapanisertib (INK128/MIN128), FK-506 (Tacrolimus), Ternatin 4 (DA3), Tigecycline, Tomivosertib (eFT-508), Verdinexor, WDB002, Zotatifin (eFT226), and a combination thereof.

[0076] Alternatively, the disclosed treatment may precede, follow, or both an additional viral treatment or preventative by intervals ranging from minutes to weeks to months. In embodiments where the disclosed treatment and the additional agent are provided separately to an individual, one would generally ensure that a significant period of time did not expire between the time of each delivery, such that the disclosed treatment and the additional agent would still be able to exert an advantageously combined effect on the cell. In such instances, it is contemplated that one may deliver both modalities within about 12-24 h of each other and, in some embodiments, within about 6-12 h of each other. In some situations, it may be desirable to extend the time period for treatment significantly, however, where several days (2, 3, 4, 5, 6 or 7) to several weeks (1, 2, 3, 4, 5, 6, 7 or 8) to several months (from 1-12), any subrange therein, and so forth, lapse between the respective administrations.

[0077] Various combinations may be employed, for example, wherein the disclosed treatment is "A" and the secondary additional viral treatment or preventative is "B":

A/B/A	B/A/B	B/B/A	A/A/B	A/B/B	B/A/A	A/B/B/B	B/A/B/B
B/B/B/A	B/B/A/B	A/A/B/B	A/B/A/B	A/B/B/A	B/B/A/A		
B/A/B/A	B/A/A/B	A/A/A/B	B/A/A/A	A/B/A/A	A/A/B/A		

[0078] Administration of the disclosed treatment to a patient will follow general protocols for the administration of drugs, taking into account the toxicity, if any, of the molecule. It is expected that the treatment cycles would be repeated as necessary. It also is contemplated that various standard therapies, as well as surgical intervention, may be applied in combination with the described therapy.

V. Kits

[0079] Therapeutic kits associated with the compositions of the present disclosure comprise another aspect of the present disclosure. Such kits will generally contain, in suitable container means, an inventive composition of the present disclosure. The kit may have a single container means that contains the inventive composition or it may have distinct container means for the inventive composition and other reagents that may be included within such kits.

[0080] The components of the kit may be provided as liquid solution(s), or as dried powder(s). When the components are provided in a liquid solution, the liquid solution is an aqueous or non-aqueous solution, including at least a sterile aqueous or non-aqueous solution. When reagents or components are provided as a dry powder, the powder can be reconstituted by the addition of a suitable solvent. It is envisioned that the solvent may also be provided in another container means.

[0081] The container means will generally include at least one vial, test tube, flask, bottle, syringe or other container means, into which the composition may be placed, and, in some embodiments, suitably aliquoted. Where a second agent is provided, the kit will also generally contain a second vial or other container into which this agent may be placed. The kits of the present disclosure will also typically include a means for containing the agent containers in close confinement for commercial sale. Such containers may include injection or blow-molded plastic containers into which the desired vials are retained, for example.

[0082] In the kit of the disclosure, the glycine (or functional derivative thereof) and the N-acetylcysteine (or functional derivative thereof) may be provided separately or in a mixture together. In some embodiments, the kit comprises one or more reagents for diagnosis of a viral infection of the *Coronaviridae* family, including SARS-CoV-2. Examples of reagents include primers for viral nucleic acid detection and/or antibodies for viral antigen detection.

VI. Examples

[0083] The following examples are included to demonstrate exemplary embodiments of the disclosure. It should be appreciated by those of skill in the art that the techniques disclosed in the examples which follow present techniques discovered by the inventors to function well in the practice of the disclosure, and thus can be considered to constitute exemplary modes for its practice. However, those of skill in the art should, in light of the present disclosure, appreciate that many changes can be made in the specific embodiments which are disclosed and still obtain a like or similar result without departing from the spirit and scope of the disclosure.

[0084] In some embodiments, patients infected with *Coronaviridae* virus have severely elevated inflammation, suppressed immune function, and viral pneumonia - specifically, suppressed plasma levels of CD4+ T-Cells, CD8+ T-Cells, B-cells, NK cells, and/or antigen-presenting cells of the immune system in these patients correlate inversely with elevated inflammatory markers IL-6, CRP, TNF-alpha, IL-10, and/or MCP-1. In certain aspects, as a *Coronaviridae* viral infection progresses, there is oxygen desaturation in the blood requiring oxygenated ventilation to save lives. *Coronaviridae* viral infections are associated with severe and harmful oxidative stress, vascular endothelial dysfunction, impaired red-blood function and impaired oxygen delivery to tissues. In certain aspects, under normal conditions cells protect themselves from the ravages of oxidative stress by synthesizing glutathione (GSH). In certain aspects, indeed, GSH is the most abundant natural intracellular antioxidant protein which combats and eliminates excess cellular oxidative stress. In certain aspects, *Coronaviridae* viral infections result in GSH deficiency, and cell-culture studies show that increasing GSH levels have a viricidal effect by inhibiting replication of *Coronaviridae* viruses. In some embodiments related to the disclosure, the combination of GSH deficiency, elevated oxidative stress, endothelial dysfunction, inflammation, and/or immunosuppression combine to contribute to the severely elevated mortality due to COVID-19.

[0085] In certain aspects, *Coronaviridae* viral infections have significantly elevated oxidative stress, inflammation and immunosuppression. In certain aspects, tracer studies demonstrate that the reason for elevated oxidative stress in *Coronaviridae* viral infections is severe deficiency of the endogenous antioxidant protein glutathione (GSH), and the GSH deficiency occurs due to diminished availability of its precursor amino-acids glycine and cysteine. In certain aspects, supplementing glycine and N-acetylcysteine (a cysteine donor) – combination termed GlyNAC – successfully corrects deficiency of intracellular glycine and cysteine, corrects GSH deficiency, and lowers oxidative stress in *Coronaviridae* viral infection patients. In certain aspects, results show correction of intracellular GSH deficiency together with a significant decrease in plasma oxidative stress (measured as plasma concentrations of TBARS, malondialdehyde, lipid-peroxide, and/or F2-isoprostanes), severely elevated inflammation (plasma IL-6, CRP, TNF-alpha, IL-10, and/or MCP-1), and endothelial dysfunction (plasma sICAM1, sVCAM1 and/or E-selectin). In certain aspects, this is associated with significant improvement of key functional measures in *Coronaviridae* viral infection patients. In certain aspects, supplementing GlyNAC in patients infected with a *Coronaviridae* virus, particularly the SARS-CoV-2 virus, effectively treats or prevents or delay onset of or reduces severity of COVID-19 by correcting GSH deficiency and lowering oxidative stress, inflammation, endothelial dysfunction and defective immune function in patients. In certain aspects, such a treatment leads to significant decline in morbidity, mortality and healthcare expenditure.

EXAMPLE 1

CORONAVIRIDAE VIRAL INFECTION AND GLUTATHIONE (GSH) DEFICIENCY

[0086] **Glutathione (GSH) in COVID-19 patients by age group**: In certain aspects, in a randomized trial, intracellular GSH concentrations are studied in patients diagnosed with COVID-19 (ages 20-90y), and results are compared to patients without COVID-19. Intracellular GSH levels are measured in all subjects from red-blood cells. Results are stratified by age and show that COVID-19 patients have a severe intracellular GSH deficiency, and this becomes progressively worse with advancing age. Regarding COVID-19, comparing young patients (age range 20-30 years), with middle aged patients (age 40-50 years) with elderly patients (60-90 years) shows that GSH levels are highest in the young group and progressively decline with advancing age to be lowest in the elderly group. Patients receive supplementation with GlyNAC (glycine and cysteine (as N-acetylcysteine)) or placebo for 14-21 days, and GSH concentratrations

improve only in patients supplemented with GlyNAC (but not placebo), but the increase in GSH levels is higher with advancing age such that at the end of the supplementation period, all patients have similar GSH values.

[0087] Glutathione in COVID-19 patients with HIV: In certain aspects, in a randomized clinical trial, intracellular GSH concentrations are studied in HIV patients diagnosed with COVID-19 before and after supplementation with cysteine plus glycine (GlyNAC) as GSH precursors, or placebo, for 14-21 days. Intracellular GSH levels are measured in all subjects from red-blood cells. Results show that GSH concentrations at the end of supplementation improve only in HIV patients with COVID-19 who receive GlyNAC supplementation, and not in patients who receive placebo.

[0088] Glutathione in COVID-19 patients with diabetes: In certain aspects, in a randomized clinical trial, intracellular GSH concentrations are studied in diabetic patients diagnosed with COVID-19 before and after supplementation with cysteine plus glycine (GlyNAC) as GSH precursors, or placebo, for 14-21 days. A group of subjects without diabetes or COVID-19 serves as a control. Intracellular GSH levels are measured in all subjects from red-blood cells. Results show that GSH concentrations at the end of supplementation improve only in diabetic patients with COVID-19 who receive GlyNAC supplementation, and not in diabetic patients who receive placebo. Further analyses show that the GSH levels in diabetic COVID-19 subjects increase to approximate values in subjects without diabetes or COVID-19.

[0089] Glutathione in COVID-19 patients with prediabetes (defined as fasting glucose values between 100-125 mg/dl): In certain aspects, in a randomized clinical trial, intracellular GSH concentrations are studied in prediabetic patients diagnosed with COVID-19 before and after supplementation with cysteine plus glycine (GlyNAC) as GSH precursors, or placebo, for 14-21 days. A group of subjects without prediabetes or diabetes or COVID-19 serves as a control. Intracellular GSH levels are measured in all subjects from red-blood cells. Results show that GSH concentrations at the end of supplementation improve only in prediabetic patients with COVID-19 who receive GlyNAC supplementation, and not in prediabetic patients who receive placebo. Further analyses show that the GSH levels in prediabetic COVID-19 subjects increase to approximate values in subjects without prediabetes or diabetes or COVID-19.

[0090] Glutathione in obese COVID-19 patients: In certain aspects, in a randomized clinical trial, intracellular GSH concentrations are studied in obese patients diagnosed

with COVID-19 before and after supplementation with cysteine plus glycine (GlyNAC) as GSH precursors, or placebo, for 14-21 days. A group of subjects without obesity, diabetes or COVID-19 serves as a control. Intracellular GSH levels are measured in all subjects from red-blood cells. Results show that GSH concentrations at the end of supplementation improve only in obese patients with COVID-19 who receive GlyNAC supplementation, and not in obese patients who receive placebo. Further analyses show that the GSH levels in obese COVID-19 subjects increase to approximate values in subjects without obesity, diabetes or COVID-19.

[0091] Thus, in certain aspects, all COVID-19 patients have greater GSH deficiency than the non-COVID-19 control group because of decreased availability of its precursors cysteine and glycine, while older COVID-19 patients have significantly lower GSH levels than younger COVID-19 patients. HIV patients with COVID-19 have significantly lower GSH levels than non-HIV non-COVID-19 patients. Diabetic and prediabetic patients with COVID-19 have significantly lower GSH levels than non-prediabetic, non-diabetic, non-COVID-19 patients. Obese patients with COVID-19 have significantly lower GSH levels than non-obese non-COVID-19 patients. Cysteine and glycine supplementation increase GSH levels in all patients with COVID-19.

EXAMPLE 2

CORONAVIRIDAE VIRAL INFECTION AND OXIDATIVE STRESS

[0092] In certain aspects, *Coronaviridae* viral infections are associated with severe and harmful oxidative stress, an imbalance between free radicals and antioxidants in the body. A surplus amount of free radicals, for example reactive oxygen species (ROS), results in cellular damage due to the oxidation of cellular lipids, proteins, and DNA. Oxidative degradation of lipids by ROS, forms highly reactive and unstable lipid peroxides. Decomposition of lipid peroxides results in the formation of Thiobarbituric Acid Reactive Substances (TBARS), malondialdehyde, lipid-peroxide, and/or F2-isoprostanes (F2-isoPs) which are useful as biomarkers for oxidative stress.

[0093] **Oxidative stress in COVID-19 patients by age group**: In certain aspects, in a randomized trial, biomarkers of oxidative stress are studied in patients diagnosed with COVID-19 (ages 20-90y), and results are compared to patients without COVID-19. Levels of biomarkers of oxidative stress are measured in all subjects as plasma levels of TBARS,

malondialdehyde, lipid-peroxide, and/or F2-isoPs in blood. Results are stratified by age and will show that COVID-19 patients will have a higher levels of biomarkers of oxidative stress, and this is progressively higher with advancing age. Regarding COVID-19, comparing young patients (age range 20-30 years), with middle aged patients (age 40-50 years) with elderly patients (60-90 years) shows levels of biomarkers of oxidative stress are lowest in the young group and progressively increase with advancing age to be highest in the elderly group. Patients receive supplementation with GlyNAC (glycine and cysteine (as N-acetylcysteine)) or placebo for 14-21 days, and levels of biomarkers of oxidative stress improve only in patients supplemented with GlyNAC (but not placebo), but the fall in levels of biomarkers of oxidative stress is greater with advancing age such that at the end of the supplementation period, all patients have similar levels of biomarkers of oxidative stress.

[0094] Biomarkers of oxidative stress in COVID-19 patients with HIV: In certain aspects, in a randomized clinical trial, levels of biomarkers of oxidative stress are studied in HIV patients diagnosed with COVID-19 before and after supplementation with cysteine plus glycine (GlyNAC) as GSH precursors, or placebo, for 14-21 days. Levels of biomarkers of oxidative stress are measured in all subjects as plasma levels of TBARS, malondialdehyde, lipid-peroxide, and/or F2-isoPs in blood. Results show that levels of biomarkers of oxidative stress improve only in HIV patients with COVID-19 who receive GlyNAC supplementation, and not in patients who receive placebo.

[0095] Biomarkers of oxidative stress COVID-19 patients with diabetes: In certain aspects, in a randomized clinical trial, levels of biomarkers of oxidative stress in plasma are studied in diabetic patients diagnosed with COVID-19 before and after supplementation with cysteine plus glycine (GlyNAC) as GSH precursors, or placebo, for 14-21 days. A group of subjects without diabetes or COVID-19 serves as a control. Levels of biomarkers of oxidative stress are measured in all subjects as plasma levels of TBARS, malondialdehyde, lipid-peroxide, and/or F2-isoPs in blood. Results show that levels of biomarkers of oxidative stress improve only in diabetic patients with COVID-19 who receive GlyNAC supplementation, and not in diabetic patients who receive placebo. Further analyses show that the levels of biomarkers of oxidative stress in diabetic COVID-19 subjects decrease to approximate values in subjects without diabetes or COVID-19.

[0096] Biomarkers of oxidative stress in COVID-19 patients with prediabetes (defined as fasting glucose values between 100-125 mg/dl): In certain aspects, in a randomized clinical trial, levels of biomarkers of oxidative stress are studied in prediabetic patients diagnosed with COVID-19 before and after supplementation with cysteine plus glycine (GlyNAC) as GSH precursors, or placebo, for 14-21 days. A group of subjects without prediabetes or diabetes or COVID-19 serves as a control. Levels of biomarkers of oxidative stress are measured in all subjects as plasma levels of TBARS, malondialdehyde, lipid-peroxide, and/or F2-isoPs in blood. Results show that levels of biomarkers of oxidative stress improve only in prediabetic patients with COVID-19 who receive GlyNAC supplementation, and not in prediabetic patients who receive placebo. Further analyses show that the levels of biomarkers of oxidative stress in prediabetic COVID-19 subjects decrease to approximate values in subjects without diabetes or COVID-19.

[0097] Biomarkers of oxidative stress in obese COVID-19 patients: In certain aspects, in a randomized clinical trial, levels of biomarkers of oxidative stress are studied in obese patients diagnosed with COVID-19 before and after supplementation with cysteine plus glycine (GlyNAC) as GSH precursors, or placebo, for 14-21 days. A group of subjects without obesity, diabetes or COVID-19 serves as a control. Levels of biomarkers of oxidative stress are measured as plasma levels of TBARS, malondialdehyde, lipid-peroxide, and/or F2-isoPs in blood in all subjects. Results show that levels of biomarkers of oxidative stress improve only in obese patients with COVID-19 who receive GlyNAC supplementation, and not in obese patients who receive placebo. Further analyses show that the levels of biomarkers of oxidative stress in obese COVID-19 subjects decrease to approximate values in subjects without obesity, diabetes or COVID-19.

[0098] Thus, in certain aspects, all COVID-19 patients have greater levels of biomarkers of oxidative stress than the non-COVID-19 control group because of decreased availability of its precursors cysteine and glycine, while older COVID-19 patients have significantly higher levels of biomarkers of oxidative stress than younger COVID-19 patients. HIV patients with COVID-19 have significantly higher levels of biomarkers of oxidative stress than non-HIV non-COVID-19 patients. Diabetic and prediabetic patients with COVID-19 have significantly higher levels of biomarkers of oxidative stress than patients without prediabetes or diabetes or COVID-19. Obese patients with COVID-19 have significantly higher levels of biomarkers of oxidative stress than non-obese non-COVID-19 patients. Cysteine and glycine supplementation lower levels of biomarkers of oxidative stress in all patients with COVID-19.

EXAMPLE 3

CORONAVIRIDAE VIRAL INFECTION AND INFLAMMATION

[0099] IL-6 is a pro-inflammatory cytokine produced in response to tissue damage and infections. Multiple cell types including fibroblasts, keratinocytes, mesangial cells, vascular endothelial cells, mast cells, macrophages, dendritic cells, and T and B cells are associated with the production of this cytokine. IL-6 has long been considered a biomarker for inflammation. Tumor necrosis factor α (TNFα) is a pro-inflammatory cytokine produced by activated macrophages, T and B lymphocytes, natural killer cells, astrocytes, endothelial cells, smooth muscle cells, some tumor cells, and epithelial cells. TNFα is also a useful biomarker for inflammation. In certain aspects, elevated IL-6 and TNFα are associated with *Coronaviridae* viral infections, where IL-6 and TNFα may lead to a 'cytokine storm' response that leads to acute lung injury or its more severe form of acute respiratory distress syndrome.

[0100] C-reactive protein (CRP) is an acute-phase protein found in the blood plasma, and is synthesized by the liver. Levels of CRP rise in response to inflammation, and therefore it is considered a biomarker for conditions associated with increased inflammation. CRP is also a useful biomarker for cardiovascular disease – levels >3 μg/ml are considered undesirable, and levels < 1μg/ml are optimal. In certain aspects, elevated CRP is linked to *Coronaviridae* viral infections.

[0101] **Inflammation in COVID-19 patients by age group**: In certain aspects, in a randomized trial, levels of biomarkers of inflammation are studied in patients diagnosed with COVID-19 (ages 20-90y), and results are compared to patients without COVID-19. Levels of biomarkers of inflammation are measured in all subjects as plasma levels of IL-6, TNFα, and/or CRP in blood. Results are stratified by age and show that COVID-19 patients have higher levels of biomarkers of inflammation, and this is progressively higher with advancing age. Regarding COVID-19, comparing young patients (age range 20-30 years), with middle aged patients (age 40-50 years) with elderly patients (60-90 years) shows levels of biomarkers of inflammation are lowest in the young group and progressively increase with advancing age to be highest in the elderly group. Patients receive supplementation with GlyNAC (glycine and cysteine (as N-acetylcysteine)) or placebo for 14-21 days, and levels of biomarkers of inflammation improve only in patients supplemented with GlyNAC (but not placebo), but the fall in levels of biomarkers of

inflammation is greater with advancing age such that at the end of the supplementation period, all patients have similar levels of biomarkers of inflammation.

[0102] Biomarkers of inflammation in COVID-19 patients with HIV: In certain aspects, in a randomized clinical trial, levels of biomarkers of inflammation are studied in HIV patients diagnosed with COVID-19 before and after supplementation with cysteine plus glycine (GlyNAC) as GSH precursors, or placebo, for 14-21 days. Levels of biomarkers of inflammation are measured in all subjects as plasma levels of IL-6, TNFα, and/or CRP in blood. Results show that levels of biomarkers of inflammation improve only in HIV patients with COVID-19 who receive GlyNAC supplementation, and not in patients who receive placebo.

[0103] Biomarkers of inflammation in COVID-19 patients with diabetes: In certain aspects, in a randomized clinical trial, levels of biomarkers of inflammation are studied in diabetic patients diagnosed with COVID-19 before and after supplementation with cysteine plus glycine (GlyNAC) as GSH precursors, or placebo, for 14-21 days. A group of subjects without diabetes or COVID-19 serves as a control. Levels of biomarkers of inflammation are measured in all subjects as plasma levels of IL-6, TNFα, and/or CRP in blood. Results show that levels of biomarkers of inflammation will improve only in diabetic patients with COVID-19 who receive GlyNAC supplementation, and not in diabetic patients who receive placebo. Further analyses show that the levels of biomarkers of inflammation in diabetic COVID-19 subjects decrease to approximate values in subjects without diabetes or COVID-19.

[0104] Biomarkers of inflammation in COVID-19 patients with prediabetes (defined as fasting glucose values between 100-125 mg/dl): In certain aspects, in a randomized clinical trial, levels of biomarkers of inflammation are studied in prediabetic patients diagnosed with COVID-19 before and after supplementation with cysteine plus glycine (GlyNAC) as GSH precursors, or placebo, for 14-21 days. A group of subjects without prediabetes or diabetes or COVID-19 serves as a control. Levels of biomarkers of inflammation will be measured in all subjects as plasma levels of IL-6, TNFα, and/or CRP in blood. Results show that levels of biomarkers of inflammation at the end of supplementation improve only in prediabetic patients with COVID-19 who receive GlyNAC supplementation, and not in prediabetic patients who receive placebo. Further analyses will show that the levels of biomarkers of inflammation in prediabetic COVID-19 subjects decrease to approximate values in subjects without diabetes or COVID-19.

[0105] Biomarkers of inflammation in obese COVID-19 patients: In certain aspects, in a randomized clinical trial, levels of biomarkers of inflammation are studied in obese patients diagnosed with COVID-19 before and after supplementation with cysteine plus glycine (GlyNAC) as GSH precursors, or placebo, for 14-21 days. A group of subjects without obesity, diabetes or COVID-19 serves as a control. Levels of biomarkers of inflammation are measured in all subjects as plasma levels of IL-6, TNFα, and/or CRP in blood. Results show that levels of biomarkers of inflammation at the end of supplementation will improve only in obese patients with COVID-19 who receive GlyNAC supplementation, and not in obese patients who receive placebo. Further analyses show that the levels of biomarkers of inflammation in obese COVID-19 subjects decrease to approximate values in subjects without obesity, diabetes or COVID-19.

[0106] Thus, in certain aspects, all COVID-19 patients have greater levels of biomarkers of inflammation than the non-COVID-19 control group because of decreased availability of its precursors cysteine and glycine, while older COVID-19 patients have significantly higher levels of biomarkers of inflammation than younger COVID-19 patients. HIV patients with COVID-19 have significantly higher levels of biomarkers of inflammation than non-HIV non-COVID-19 patients. Diabetic and prediabetic patients with COVID-19 have significantly higher levels of biomarkers of inflammation than non-prediabetic, non-diabetic, non-COVID-19 patients. Obese patients with COVID-19 have significantly higher levels of biomarkers of inflammation than non-obese non-COVID-19 patients. Cysteine and glycine supplementation lower levels of biomarkers of inflammation in all patients with COVID-19.

EXAMPLE 4

CORONAVIRIDAE VIRAL INFECTION AND IMMUNOSUPPRESSION

[0107] In certain aspects, for *Coronaviridae* viral infections, plasma levels of CD4+ T-Cells, CD8+ T-Cells, B-cells, NK cells, and/or antigen-presenting cells of the immune system in patients correlate inversely with elevated inflammatory markers IL-6 and C-reactive protein (CRP).

[0108] Immunosuppression in COVID-19 patients by age group: In certain aspects, in a randomized trial, immunosuppression are studied in patients diagnosed with COVID-19 (ages 20-90y), and results compared to patients without COVID-19. Immunosuppression is measured in all subjects as blood levels of CD4+ T-Cells, CD8+ T-Cells, B-cells, NK cells, and/or

antigen-presenting cells in blood. Results are stratified by age and show that COVID-19 patients have a severe immune cell deficiency, and this becomes progressively worse with advancing age. Regarding COVID-19, comparing young patients (age range 20-30 years), with middle aged patients (age 40-50 years) with elderly patients (60-90 years) shows that plasma immune cell levels are highest in the young group and progressively decline with advancing age to be lowest in the elderly group. Patients receive supplementation with GlyNAC (glycine and cysteine (as N-acetylcysteine)) or placebo for 14-21 days, and immune cell levels improve only in patients supplemented with GlyNAC (but not placebo), but the increase in immune cell levels is higher with advancing age.

[0109] Immunosuppression in COVID-19 patients with HIV: In certain aspects, in a randomized clinical trial, immunosuppression is studied in HIV patients diagnosed with COVID-19 before and after supplementation with cysteine plus glycine (GlyNAC) as GSH precursors, or placebo, for 14-21 days. Immunosuppression is measured in all subjects as levels of CD4+ T-Cells, CD8+ T-Cells, B-cells, NK cells, and/or antigen-presenting cells in blood. Results show that immune cell levels at the end of supplementation improve only in HIV patients with COVID-19 who receive GlyNAC supplementation, and not in patients who receive placebo.

[0110] Immunosuppression in COVID-19 patients with diabetes: In certain aspects, in a randomized clinical trial, immunosuppression is studied in diabetic patients diagnosed with COVID-19 before and after supplementation with cysteine plus glycine (GlyNAC) as GSH precursors, or placebo, for 14-21 days. A group of subjects without diabetes or COVID-19 serves as a control. Immunosuppression is measured in all subjects as plasma levels of CD4+ T-Cells, CD8+ T-Cells, B-cells, NK cells, and/or antigen-presenting cells in blood. Results show that plasma immune cell levels at the end of supplementation improve only in diabetic patients with COVID-19 who receive GlyNAC supplementation, and not in diabetic patients who receive placebo. Further analyses show that the plasma immune cell levels in diabetic COVID-19 subjects increase to approximate values in subjects without diabetes or COVID-19.

[0111] Immunosuppression in COVID-19 patients with prediabetes (defined as fasting glucose values between 100-125 mg/dl): In certain aspects, in a randomized clinical trial, immunosuppression is studied in prediabetic patients diagnosed with COVID-19 before and after supplementation with cysteine plus glycine (GlyNAC) as GSH precursors, or placebo, for 14-21 days. A group of subjects without prediabetes or diabetes or COVID-19 serves as a control.

Immunosuppression is measured in all subjects as levels of CD4+ T-Cells, CD8+ T-Cells, B-cells, NK cells, and/or antigen-presenting cells in blood. Results show that immune cell levels at the end of supplementation improve only in prediabetic patients with COVID-19 who receive GlyNAC supplementation, and not in prediabetic patients who receive placebo. Further analyses show that the immune cell levels in prediabetic COVID-19 subjects increase to approximate values in subjects without diabetes or COVID-19.

[0112] **Immunosuppression in obese COVID-19 patients**: In certain aspects, in a randomized clinical trial, immunosuppression is studied in obese patients diagnosed with COVID-19 before and after supplementation with cysteine plus glycine (GlyNAC) as GSH precursors, or placebo, for 14-21 days. A group of subjects without obesity, diabetes or COVID-19 serves as a control. Immunosuppression is measured in all subjects as levels of CD4+ T-Cells, CD8+ T-Cells, B-cells, NK cells, and/or antigen-presenting cells in blood. Results show that immune cell levels at the end of supplementation improve only in obese patients with COVID-19 who receive GlyNAC supplementation, and not in obese patients who receive placebo. Further analyses show that the immune cell levels in obese COVID-19 subjects increase to approximate values in subjects without obesity, diabetes or COVID-19.

[0113] Thus, in certain aspects, all COVID-19 patients have a greater immune cell deficiency than the non-COVID-19 control group, while older COVID-19 patients have significantly lower immune cell levels than younger COVID-19 patients. HIV patients with COVID-19 have significantly lower immune cell levels than non-HIV non-COVID-19 patients. Diabetic and prediabetic patients with COVID-19 have significantly lower immune cell levels than patients without prediabetes or diabetes or COVID-19. Obese patients with COVID-19 have significantly lower plasma immune cell levels than non-obese non-COVID-19 patients. Cysteine and glycine supplementation increase immune cell levels in all patients with COVID-19.

EXAMPLE 5

CORONAVIRIDAE VIRAL INFECTION AND ENDOTHELIAL DYSFUNCTION

[0114] Cell adhesion molecules (CAMs) are a class of cell surface binding proteins that are secreted from the surface of dysfunctional endothelium cells. In certain aspects, elevated plasma levels of soluble CAMs, including sICAM1, sVCAM1, and E-selectin, are linked to endothelium dysfunction associated with *Coronaviridae* viral infections.

[0115] Endothelial dysfunction in COVID-19 patients by age group: In certain aspects, in a randomized trial, levels of biomarkers of endothelial dysfunction are studied in patients diagnosed with COVID-19 (ages 20-90y), and results are compared to patients without COVID-19. Levels of biomarkers of endothelial dysfunction are measured in all subjects as plasma levels of sICAM1, sVCAM1, and/or E-selectin in blood. Results are stratified by age and show that COVID-19 patients have elevated levels of biomarkers of endothelial dysfunction, and this becomes progressively worse with advancing age. Regarding COVID-19, comparing young patients (age range 20-30 years), with middle aged patients (age 40-50 years) with elderly patients (60-90 years) shows that levels of biomarkers of endothelial dysfunction are lowest in the young group and progressively increase with advancing age to be highest in the elderly group. Patients receive supplementation with GlyNAC (glycine and cysteine (as N-acetylcysteine)) or placebo for 14-21 days, and levels of biomarkers of endothelial dysfunction improve only in patients supplemented with GlyNAC (but not placebo), but the decrease in levels of biomarkers of endothelial dysfunction is higher with advancing age, such that at the end of the supplementation period all patients have similar levels of biomarkers of endothelial dysfunction.

[0116] Biomarkers of endothelial dysfunction in COVID-19 patients with HIV: In certain aspects, in a randomized clinical trial, levels of biomarkers of endothelial dysfunction are studied in HIV patients diagnosed with COVID-19 before and after supplementation with cysteine plus glycine (GlyNAC) as GSH precursors, or placebo, for 14-21 days. Levels of biomarkers of endothelial dysfunction are measured in all subjects as plasma levels of sICAM1, sVCAM1, and/or E-selectin in blood. Results show that levels of biomarkers of endothelial dysfunction improve only in HIV patients with COVID-19 who receive GlyNAC supplementation, and not in patients who receive placebo.

[0117] Biomarkers of endothelial dysfunction in COVID-19 patients with diabetes: In certain aspects, in a randomized clinical trial, levels of biomarkers of endothelial dysfunction are studied in diabetic patients diagnosed with COVID-19 before and after supplementation with cysteine plus glycine (GlyNAC) as GSH precursors, or placebo, for 14-21 days. A group of subjects without diabetes or COVID-19 serves as a control. Levels of biomarkers of endothelial dysfunction are measured in all subjects as plasma levels of sICAM1, sVCAM1, and/or E-selectin in blood. Results show that levels of biomarkers of endothelial dysfunction improve only in diabetic patients with COVID-19 who receive GlyNAC supplementation, and not in diabetic patients who receive placebo. Further analyses show that the levels of biomarkers of

endothelial dysfunction in diabetic COVID-19 subjects decrease to approximate values in subjects without diabetes or COVID-19.

[0118] Biomarkers of endothelial dysfunction in COVID-19 patients with prediabetes (defined as fasting glucose values between 100-125 mg/dl): In certain aspects, in a randomized clinical trial, levels of biomarkers of endothelial dysfunction are studied in prediabetic patients diagnosed with COVID-19 before and after supplementation with cysteine plus glycine (GlyNAC) as GSH precursors, or placebo, for 14-21 days. A group of subjects without prediabetes or diabetes or COVID-19 serves as a control. Levels of biomarkers of endothelial dysfunction are measured in all subjects as plasma levels of sICAM1, sVCAM1, and/or E-selectin in blood. Results show that levels of biomarkers of endothelial dysfunction at the end of supplementation improve only in prediabetic patients with COVID-19 who receive GlyNAC supplementation, and not in prediabetic patients who receive placebo. Further analyses show that the levels of biomarkers of endothelial dysfunction in prediabetic COVID-19 subjects decrease to approximate values in subjects without diabetes or COVID-19.

[0119] Biomarkers of endothelial dysfunction in obese COVID-19 patients: In certain aspects, in a randomized clinical trial, levels of biomarkers of endothelial dysfunction are studied in obese patients diagnosed with COVID-19 before and after supplementation with cysteine plus glycine (GlyNAC) as GSH precursors, or placebo, for 14-21 days. A group of subjects without obesity, diabetes or COVID-19 serves as a control. Levels of biomarkers of endothelial dysfunction are measured in all subjects as plasma levels of sICAM1, sVCAM1, and/or E-selectin in blood. Results show that levels of biomarkers of endothelial dysfunction at the end of supplementation improve only in obese patients with COVID-19 who receive GlyNAC supplementation, and not in obese patients who receive placebo. Further analyses show that the levels of biomarkers of endothelial dysfunction in obese COVID-19 subjects decrease to approximate values in subjects without obesity, diabetes or COVID-19.

[0120] Thus, in certain aspects, all COVID-19 patients have greater levels of biomarkers of endothelial dysfunction than the non-COVID-19 control group, while older COVID-19 patients have significantly higher levels of biomarkers of endothelial dysfunction than younger COVID-19 patients. HIV patients with COVID-19 have significantly higher levels of biomarkers of endothelial dysfunction than non-HIV non-COVID-19 patients. Diabetic and prediabetic patients with COVID-19 have significantly higher levels of biomarkers of endothelial

dysfunction than non-diabetic non-COVID-19 patients. Obese patients with COVID-19 have significantly higher levels of biomarkers of endothelial dysfunction than non-obese non-COVID-19 patients. Cysteine and glycine supplementation lower the levels of biomarkers of endothelial dysfunction in all patients with COVID-19.

EXAMPLE 6

CORONAVIRIDAE VIRAL INFECTION AND MITOCHONDRIAL DYSFUNCTION

[0121] Low levels of GSH are correlated with whole-body and cellular mitochondrial dysfunction. GSH is the most abundant endogenous intracellular antioxidant and a key component of mitochondrial antioxidant defenses, is known to be deficient in COVID-19 patients. GSH deficiency leads to defective mitochondrial fuel oxidation, (fasted impaired fatty-acid oxidation and abnormally elevated fasted glucose oxidation) and supplementation with GlyNAC can reverse these defects. Although not to be limited by theory, GSH deficiency results in impaired fasted mitochondrial nonesterified fatty acid (NEFA) oxidation, forcing a shift to glucose oxidation for energy needs. Under physiological conditions, the fuel of choice in the fasted state is fatty acids (FA), and not glucose. In certain aspects, severely impaired fasted FA oxidation and higher fasted glucose oxidation levels are linked to mitochondrial defect associated with a *Coronaviridae* viral infection.

[0122] **Mitochondrial dysfunction in COVID-19 patients by age group**: In certain aspects, in a randomized trial, mitochondrial dysfunction is studied in patients diagnosed with COVID-19 (ages 20-90y), and results are compared to patients without COVID-19. Mitochondrial dysfunction are measured in all subjects as impaired FA oxidation and as elevated fasting glucose oxidation at the whole-body and at the cellular levels. Results are stratified by age and will show that COVID-19 patients have severe mitochondrial dysfunction, and this becomes progressively worse with advancing age. Regarding COVID-19, comparing young patients (age range 20-30 years), with middle aged patients (age 40-50 years) with elderly patients (60-90 years) shows that mitochondrial fuel oxidation is most optimal and efficient in the young group and progressively deteriorates with advancing age to be the most impaired in the elderly group. Patients receive supplementation with GlyNAC (glycine and cysteine (as N-acetylcysteine)) or placebo for 14-21 days, and mitochondrial function improves only in patients supplemented with GlyNAC (but not placebo), but the improvement in mitochondrial function is higher with

advancing age, such that at the end of the supplementation period all patients have similar levels of mitochondrial dysfunction.

[0123] Mitochondrial dysfunction in COVID-19 patients with HIV: In certain aspects, in a randomized clinical trial, mitochondrial dysfunction are studied in HIV patients diagnosed with COVID-19 before and after supplementation with cysteine plus glycine (GlyNAC) as GSH precursors, or placebo, for 14-21 days. Mitochondrial dysfunction are measured in all subjects as impaired FA oxidation and as elevated fasting glucose oxidation at the whole-body and at the cellular levels. Results show that mitochondrial dysfunction will improve only in HIV patients with COVID-19 who receive GlyNAC supplementation, and not in patients who receive placebo.

[0124] Mitochondrial dysfunction in COVID-19 patients with diabetes: In certain aspects, in a randomized clinical trial, mitochondrial dysfunction is studied in diabetic patients diagnosed with COVID-19 before and after supplementation with cysteine plus glycine (GlyNAC) as GSH precursors, or placebo, for 14-21 days. A group of subjects without diabetes or COVID-19 serves as a control. Mitochondrial dysfunction are measured in all subjects as impaired FA oxidation and as elevated fasting glucose oxidation at the whole-body and at the cellular levels. Results show that mitochondrial dysfunction improves only in diabetic patients with COVID-19 who receive GlyNAC supplementation, and not in diabetic patients who receive placebo. Further analyses show that mitochondrial dysfunction in diabetic COVID-19 subjects improves to approximate values in subjects without diabetes or COVID-19.

[0125] Mitochondrial dysfunction in COVID-19 patients with prediabetes (defined as fasting glucose values between 100-125 mg/dl): In certain aspects, in a randomized clinical trial, mitochondrial dysfunction is studied in prediabetic patients diagnosed with COVID-19 before and after supplementation with cysteine plus glycine (GlyNAC) as GSH precursors, or placebo, for 14-21 days. A group of subjects without prediabetes or diabetes or COVID-19 serves as a control. Mitochondrial dysfunction are measured in all subjects as impaired FA oxidation and as elevated fasting glucose oxidation at the whole-body and at the cellular levels. Results show that mitochondrial dysfunction at the end of supplementation improves only in prediabetic patients with COVID-19 who receive GlyNAC supplementation, and not in prediabetic patients who receive placebo. Further analyses show that mitochondrial dysfunction in prediabetic COVID-19 subjects improves to approximate values in subjects without diabetes or COVID-19.

[0126] **Mitochondrial dysfunction in obese COVID-19 patients**: In certain aspects, in a randomized clinical trial, mitochondrial dysfunction is studied in obese patients diagnosed with COVID-19 before and after supplementation with cysteine plus glycine (GlyNAC) as GSH precursors, or placebo, for 14-21 days. A group of subjects without obesity, diabetes or COVID-19 serves as a control. Mitochondrial dysfunction are measured in all subjects as impaired FA oxidation and as elevated fasting glucose oxidation at the whole-body and at the cellular levels. Results show that mitochondrial dysfunction at the end of supplementation improves only in obese patients with COVID-19 who receive GlyNAC supplementation, and not in obese patients who receive placebo. Further analyses show that mitochondrial dysfunction in obese COVID-19 subjects improves to approximate values in subjects without obesity, diabetes or COVID-19.

[0127] Thus, in certain aspects, all COVID-19 patients have greater mitochondrial dysfunction than the non-COVID-19 control group, while older COVID-19 patients have significantly higher mitochondrial dysfunction than younger COVID-19 patients. HIV patients with COVID-19 will have significantly higher mitochondrial dysfunction than non-HIV non-COVID-19 patients. Diabetic and prediabetic patients with COVID-19 have significantly higher mitochondrial dysfunction than non-diabetic non-COVID-19 patients. Obese patients with COVID-19 have significantly higher mitochondrial dysfunction than non-obese non-COVID-19 patients. Cysteine and glycine supplementation lower mitochondrial dysfunction by improving mitochondrial function in all patients with COVID-19.

EXAMPLE 7

CORONAVIRIDAE VIRAL INFECTION AND INSULIN RESISTANCE

[0128] Low levels of GSH are correlated with insulin resistance (low insulin sensitivity). In certain aspects, insulin resistance is correlated to low levels of GSH which is associated with a *Coronaviridae* viral infection. Insulin sensitivity can be measured by the homeostatic modeling assessment (HOMA-IR), fasting glucose and insulin levels, and also by the clamp methods, such as the hyperglycemic clamp method and the hyperinsulinemic-euglycemic clamp method.

[0129] **Insulin resistance in COVID-19 patients by age group**: In certain aspects, in a randomized trial, insulin resistance is studied in patients diagnosed with COVID-19 (ages 20-90y), and results compared to patients without COVID-19. Insulin resistance is measured

in all subjects. Results are stratified by age and show that COVID-19 patients have severe insulin resistance, and this becomes progressively worse with advancing age. Regarding COVID-19, comparing young patients (age range 20-30 years), with middle aged patients (age 40-50 years) with elderly patients (60-90 years) shows that insulin resistance is lowest in the young group and progressively increases with advancing age to be highest in the elderly group. Patients receive supplementation with GlyNAC (glycine and cysteine (as N-acetylcysteine)) or placebo for 14-21 days, and insulin resistance improves only in patients supplemented with GlyNAC (but not placebo), but the decrease in insulin resistance is higher with advancing age, such that at the end of the supplementation period all patients have similar insulin resistance.

[0130] Insulin resistance in COVID-19 patients with HIV: In certain aspects, in a randomized clinical trial, insulin resistance is studied in HIV patients diagnosed with COVID-19 before and after supplementation with cysteine plus glycine (GlyNAC) as GSH precursors, or placebo, for 14-21 days. Insulin resistance is measured in all subjects. Results show that insulin resistance improves only in HIV patients with COVID-19 who receive GlyNAC supplementation, and not in patients who receive placebo.

[0131] Insulin resistance in COVID-19 patients with diabetes: In certain aspects, in a randomized clinical trial, insulin resistance is studied in diabetic patients diagnosed with COVID-19 before and after supplementation with cysteine plus glycine (GlyNAC) as GSH precursors, or placebo, for 14-21 days. A group of subjects without diabetes or COVID-19 serves as a control. Insulin resistance is measured in all subjects. Results show that insulin resistance improves only in diabetic patients with COVID-19 who receive GlyNAC supplementation, and not in diabetic patients who receive placebo. Further analyses show that insulin resistance in diabetic COVID-19 subjects decreases to approximate insulin resistance values in subjects without diabetes or COVID-19.

[0132] Insulin resistance in COVID-19 patients with prediabetes (defined as fasting glucose values between 100-125 mg/dl): In certain aspects, in a randomized clinical trial, insulin resistance is studied in prediabetic patients diagnosed with COVID-19 before and after supplementation with cysteine plus glycine (GlyNAC) as GSH precursors, or placebo, for 14-21 days. A group of subjects without prediabetes or diabetes or COVID-19 serves as a control. Insulin resistance will be measured in all subjects. Results will show that insulin resistance at the end of supplementation will improve only in prediabetic patients with COVID-19 who receive

GlyNAC supplementation, and not in prediabetic patients who receive placebo. Further analyses will show that insulin resistance in prediabetic COVID-19 subjects will decrease to approximate insulin resistance values in subjects without prediabetes, diabetes, or COVID-19.

[0133] **Insulin resistance in obese COVID-19 patients**: In certain aspects, in a randomized clinical trial, insulin resistance is studied in obese patients diagnosed with COVID-19 before and after supplementation with cysteine plus glycine (GlyNAC) as GSH precursors, or placebo, for 14-21 days. A group of subjects without obesity, diabetes, or COVID-19, serves as a control. Insulin resistance is measured in all subjects. Results show that insulin resistance at the end of supplementation improves only in obese patients with COVID-19 who receive GlyNAC supplementation, and not in obese patients who receive placebo. Further analyses show that insulin resistance in obese COVID-19 subjects decreases to approximate insulin resistance values in subjects without obesity, diabetes or COVID-19.

[0134] Thus, in certain aspects, all COVID-19 patients have greater insulin resistance than the non-COVID-19 control group, while older COVID-19 patients have significantly higher levels of insulin resistance than younger COVID-19 patients. HIV patients with COVID-19 have significantly higher insulin resistance than non-HIV non-COVID-19 patients. Diabetic and prediabetic patients with COVID-19 have significantly higher insulin resistance than non-diabetic non-COVID-19 patients. Obese patients with COVID-19 have significantly higher insulin resistance than non-obese non-COVID-19 patients. Cysteine and glycine supplementation lower insulin resistance in all patients with COVID-19.

EXAMPLE 8

CORONAVIRIDAE VIRAL INFECTION AND COGNITIVE IMPAIRMENT

[0135] Low levels of GSH are correlated cognitive impairment. In certain aspects, cognitive impairment is correlated with low levels of GSH which is associated with a *Coronaviridae* viral infection. Neuropsychological assessments for cognitive function include, for example, the Mini-Mental State Exam (MMSE) and Montreal cognitive assessment (MoCA) which are widely used tests of cognitive function which tests orientation, attention, memory, language and visual-spatial skills.

[0136] Cognitive impairment in COVID-19 patients by age group: In certain aspects, in a randomized trial, cognitive impairment is studied in patients diagnosed with COVID-19 (ages 20-90y), and results compared to patients without COVID-19. Cognitive impairment is measured in all subjects. Results are stratified by age and show that COVID-19 patients have cognitive impairment, and this becomes progressively worse with advancing age. Regarding COVID-19, comparing young patients (age range 20-30 years), with middle aged patients (age 40-50 years) with elderly patients (60-90 years) shows that cognitive impairment is lowest in the young group and progressively increases with advancing age to be highest in the elderly group. Patients receive supplementation with GlyNAC (glycine and cysteine (as N-acetylcysteine)) or placebo for 14-21 days, and cognitive impairment improves only in patients supplemented with GlyNAC (but not placebo), but the decrease in cognitive impairment is higher with advancing age, such that at the end of the supplementation period all patients have similar levels of cognitive function.

[0137] Cognitive impairment in COVID-19 patients with HIV: In certain aspects, in a randomized clinical trial, cognitive impairment is studied in HIV patients diagnosed with COVID-19 before and after supplementation with cysteine plus glycine (GlyNAC) as GSH precursors, or placebo, for 14-21 days. Cognitive impairment is measured in all subjects. Results show that cognitive impairment improves only in HIV patients with COVID-19 who receive GlyNAC supplementation, and not in patients who receive placebo.

[0138] Cognitive impairment in COVID-19 patients with diabetes: In certain aspects, in a randomized clinical trial, cognitive impairment is studied in diabetic patients diagnosed with COVID-19 before and after supplementation with cysteine plus glycine (GlyNAC) as GSH precursors, or placebo, for 14-21 days. A group of subjects without diabetes or COVID-19 serves as a control. Cognitive impairment is measured in all subjects and will be lower in diabetic patients. Results show that cognitive impairment improves only in diabetic patients with COVID-19 who receive GlyNAC supplementation, and not in diabetic patients who receive placebo. Further analyses show that cognitive impairment in diabetic COVID-19 subjects decreases to approximate cognitive function in subjects without diabetes or COVID-19.

[0139] Cognitive impairment in COVID-19 patients with prediabetes (defined as fasting glucose values between 100-125 mg/dl): In certain aspects, in a randomized clinical trial, cognitive impairment is studied in prediabetic patients diagnosed with COVID-19 before and

after supplementation with cysteine plus glycine (GlyNAC) as GSH precursors, or placebo, for 14-21 days. A group of subjects without prediabetes or diabetes or COVID-19 serves as a control. Cognitive impairment is measured in all subjects, and will be lower in prediabetic patients. Results show that cognitive impairment at the end of supplementation improves only in prediabetic patients with COVID-19 who receive GlyNAC supplementation, and not in prediabetic patients who receive placebo. Further analyses show that cognitive impairment in prediabetic COVID-19 subjects decreases to approximate cognitive function in subjects without diabetes or COVID-19.

[0140] **Cognitive impairment in obese COVID-19 patients**: In certain aspects, in a randomized clinical trial, cognitive impairment is studied in obese patients diagnosed with COVID-19 before and after supplementation with cysteine plus glycine (GlyNAC) as GSH precursors, or placebo, for 14-21 days. A group of subjects without obesity, diabetes or COVID-19 serves as a control. Cognitive impairment is measured in all subjects, and is lower in obese subjects. Results show that cognitive impairment at the end of supplementation improves only in obese patients with COVID-19 who receive GlyNAC supplementation, and not in obese patients who receive placebo. Further analyses show that cognitive impairment in obese COVID-19 subjects decreases to approximate cognitive function in subjects without obesity, diabetes or COVID-19.

[0141] Thus, in certain aspects, all COVID-19 patients have greater cognitive impairment than the non-COVID-19 control group, while older COVID-19 patients have significantly higher cognitive impairment than younger COVID-19 patients. HIV patients with COVID-19 have significantly higher cognitive impairment than non-HIV/non-COVID-19 patients. Diabetic and prediabetic patients with COVID-19 have significantly higher cognitive impairment than non-diabetic non-COVID-19 patients. Obese patients with COVID-19 have significantly higher cognitive impairment than non-obese non-COVID-19 patients. Cysteine and glycine supplementation lower cognitive impairment in all patients with COVID-19.

EXAMPLE 9

CORONAVIRIDAE VIRAL INFECTION AND FUNCTIONAL LIMITATION

[0142] Low levels of GSH are correlated with mitochondrial dysfunction, which further correlates to functional limitation, including at least declines in muscle strength and/or muscle mass, gait speed, and exercise capacity. In certain aspects, GSH-deficient COVID-19

patients have impaired fasted FA oxidation and higher fasted glucose oxidation, suggesting a mitochondrial defect. Because elevated glucose oxidation in the fasted state occurs either by increased gluconeogenesis mainly from muscle protein, or by direct utilization of muscle proteins for energy needs, both routes lead to muscle loss. In certain aspects, loss of muscle strength and/or mass, gait speed, 6-minute walk test and exercise capacity correlate to low levels of GSH associated with a *Coronaviridae* viral infection.

[0143] Functional limitation in COVID-19 patients by age group: In certain aspects, in a randomized trial, functional limitation is studied in patients diagnosed with COVID-19 (ages 20-90y), and results are compared to patients without COVID-19. Functional limitation is measured in all subjects as decreased muscle mass and/or muscle strength, gait speed, 6-minute walk test and exercise capacity. Results are stratified by age and show that COVID-19 patients have elevated functional limitation, and this becomes progressively worse with advancing age. Regarding COVID-19, comparing young patients (age range 20-30 years), with middle aged patients (age 40-50 years) with elderly patients (60-90 years) shows that functional limitation is lowest in the young group and progressively increases with advancing age to be highest in the elderly group. Patients receive supplementation with GlyNAC (glycine and cysteine (as N-acetylcysteine)) or placebo for 14-21 days, and functional limitation improves only in patients supplemented with GlyNAC (but not placebo), but the improvement in functional limitation is higher with advancing age, such that at the end of the supplementation period all patients have similar functional ability.

[0144] Functional limitation in COVID-19 patients with HIV: In certain aspects, in a randomized clinical trial, functional limitation is studied in HIV patients diagnosed with COVID-19 before and after supplementation with cysteine plus glycine (GlyNAC) as GSH precursors, or placebo, for 14-21 days. Functional limitation is measured in all subjects as muscle mass and/or muscle strength, gait speed, 6-minute walk test and exercise capacity. Results show that functional limitation improves only in HIV patients with COVID-19 who receive GlyNAC supplementation, and not in patients who receive placebo.

[0145] Functional limitation in COVID-19 patients with diabetes: In certain aspects, in a randomized clinical trial, functional limitation is studied in diabetic patients diagnosed with COVID-19 before and after supplementation with cysteine plus glycine (GlyNAC) as GSH precursors, or placebo, for 14-21 days. A group of subjects without diabetes or COVID-19 serves

as a control. Functional limitation is measured in all subjects as muscle mass and/or muscle strength, gait speed, 6-minute walk test and exercise capacity. Results show that functional limitation improves only in diabetic patients with COVID-19 who receive GlyNAC supplementation, and not in diabetic patients who receive placebo. Further analyses show that functional limitation in diabetic COVID-19 subjects decreases to approximate functional ability in subjects without diabetes or COVID-19.

[0146] Functional limitation in COVID-19 patients with prediabetes (defined as fasting glucose values between 100-125 mg/dl): In certain aspects, in a randomized clinical trial, functional limitation is studied in prediabetic patients diagnosed with COVID-19 before and after supplementation with cysteine plus glycine (GlyNAC) as GSH precursors, or placebo, for 14-21 days. A group of subjects without prediabetes or diabetes or COVID-19 serves as a control. Functional limitation is measured in all subjects as muscle mass and/or muscle strength, gait speed, 6-minute walk test and exercise capacity. Results show that functional limitation at the end of supplementation improves only in prediabetic patients with COVID-19 who receive GlyNAC supplementation, and not in prediabetic patients who receive placebo. Further analyses show that functional limitation in prediabetic COVID-19 subjects decreases to approximate functional ability in subjects without diabetes or COVID-19.

[0147] Functional limitation in obese COVID-19 patients: In certain aspects, in a randomized clinical trial, functional limitation is studied in obese patients diagnosed with COVID-19 before and after supplementation with cysteine plus glycine (GlyNAC) as GSH precursors, or placebo, for 14-21 days. A group of subjects without obesity, diabetes or COVID-19 serves as a control. Functional limitation is measured in all subjects as muscle mass and/or muscle strength, gait speed, 6-minute walk test and exercise capacity. Results show that functional limitation at the end of supplementation improves only in obese patients with COVID-19 who receive GlyNAC supplementation, and not in obese patients who receive placebo. Further analyses show that functional limitation in obese COVID-19 subjects decreases to approximate functional ability in subjects without obesity, diabetes or COVID-19.

[0148] Thus, in certain aspects, all COVID-19 patients have greater functional limitation than the non-COVID-19 control group, while older COVID-19 patients have significantly higher functional limitation than younger COVID-19 patients. HIV patients with COVID-19 have significantly higher functional limitation than non-HIV non-COVID-19 patients.

Diabetic and prediabetic patients with COVID-19 have significantly higher functional limitation than non-diabetic non-COVID-19 patients. Obese patients with COVID-19 have significantly higher functional limitation than non-obese non-COVID-19 patients. Cysteine and glycine supplementation lower the functional limitation in muscle strength, gait speed, 6-minute walk test, exercise capacity and muscle loss in all patients with COVID-19.

EXAMPLE 10

CORONAVIRIDAE VIRAL INFECTION AND LIMITATION IN LUNG FUNCTION[NRF1]

[0149] Low levels of GSH are correlated with mitochondrial dysfunction, which further correlates to functional limitation, including at least declines in muscle strength and/or muscle mass, gait speed, and exercise capacity. In certain aspects, GSH-deficient COVID-19 patients have impaired fasted FA oxidation and higher fasted glucose oxidation, suggesting a mitochondrial defect. Because the process of breathing (respiration) requires adequate strength in the muscles of respiration, GSH deficient COVID-19 patients have decreased lung function as measured by standard clinical pulmonary function tests and oxygen saturation tests. In certain aspects, limitation in lung function correlates to low levels of GSH associated with a *Coronaviridae* viral infection.

[0150] **Limitation in pulmonary function and oxygen saturation in COVID-19 patients by age group**: In certain aspects, in a randomized trial, limitation in pulmonary function and oxygen saturation is studied in patients diagnosed with COVID-19 (ages 20-90y), and results are compared to patients without COVID-19. Pulmonary function and oxygen saturation are measured in all subjects. Results are stratified by age and show that COVID-19 patients have limitations in pulmonary function and oxygen saturation, and this becomes progressively worse with advancing age. Regarding COVID-19, comparing young patients (age range 20-30 years), with middle aged patients (age 40-50 years) with elderly patients (60-90 years) shows that limitations in pulmonary function and oxygen saturation are lowest in the young group and progressively increase with advancing age to be highest in the elderly group. Patients receive supplementation with GlyNAC (glycine and cysteine (as N-acetylcysteine)) or placebo for 14-21 days, and limitations in pulmonary function and oxygen saturation improve only in patients supplemented with GlyNAC (but not placebo), but the improvement in pulmonary function and

oxygen saturation is higher with advancing age, such that at the end of the supplementation period all patients have similar pulmonary function and oxygen saturation.

[0151] Limitation in pulmonary function and oxygen saturation in COVID-19 patients with HIV: In certain aspects, in a randomized clinical trial, limitation in pulmonary function and oxygen saturation are is studied in HIV patients diagnosed with COVID-19 before and after supplementation with cysteine plus glycine (GlyNAC) as GSH precursors, or placebo, for 14-21 days. Pulmonary function and oxygen saturation are measured in all subjects. Results show that pulmonary function and oxygen saturation improve only in HIV patients with COVID-19 who receive GlyNAC supplementation, and not in patients who receive placebo.

[0152] Limitation in pulmonary function and oxygen saturation in COVID-19 patients with diabetes: In certain aspects, in a randomized clinical trial, limitation in pulmonary function and oxygen saturation is studied in diabetic patients diagnosed with COVID-19 before and after supplementation with cysteine plus glycine (GlyNAC) as GSH precursors, or placebo, for 14-21 days. A group of subjects without diabetes or COVID-19 serves as a control. Pulmonary function and oxygen saturation are measured in all subjects. Results show that pulmonary function and oxygen saturation improve only in diabetic patients with COVID-19 who receive GlyNAC supplementation, and not in diabetic patients who receive placebo. Further analyses show that limitation in pulmonary function and oxygen saturation in diabetic COVID-19 subjects decreases to approximate functional ability in subjects without diabetes or COVID-19.

[0153] Limitation in pulmonary function and oxygen saturation in COVID-19 patients with prediabetes (defined as fasting glucose values between 100-125 mg/dl): In certain aspects, in a randomized clinical trial, limitation in pulmonary function and oxygen saturation is studied in prediabetic patients diagnosed with COVID-19 before and after supplementation with cysteine plus glycine (GlyNAC) as GSH precursors, or placebo, for 14-21 days. A group of subjects without prediabetes or diabetes or COVID-19 serves as a control. Pulmonary function and oxygen saturation are measured in all subjects. Results show that pulmonary function and oxygen saturation at the end of supplementation improve only in prediabetic patients with COVID-19 who receive GlyNAC supplementation, and not in prediabetic patients who receive placebo. Further analyses show that limitation in pulmonary function and oxygen saturation in prediabetic COVID-19 subjects decreases to approximate pulmonary function and oxygen saturation in subjects without diabetes or COVID-19.

[0154] Limitation in pulmonary function and oxygen saturation in obese COVID-19 patients: In certain aspects, in a randomized clinical trial, limitation in pulmonary function and oxygen saturation is studied in obese patients diagnosed with COVID-19 before and after supplementation with cysteine plus glycine (GlyNAC) as GSH precursors, or placebo, for 14-21 days. A group of subjects without obesity, diabetes or COVID-19 serves as a control. Pulmonary function and oxygen saturation are measured in all subjects. Results show that pulmonary function and oxygen saturation at the end of supplementation improve only in obese patients with COVID-19 who receive GlyNAC supplementation, and not in obese patients who receive placebo. Further analyses show that limitation in pulmonary function and oxygen saturation in obese COVID-19 subjects decreases to approximate pulmonary function and oxygen saturation in subjects without obesity, diabetes or COVID-19.

[0155] Thus, in certain aspects, all COVID-19 patients have greater limitation in pulmonary function and oxygen saturation than the non-COVID-19 control group, while older COVID-19 patients have significantly higher limitation in pulmonary function and oxygen saturation than younger COVID-19 patients. HIV patients with COVID-19 have significantly higher limitation in pulmonary function and oxygen saturation than non-HIV non-COVID-19 patients. Diabetic and prediabetic patients with COVID-19 have significantly higher limitation in pulmonary function and oxygen saturation than non-diabetic non-COVID-19 patients. Obese patients with COVID-19 have significantly higher limitation in pulmonary function and oxygen saturation than non-obese non-COVID-19 patients. Cysteine and glycine supplementation lower the limitation in pulmonary function and oxygen saturation in all patients with COVID-19.

EXAMPLE 11

CORONAVIRIDAE VIRAL INFECTION AND POST-INFECTION EFFECTS

[0156] *Coronaviridae* infections, including those that cause COVID-19, are associated with increased mortality, and have been linked to a "cytokine inflammatory storm". Populations at higher risk of COVID complications and mortality include the elderly, obese individuals, diabetic patients and immunocompromised patients (such as from HIV or cancer treatment). Studies of these 3 populations over the past 20 years have found that they all have deficiency of the endogenous antioxidant protein glutathione (GSH), elevated oxidative stress, inflammation, impaired mitochondrial function, immune dysfunction, and endothelial dysfunction.

[0157] It is known and established that GSH adequacy is necessary for neutralizing harmful oxidative stress, and that elevated oxidative stress appears to promote mitochondrial dysfunction. The combination of oxidative stress and mitochondrial dysfunction have also been linked to inflammation, immune dysfunction, and endothelial dysfunction. In prior studies in aging, it has been identified that supplementing glutathione precursor amino-acids glycine and cysteine (provided as N-acetylcysteine) improves GSH deficiency and mitochondrial function, and lowers oxidative stress, inflammation, and endothelial dysfunction. As used herein, the term GlyNAC refers to the combination of glycine and N-acetylcysteine.

[0158] In certain aspects, the prevalence and extent of these defects are evaluated in individuals with COVID-19 admitted to the hospital, and the response to supplementing GlyNAC or placebo for 2-weeks is also evaluated. Because individuals with COVID-19 are also being reported to have fatigue and cognitive impairment, certain aspects measure fatigue and cognition at admission, 1-week, and 2-weeks after beginning supplementation with GlyNAC. The supplementation is stopped after completing 2-weeks, and these outcomes are measured again after 4-weeks and 8-weeks after stopping supplementation.

[0159] Certain aspects characterize associated defects in the following two populations of patients with COVID-19: (1) a GlyNAC supplemented population, and (2) a placebo population. Hospitalized patients admitted for COVID-19 will sign an informed consent form, and be randomized to receive either active (Glycine plus N-acetylcysteine) or a placebo (alanine) supplementation for 2-weeks. On day-0, the participants have a single blood draw to measure oxidative stress, Glutathione levels, inflammatory cytokines, endothelial dysfunction, mitochondrial dysfunction, immune dysfunction, and complete questionnaires to assess fatigue, activity and cognition. Additional clinical and lab information is obtained from the hospital electronic medical records. These measurements will be repeated 1-week and 2-weeks after starting supplementation, and at 4-weeks and 8-weeks after stopping supplementation.

EXAMPLE 12

COVID-19, OXIDATIVE STRESS, AND DAMAGE DUE TO OXIDATIVE STRESS

[0160] Oxidative stress is a harmful condition caused by elevated levels of toxic reactive oxygen species, and results in oxidant damage to cells, tissues and organs. Elevated oxidative stress has been implicated in many human illnesses involving aging, diabetes and HIV-

infection, which also happen to be three key, highly vulnerable populations for COVID-related morbidity and mortality. However, no studies have measured oxidative stress in patients infected with COVID-19.

[0161] In prior studies in older humans, diabetic patients and HIV-patients, it has been shown that supplementing GlyNAC can successfully lower both oxidative stress (due to ROS) and lower damage caused by oxidative stress. Therefore, it is essential to first establish that COVID patients have elevated oxidative stress, and ongoing damage due to oxidative stress to determine whether GlyNAC could be effective in COVID. Plasma levels of TBARS (a biomarker for oxidative stress) and F2-isoprostanes (a biomarker of damage due to oxidative stress) were measured in nine COVID patients and 27 healthy controls. As seen in FIG. 1, plasma TBARS levels (left panel) in patients with COVID-19 are 876% higher than in healthy controls, and plasma F2-I levels (right panel) are 366% higher than in healthy controls.

[0162] Thus, patients with COVID-19 have severely elevated oxidative stress and oxidant damage. Because elevated oxidative stress and oxidant damage are efficiently corrected by GlyNAC, certain embodiments provide for a viable role for GlyNAC supplementation to improve the health of patients infected with COVID-19.

EXAMPLE 13

SEVERE GLUTATHIONE DEFICIENCY AND OXIDATIVE STRESS IN HOSPITALIZED PATIENTS WITH COVID-19

[0163] The global pandemic caused by the novel coronavirus Sars-Cov-2 results in the disease known as COVID-19, with development of a viral pneumonia, dyspnea, progressing to respiratory distress requiring oxygen and possibly ventilatory support. COVID-19 has ravaged the world and resulted in over 560,000 American deaths, and currently exploding in India with over 450,000 cases being reported every day. Despite intensive research the mechanistic abnormalities are not well understood, and effective interventions are limited. The key drug Remdesivir has not worked, and there is an advisory from the World Health Organization on its failure in COVID-19. There is a heightened sense of urgency on increasing our understanding on why COVID-19 leads to health compromise, respiratory distress, organ failure, and death.

[0164] Oxidative stress is a toxic and damaging state which occurs due to increased accumulation of damaging and toxic reactive oxygen species, and results in oxidant damage. Under normal conditions, the endogenous tripeptide antioxidant Glutathione (GSH) combats excessive oxidative stress within the body to protect cells from its toxic effects. It has previously been reported that GSH levels are low in older humans, diabetic patients and HIV patients, and oxidative stress and damage caused by oxidative stress is highly elevated in these populations (Sekhar et al., 2011; Sekhar et al., 2010; Nguyen et al., 2013; Kumar et al., 2020; Kumar et al., 2021). It has also been reported that supplementing GlyNAC (combination of the GSH precursors glycine and N-acetylcysteine) successfully corrects deficient GSH synthesis and restores concentrations, with a resulting improvement (lowering) of oxidative stress and oxidant damage (Sekhar et al., 2011; Sekhar et al., 2010; Nguyen et al., 2013; Kumar et al., 2020; Kumar et al., 2021). Interestingly, oxidative stress or glutathione deficiency have not been well explored in patients with COVID-19.

[0165] The present example concerns a study to measure intracellular GSH concentrations (in red blood cells), oxidative stress (as concentrations of TBARS) and oxidant damage (as plasma concentrations of F2-isoprostanes) in patients admitted to the hospital with COVID-19. Patients admitted for any reason other than complications associated with COVID-19 were excluded.

1: Red-blood cell glutathione concentrations:

[0166] As can be seen in FIG. 2, there is a strong negative correlation between RBC-GSH concentrations and increasing age. This means that older humans have the lowest GSH levels. This could be clinically important because patients with increased age are the most vulnerable high-risk group for complications, and for COVID-related mortality. It is for this reason, that older humans were vaccinated at the highest level of priority in the USA.

[0167] FIG. 3 shows the relation between older humans in the 60-80y age group when comparing those with COVID and without COVID. As can be seen, the patients with COVID had the lowest levels of intracellular RBC-GSH concentrations. This indicates that these older humans could be at high risk of oxidative stress and oxidant damage (Table 1).

[0168] FIG. 4 shows the relation between younger humans in the 21-60y age group when comparing those with COVID and without COVID. As can be seen, the patients with COVID again had the lowest levels of intracellular RBC-GSH concentrations. This is particularly

surprising because people in this age range without COVID do not have GSH deficiency, and these data indicates that when younger humans become infected with the coronavirus to develop COVID, they have severe glutathione deficiency (Table 1).

2: Oxidative stress:

[0169] As can be seen in FIG. 5, there is a strong positive correlation between oxidative stress and age. This means that oxidative stress increases with age in COVID patients. This could be clinically important because patients with increased age are the most vulnerable high-risk group for complications, and for COVID-related mortality.

[0170] FIG. 6 shows the relation between humans in the 60-80y age group when comparing those with COVID and without COVID for oxidative stress. As can be seen, COVID-positive patients had significantly higher oxidative stress compared to COVID-negative people (Table 1).

[0171] FIG. 7 shows the relation between younger humans in the 21-60y age group when comparing COVID-positive and COVID-negative humans. COVID patients had significantly highest oxidative stress (Table 1). This is particularly surprising because younger people without COVID do not have elevated oxidative stress. These data indicates that when younger humans develop COVID, they have severe oxidative stress (Table 1).

3: Oxidant damage:

[0172] There is a strong positive correlation between oxidant damage and age (FIG. 8). This means that oxidative stress increases with age in COVID patients. This could be clinically important because patients with increased age are the most vulnerable high-risk group for complications, and for COVID-related mortality.

[0173] The relation between COVID-positive and COVID-negative younger humans in the 21-60y age group is shown in FIG. 9. COVID-positive patients had significantly higher oxidant damage (Table 1). This is surprising because younger people without COVID are not expected to have elevated oxidant damage.

[0174] FIG. 10 shows the relation between humans in the 60-80y age group when comparing those with COVID and without COVID for oxidant damage. As can be seen, COVID-

positive patients had significantly higher oxidant damage compared to COVID-negative people (Table 1).

[0175] Table 1: Comparison of COVID vs. non-COVID patients, with age breakdown (Mean ± SD)

Comparison of COVID-positive vs. COVID-negative humans: All ages			
	COVID negative	**COVID positive**	**Statistical significance**
Age	54.7 ± 21.1	54.0 ± 11.3	P = ns
RBC-glutathione concentrations (mmol/L.RBC)	0.83 ± 0.63	0.29 ± 0.18	P<0.000
Oxidative stress (TBARS concentrations, μM)	13.5 ± 9.9	32.1 ± 8.4	P<0.000
Oxidant damage (F2-isoprostane concentrations (pg/ml)	136.7 ± 82.2	208.9 ± 38.4	P<0.000
Comparison of COVID-positive vs. COVID-negative humans: Age 20-60 years			
RBC-glutathione concentrations (mmol/L.RBC)	1.47 ± 0.40	0.35 ± 0.15	P<0.000
Oxidative stress (TBARS concentrations, μM)	3.2 ± 1.3	29.5 ± 4.6	P<0.000
Oxidant damage (F2-isoprostane concentrations (pg/ml)	136.7 ± 82.2	208.9 ± 38.4	P<0.000
Comparison of COVID-positive vs. COVID-negative humans: Age 60-80 years			
RBC-glutathione concentrations (mmol/L.RBC)	0.37 ± 0.09	0.17 ± 0.02	P<0.001
Oxidative stress (TBARS concentrations, μM)	22.2 ± 3.4	39.7 ± 3.1	P<0.000
Oxidant damage (F2-isoprostane concentrations (pg/ml)	209.2 ± 23.5	256.2 ± 20.5	P<0.000

[0176] Adult patients with COVID-19 have severe GSH deficiency, oxidative stress and oxidant damage in all age groups. Because GlyNAC supplementation has been reported to improve GSH levels, oxidative stress and oxidant damage in older humans, diabetic patients, and HIV patients in previously published studies, GlyNAC supplementation is an important nutritional approach to improving the health of patients with COVID-19, in particular embodiments.

REFERENCES

[0177] All patents and publications mentioned in this specification are indicative of the level of those skilled in the art to which the disclosure pertains. All patents and publications herein are incorporated by reference to the same extent as if each individual publication was specifically and individually indicated to be incorporated by reference in their entirety.

PUBLICATIONS

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Sekhar RV et al. Correcting glutathione deficiency and mitochondrial dysfunction in older humans: a randomized clinical trial. Innov Aging. 2019 Nov; 3(Suppl 1): S416. doi: 10.1093/geroni/igz038.15 PMCID: PMC6840014

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[0178] Although the present disclosure and its advantages have been described in detail, it should be understood that various changes, substitutions and alterations can be made herein without departing from the disclosure as defined by the claims. Moreover, the scope of the present application is not intended to be limited to the particular embodiments of the process, machine, manufacture, composition of matter, means, methods and steps described in the specification. As one will readily appreciate from the disclosure, processes, machines, manufacture, compositions of matter, means, methods, or steps, presently existing or later to be developed that perform substantially the same function or achieve substantially the same result as the corresponding embodiments described herein may be utilized. Accordingly, the claims are intended to include within their scope such processes, machines, manufacture, compositions of matter, means, methods, or steps.

CLAIMS

The claimed invention is:

1. A method for treating, preventing, delaying onset of, and/or reducing severity of a viral infection in an individual in need thereof comprising administering to the individual an effective amount of a composition comprising glycine or a functional derivative or a precursor thereof, and N-acetylcysteine or a functional derivative or a precursor thereof, wherein the viral infection is caused by a virus belonging to the *Coronaviridae* family.

2. The method of claim 1, wherein the glycine or functional derivative or precursor thereof and the N-acetylcysteine or functional derivative or precursor thereof are provided to the individual in the same composition.

3. The method of claim 1 or 2, wherein the glycine or functional derivative or precursor thereof and the N-acetylcysteine or functional derivative or precursor thereof are provided to the individual in different compositions.

4. The method of any one of claims 1 to 3, wherein the glycine or functional derivative or precursor thereof and the N-acetylcysteine or functional derivative or precursor thereof are provided orally to the individual.

5. The method of any one of claims 1 to 4, wherein the glycine derivative is selected from the group consisting of D-Allylglycine; N-[Bis(methylthio)methylene]glycine methyl ester; Boc-allyl-Gly-OH (dicyclohexylammonium) salt; Boc-D-Chg-OH; Boc-Chg-OH; (R)-N-Boc-(2′-chlorophenyl)glycine; Boc-L-cyclopropylglycine; Boc-L-cyclopropylglycine; (R)-N-Boc-4-fluorophenylglycine; Boc-D-propargylglycine; Boc-(S)-3-thienylglycine; Boc-(R)-3-thienylglycine; D-α-Cyclohexylglycine; L-α-Cyclopropylglycine; N-(2-fluorophenyl)-N-(methylsulfonyl) glycine; N-(4-fluorophenyl)-N-(methylsulfonyl)glycine; Fmoc-N-(2,4-dimethoxybenzyl)-Gly-OH; N-(2-Furoyl)glycine; L-α-Neopentylglycine; D-Propargylglycine; sarcosine; Z-α-Phosphonoglycine trimethyl ester, and a mixture thereof.

6. The method of any one of claims 1 to 5, wherein the glycine and N-acetylcysteine are comprised in a dipeptide.

7. The method of claim 6, wherein the dipeptide comprises N-acetylcysteinylglycine or cysteinylglycine.

8. The method of any one of claims 1 to 7, wherein the glycine precursor comprises serine and/or methionine, and/or wherein the n-acetylcysteine precursor comprises serine and/or methionine.

9. The method of any one of claims 1 to 8, wherein the virus belonging to the *Coronaviridae* family is betacoronavirus.

10. The method of any one of claims 1 to 9, wherein the virus is SARS-CoV-2.

11. The method of any one of claims 1 to 10, wherein the individual has or has not been tested for the viral infection, has or has not tested positively for the viral infection, is or is not symptomatic for the viral infection, has or has not been exposed to an individual infected with the virus, or has or has not been vaccinated for the virus.

12. The method of any one of claims 1 to 11, wherein the individual has GSH deficiency, elevated oxidative stress, inflammation, immunosuppression, endothelial dysfunction, mitochondrial dysfunction, genomic damage, impaired autophagy, impaired mitophagy, insulin resistance, cellular senescence, stem cell defects, epigenetic alterations, cognitive impairment, functional limitation, tinnitus, physical limitations, decrease in exercise capacity or muscle strength or gait speed, fatigability, limitation in lung function, or a combination thereof.

13. The method of any one of claims 1 to 12, wherein the individual is an elderly individual.

14. The method of any one of claims 1 to 13, wherein the individual is an individual with diabetes.

15. The method of any one of claims 1 to 14, wherein the individual is an, the individual is an obese individual.

16. The method of any one of claims 1 to 15, wherein the individual is an immuno-compromised individual.

17. The method of any one of claims 1 to 16, wherein the administering step reduces intracellular GSH deficiency in the individual.

18. The method of any one of claims 1 to 17, wherein the administering step increases the intracellular concentration of glycine and/or cysteine in the individual.

19. The method of any one of claims 1 to 18, wherein the administering step increases the intracellular concentration of GSH in the individual.

20. The method of any one of claims 1 to 19, wherein the administering step reduces and/or prevents oxidative stress in the individual.

21. The method of an one of claims 1 to 20, wherein the administering step reduces the plasma concentration of markers of oxidative stress and/or damage due to oxidative stress in the individual.

22. The method of claim 21, wherein the markers of oxidative stress are thiobarbituric acid reactive substances (TBARS), malondialdehyde, lipid-peroxide, F2-isoprostane levels, plasma F3-isoprostane, F2-isoprostane levels, neuroprostanes, F4-isoprostane levels, a hydroxynonenal or a combination thereof.

23. The method of any one of claims 1 to 22, wherein the administering step reduces endothelium dysfunction in the individual.

24. The method of any one of claims 1 to 23, wherein the administering step reduces the plasma concentration of endothelium dysfunction markers in the individual.

25. The method of claim 24, wherein said endothelium dysfunction markers are sICAM1, sVCAM1, E-selectin, EndoPAT, vascular reactivity, ultrasound flow mediated dilation, or a combination thereof.

26. The method of any one of claims 1 to 25, wherein the administering step reduces inflammation in the individual.

27. The method of any one of claim 1 to 26, wherein the administering step reduces the plasma concentration of one or more inflammatory markers in the individual.

28. The method of claim 27, wherein said inflammatory markers are IL-6, CRP, TNF-alpha, IL-1-to-[NRF2]IL-10, MCP-1, or a combination thereof.

29. The method of any one of claims 1 to 28, wherein the administering step reduces immunosuppression in the individual.

30. The method of any one of claims 2 to 29, wherein the administering step increases the plasma concentration of immune cells in the individual.

31. The method of claim 30, wherein said immune cells are CD4+ T-Cells, CD8+ T-Cells, B-cells, NK cells, antigen-presenting cells, or a combination thereof.

32. The method of any one of claims 1 to 31, wherein the administering step prevents the synthesis of viral RNA, inhibits viral replication, blocks viral binding to cell receptors, inhibits viral self-assembly, and/or counters viral associated gene expression, in the individual.

33. The method of any one of claims 1 to 32, wherein the administering step inhibits papain-like protease (PLpro) in a host cell.

34. The method of any one of claims 1 to 33, wherein the administering step inhibits binding of the virus to a host cell angiotensin-converting enzyme 2 (ACE2) receptor.

35. The method of any one of claims 1 to 34, wherein the administering step inhibits virus associated gene expression in a host cell.

36. The method of any one of claims 1 to 35, wherein the administering step inhibits virus associated gene expression of genes selected from the group consisting of: IFIH1, OAS2, DDX58, RTP4, TRIM21, CD86, CH25H, TDRD7, TIMELESS, FCGR2C, TANK, EDEM1, LCP2, and APOL6.

37. The method of any one of claims 1 to 36, wherein the administering step prevents or reverses mitochondrial dysfunction in the individual.

38. The method of claim any one of claims 1 to 37, wherein the administering step increases fasted NEFA oxidation, decreases fasted carbohydrate oxidation, or a combination thereof, in the individual.

39. The method of any one of claims 1 to 38, wherein the administering step prevents or reverses insulin resistance in the individual.

40. The method of any one of claims 1 to 39, wherein the administering step prevents or reverses cognitive impairment in the individual.

41. The method of any one of claims 1 to 40, wherein the administering step prevents or reverses impaired awareness, perception, reasoning, judgment, or memory in the individual.

42. The method of any one of claims 1 to 41, wherein the administering step prevents or reverses functional limitation in the individual.

43. The method of any one of claims 1 to 42, wherein the administering step prevents or reverses weight loss, fatigue, muscle atrophy, loss of muscle strength, loss of muscle endurance, loss of muscle recovery, reduced gait speed, reduced exercise capacity, loss of bone mass, loss of bone strength, osteopenia, osteoporosis, or a combination thereof.

44. The method of any one of claims 1 to 43, wherein the administering step prevents or reverses limitation in pulmonary function, limitation in oxygen saturation, or a combination thereof.

45. The method of any one of claims 1 to 44, wherein the administering step prevents or reverses genomic damage in the individual.

46. The method of any one of claims 1 to 45, wherein the administering step prevents or reverses impaired autophagy or impaired mitophagy in the individual.

47. The method of any one of claims 1 to 46, wherein the administering step prevents or reverses cellular senescence and/or prevents or reverses stem cell fatigue, stem cell impairment, stem cell failure, or a combination thereof in the individual.

48. A method for reducing or preventing post-infection effects of a viral infection in an individual in need thereof, comprising administering to the individual an effective amount of a composition comprising glycine or a functional derivative or precursor thereof and N-acetylcysteine or a functional derivative or precursor thereof, wherein the viral infection is caused by a virus belonging to the *Coronaviridae* family.

49. The method of claim 48, wherein the post-infection effects comprise a symptom selected from the group consisting of fatigue, shortness of breath, cough, congestion, joint pain, chest pain, abdominal pain, difficulty with thinking, difficulty with concentration, brain fog, confusion, depression, muscle pain, headache, tinnitus, intermittent fever, fast-beating hear, pounding heart, heart palpitations, dizziness, diarrhea, nausea, cardiovascular issues, impairment of exercise capacity, pulmonary embolism, stroke, blot clots, immunological issues, respiratory issues, renal issues, dermatologic issues, neurological issues, psychiatric issues and a combination thereof.

50. The method of claim 48 or 49, wherein the individual has recovered from the viral infection.

51. The method of any one of claims 48 to 50, wherein the glycine or functional derivative or precursor thereof and the N-acetylcysteine or functional derivative or precursor thereof are provided to the individual in the same composition.

52. The method of any one of claims 48 to 51, wherein the glycine or functional derivative or precursor thereof and the N-acetylcysteine or functional derivative or precursor thereof are provided to the individual in different compositions.

53. The method of any one of claims 48 to 52, wherein the glycine or functional derivative or precursor thereof and the N-acetylcysteine or functional derivative or precursor thereof are provided orally to the individual.

54. The method of any one of claims 48 to 53, wherein the glycine derivative is selected from the group consisting of D-Allylglycine; N-[Bis(methylthio)methylene]glycine methyl ester; Boc-allyl-Gly-OH (dicyclohexylammonium) salt; Boc-D-Chg-OH; Boc-Chg-OH; (R)-N-Boc-(2′-chlorophenyl)glycine; Boc-L-cyclopropylglycine; Boc-L-cyclopropylglycine; (R)-N-Boc-4-fluorophenylglycine; Boc-D-propargylglycine; Boc-(S)-3-thienylglycine; Boc-(R)-3-thienylglycine; D-α-Cyclohexylglycine; L-α-Cyclopropylglycine; N-(2-fluorophenyl)-N-(methylsulfonyl) glycine; N-(4-fluorophenyl)-N-(methylsulfonyl)glycine; Fmoc-N-(2,4-dimethoxybenzyl)-Gly-OH; N-(2-Furoyl)glycine; L-α-Neopentylglycine; D-Propargylglycine; sarcosine; Z-α-Phosphonoglycine trimethyl ester, and a mixture thereof.

55. The method of any one of claims 48 to 54, wherein the glycine and N-acetylcysteine are comprised in a dipeptide.

56. The method of claim 55, wherein the dipeptide comprises N-acetylcysteinylglycine or cysteinylglycine.

57. The method of any one of claims 48 to 56, wherein the glycine precursor comprises serine and/or methionine, and/or wherein the n-acetylcysteine precursor comprises serine and/or methionine.

58. The method of any one of claims 48 to 57, wherein virus belonging to the *Coronaviridae* family is a betacoronavirus.

59. The method of any one of claims 48 to 58, wherein the virus is SARS-CoV-2.

60. The method of any one of claims 48 to 59, wherein the individual has or has not been tested for the viral infection, has or has not tested positively for the viral infection, is or is not symptomatic for the viral infection, or has or has not been exposed to an individual infected with the virus.

61. The method of any one of claims 48 to 60, wherein the individual has GSH deficiency, elevated oxidative stress, inflammation, immunosuppression, endothelial dysfunction, mitochondrial dysfunction, genomic damage, impaired autophagy, impaired mitophagy, insulin resistance, cellular senescence, stem cell defects, epigenetic alterations, cognitive impairment, functional limitation, physical limitations, decrease in exercise capacity or muscle strength or gait speed, fatigability, limitation in lung function, or a combination thereof.

62. The method of any one of claims 48 to 61, wherein the individual is an elderly individual.

63. The method of any one of claims 48 to 62, wherein the individual is an individual with diabetes.

64. The method of any one of claims 48 to 63, wherein the individual is an, the individual is an obese individual.

65. The method of any one of claims 48 to 64, wherein the individual is an immuno-compromised individual.

66. The method of any one of claims 48 to 65, wherein the administering step reduces intracellular GSH deficiency in the individual.

67. The method of any one of claims 48 to 66, wherein the administering step increases the intracellular concentration of glycine and/or cysteine in the individual.

68. The method of any one of claims 48 to 67, wherein the administering step increases the intracellular concentration of GSH in the individual.

69. The method of any one of claims 48 to 68, wherein the administering step reduces and/or prevents oxidative stress in the individual.

70. The method of an one of claims 48 to 69, wherein the administering step reduces the plasma concentration of markers of oxidative stress and/or damage due to oxidative stress in the individual

71. The method of claim 70, wherein said oxidative stress markers are thiobarbituric acid reactive substances (TBARS), malondialdehyde, lipid-peroxide, F2-isoprostane levels, plasma F3-isoprostane, F2-isoprostane levels, neuroprostanes, F4-isoprostane levels, a hydroxynonenal or a combination thereof.

72. The method of any one of claims 48 to 71, wherein the administering step reduces endothelium dysfunction in the individual.

73. The method of any one of claims 48 to 72, wherein the administering step reduces the plasma concentration of endothelium dysfunction markers in the individual.

74. The method of claim 73, wherein said endothelium dysfunction markers are sICAM1, sVCAM1, E-selectin, EndoPAT, vascular reactivity, ultrasound flow mediated dilation, or a combination thereof.

75. The method of any one of claims 48 to 74, wherein the administering step reduces inflammation in the individual.

76. The method of any one of claim 47 to 75, wherein the administering step reduces the plasma concentration of inflammatory markers in the individual.

77. The method of claim 76, wherein said inflammatory markers are IL-6, CRP, TNF-alpha, IL-10, MCP-1, or a combination thereof.

78. The method of any one of claims 48 to 77, wherein the administering step reduces immunosuppression in the individual.

79. The method of any one of claims 50 to 78, wherein the administering step increases the plasma concentration of immune cells in the individual.

80. The method of claim 79, wherein said immune cells are CD4+ T-Cells, CD8+ T-Cells, B-cells, NK cells, antigen-presenting cells, or a combination thereof.

81. The method of any one of claims 48 to 80, wherein the administering step prevents the synthesis of viral RNA, inhibits viral replication, blocks viral binding

to cell receptors, inhibits viral self-assembly, and/or counters viral associated gene expression, in the individual.

82. The method of any one of claims 48 to 81, wherein the administering step inhibits papain-like protease (PLpro) in a host cell.

83. The method of any one of claims 48 to 82, wherein the administering step inhibits binding of the virus to a host cell angiotensin-converting enzyme 2 (ACE2) receptor.

84. The method of any one of claims 48 to 83, wherein the administering step inhibits virus associated gene expression in a host cell.

85. The method of any one of claims 48 to 84, wherein the administering step inhibits virus associated gene expression of genes selected from the group consisting of: IFIH1, OAS2, DDX58, RTP4, TRIM21, CD86, CH25H, TDRD7, TIMELESS, FCGR2C, TANK, EDEM1, LCP2, and APOL6.

86. The method of any one of claims 48 to 85, wherein the administering step prevents or reverses mitochondrial dysfunction in the individual.

87. The method of claim any one of claims 48 to 86, wherein the administering step increases fasted NEFA oxidation, decreases fasted carbohydrate oxidation, or a combination thereof, in the individual.

88. The method of any one of claims 48 to 87, wherein the administering step prevents or reverses insulin resistance in the individual.

89. The method of any one of claims 48 to 88, wherein the administering step prevents or reverses cognitive impairment in the individual.

90. The method of any one of claims 48 to 89, wherein the administering step prevents or reverses impaired awareness, perception, reasoning, judgment, or memory in the individual.

91. The method of any one of claims 48 to 90, wherein the administering step prevents or reverses functional limitation in the individual.

92. The method of any one of claims 48 to 91, wherein the administering step prevents or reverses weight loss, fatigue, muscle atrophy, loss of muscle strength, loss of muscle endurance, loss of muscle recovery, reduced gait speed, reduced exercise capacity, loss of bone mass, loss of bone strength, osteopenia, osteoporosis, or a combination thereof.

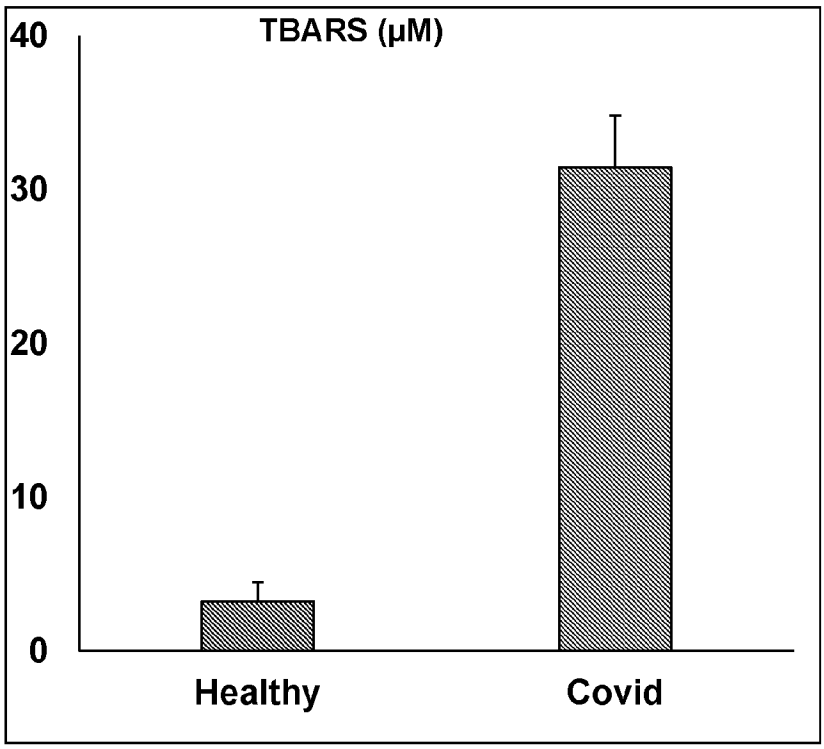
93. The method of any one of claims 48 to 92, wherein the administering step prevents or reverses limitation in pulmonary function, limitation in oxygen saturation, or a combination thereof.

94. The method of any one of claims 48 to 93, wherein the administering step prevents or reverses genomic damage in the individual.

95. The method of any one of claims 48 to 94, wherein the administering step prevents or reverses impaired autophagy or impaired mitophagy in the individual.

96. The method of any one of claims 48 to 95, wherein the administering step prevents or reverses cellular senescence and/or prevents or reverses stem cell fatigue, stem cell impairment, stem cell failure, or a combination thereof in the individual.

FIG. 1


TBARS (μM)
40
30
20
10
0
Healthy
Covid

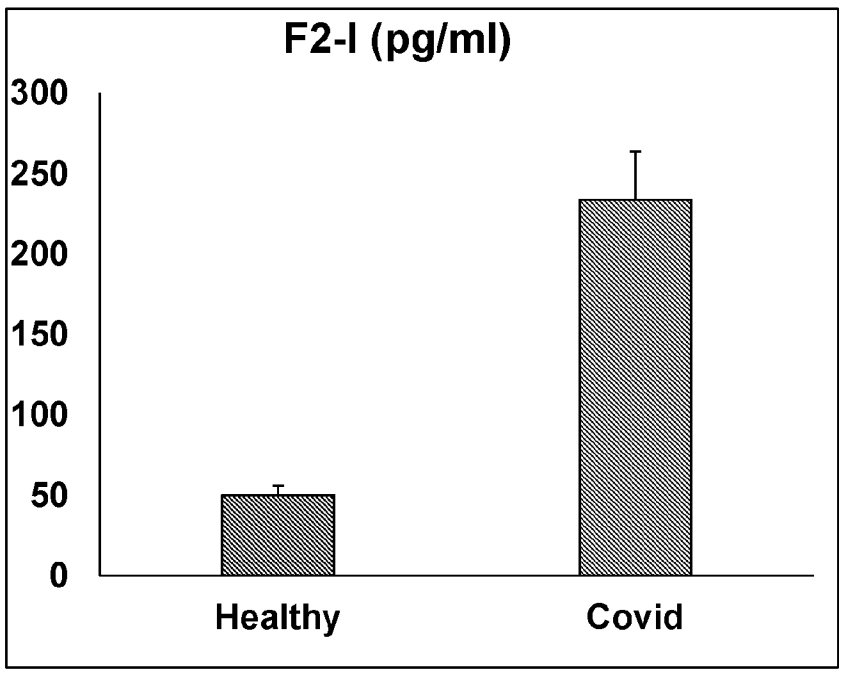

F2-I (pg/ml)
300
250
200
150
100
50
0
Healthy
Covid

FIG. 2

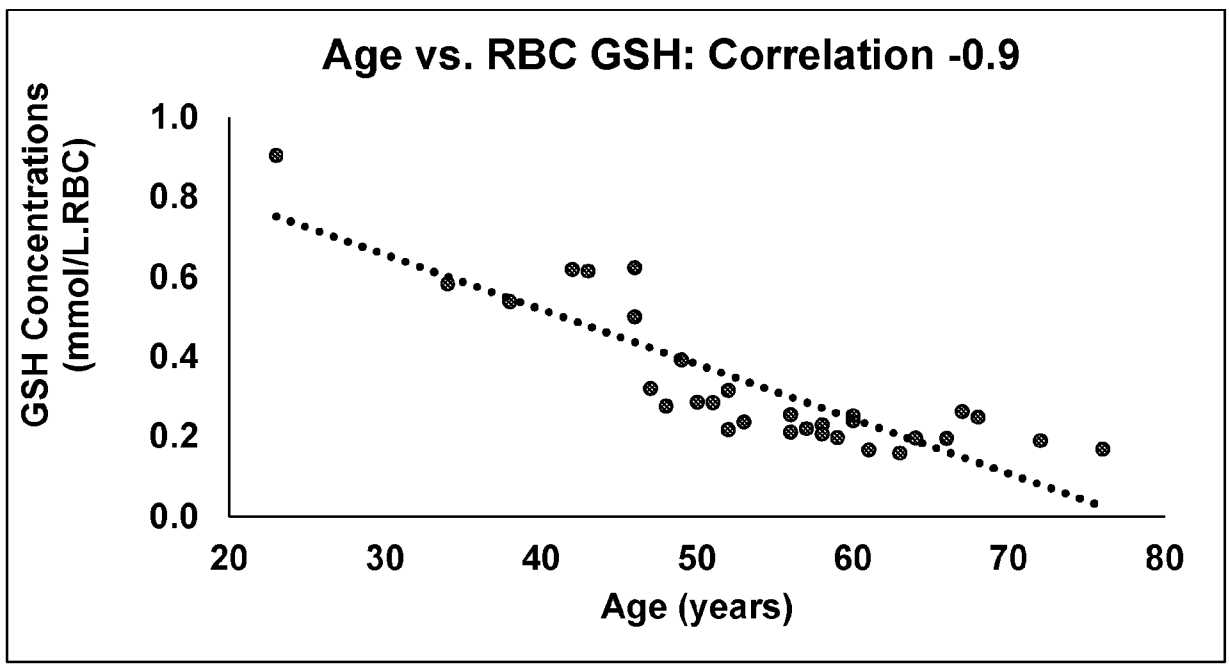

Age vs. RBC GSH: Correlation -0.9
GSH Concentrations (mmol/L.RBC)
1.0
0.8
0.6
0.4
0.2
0.0
20
30
40
50
60
70
80
Age (years)

FIG. 3

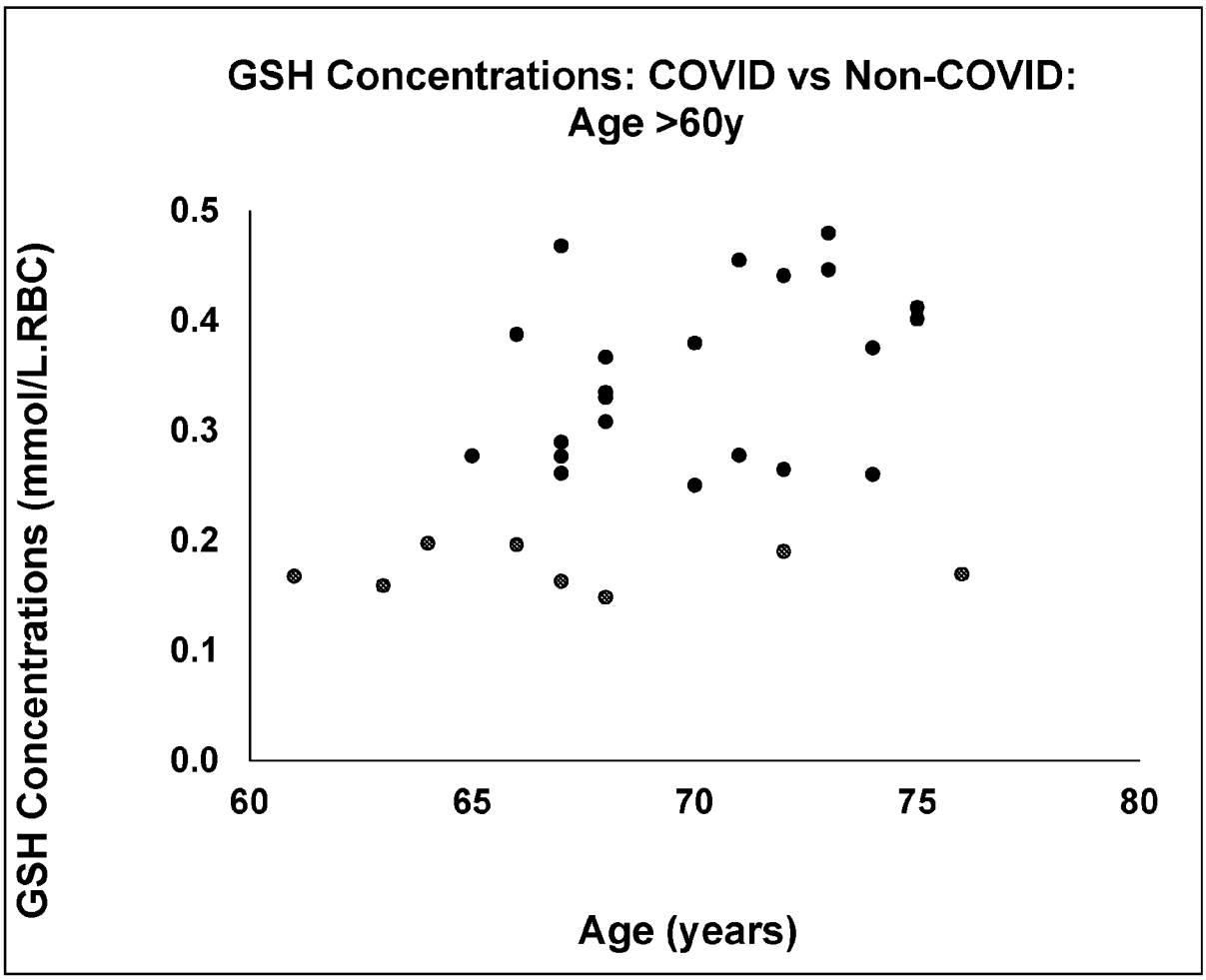

GSH Concentrations: COVID vs Non-COVID:
Age >60y
GSH Concentrations (mmol/L.RBC)
0.5
0.4
0.3
0.2
0.1
0.0
60
65
70
75
80
Age (years)

FIG. 4

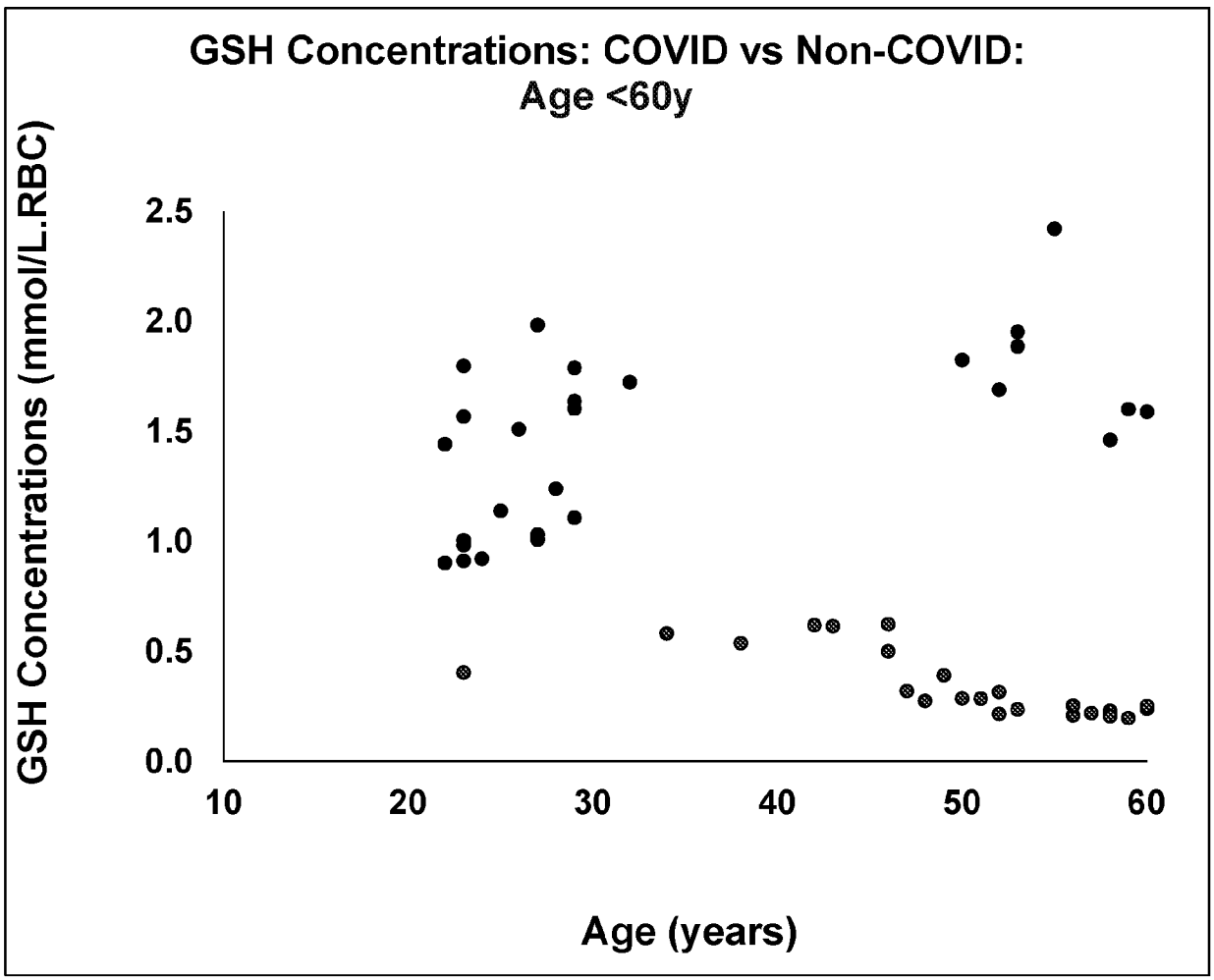

GSH Concentrations: COVID vs Non-COVID:
Age <60y
GSH Concentrations (mmol/L.RBC)
2.5
2.0
1.5
1.0
0.5
0.0
10
20
30
40
50
60
Age (years)

FIG. 5

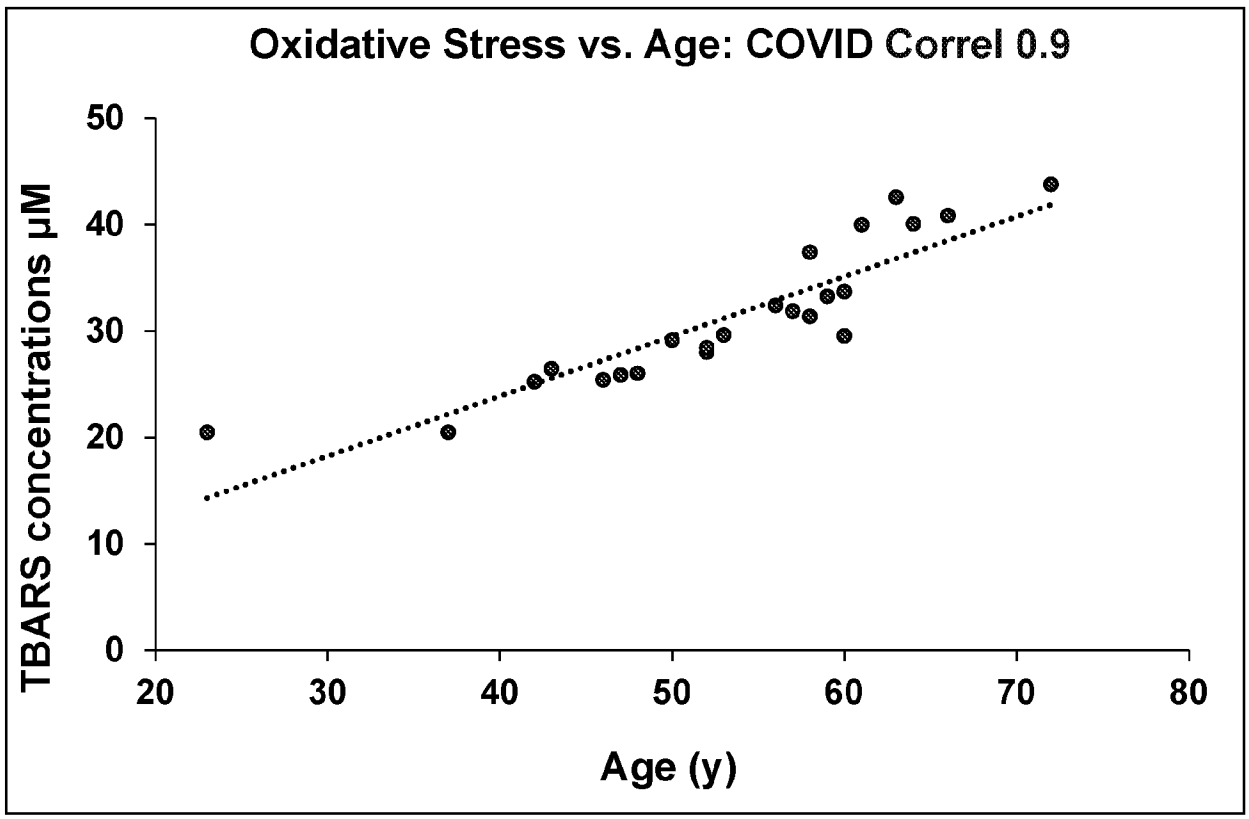

Oxidative Stress vs. Age: COVID Correl 0.9
TBARS concentrations µM
50
40
30
20
10
0
20
30
40
50
60
70
80
Age (y)

FIG. 6

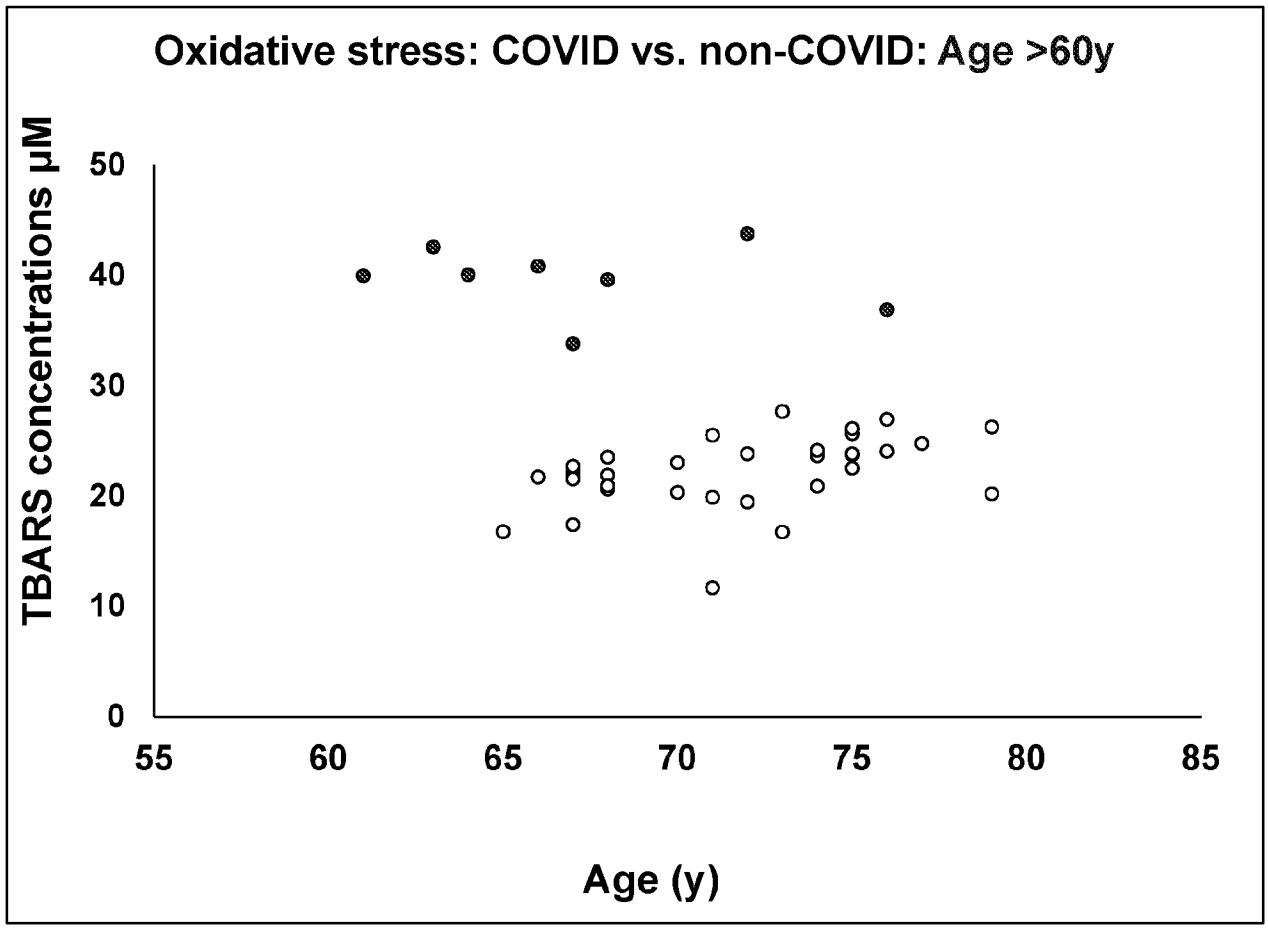

Oxidative stress: COVID vs. non-COVID: Age >60y
TBARS concentrations µM
50
40
30
20
10
0
55
60
65
70
75
80
85
Age (y)

FIG. 7

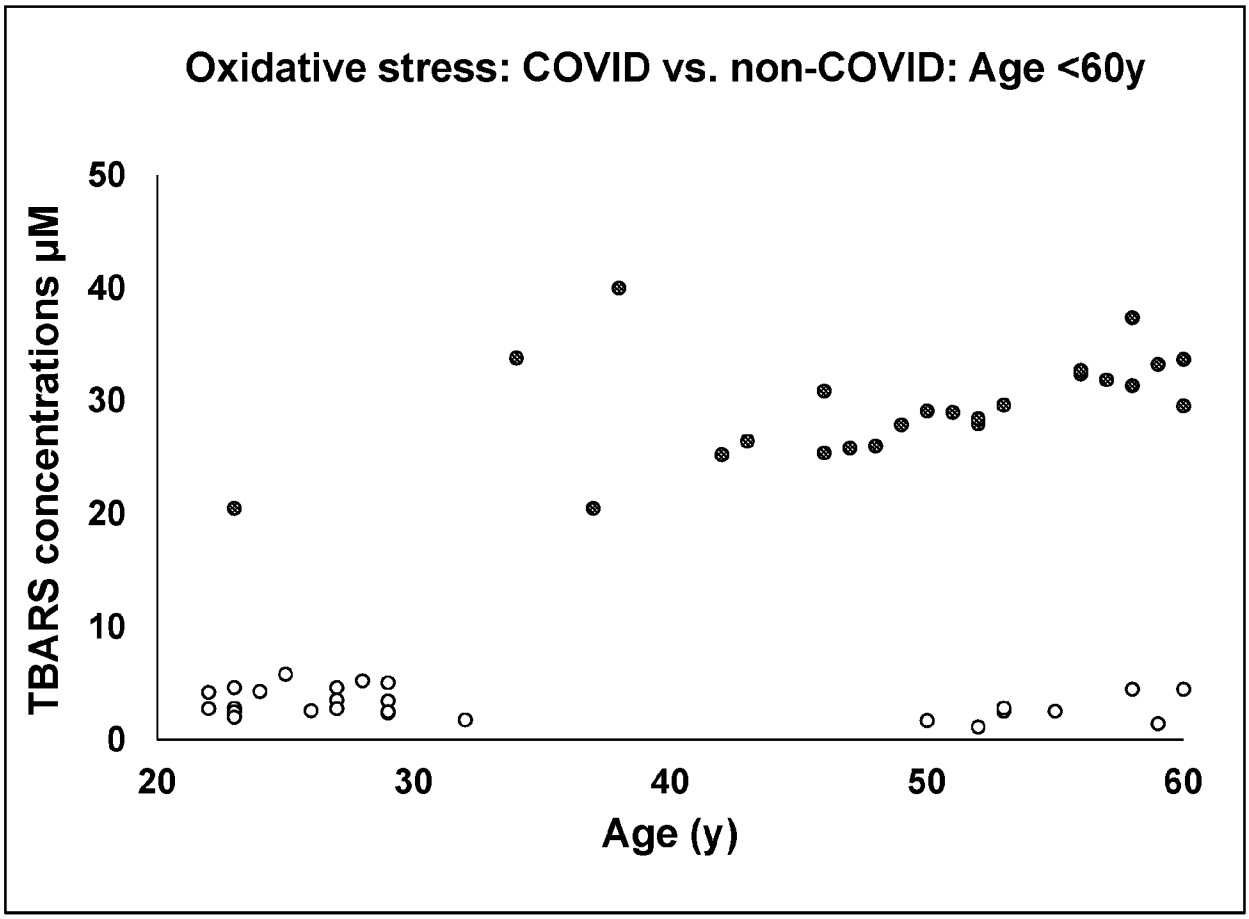

Oxidative stress: COVID vs. non-COVID: Age <60y
TBARS concentrations µM
50
40
30
20
10
0
20
30
40
50
60
Age (y)

FIG. 8

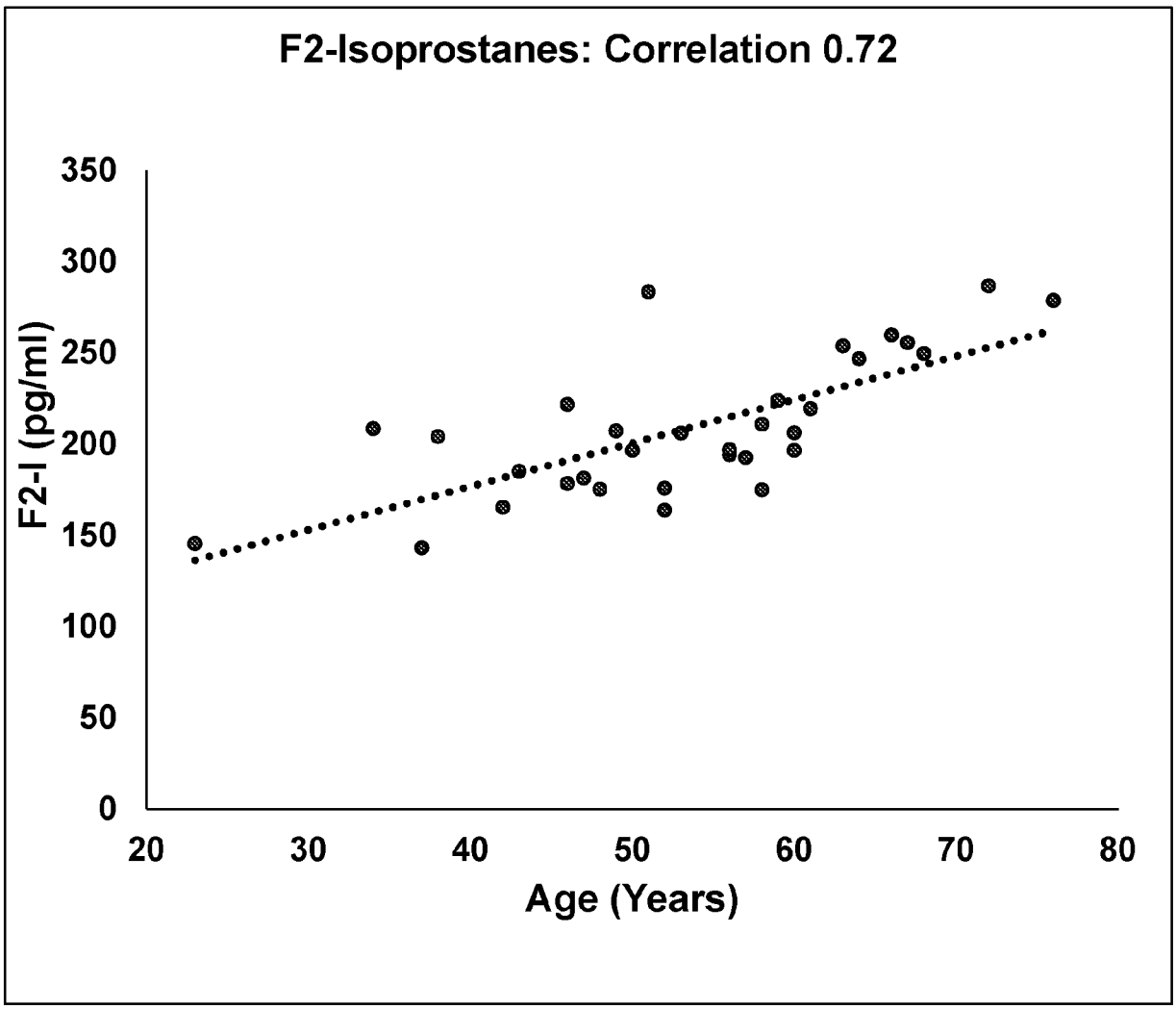

F2-Isoprostanes: Correlation 0.72
F2-I (pg/ml)
350
300
250
200
150
100
50
0
20
30
40
50
60
70
80
Age (Years)

FIG. 9

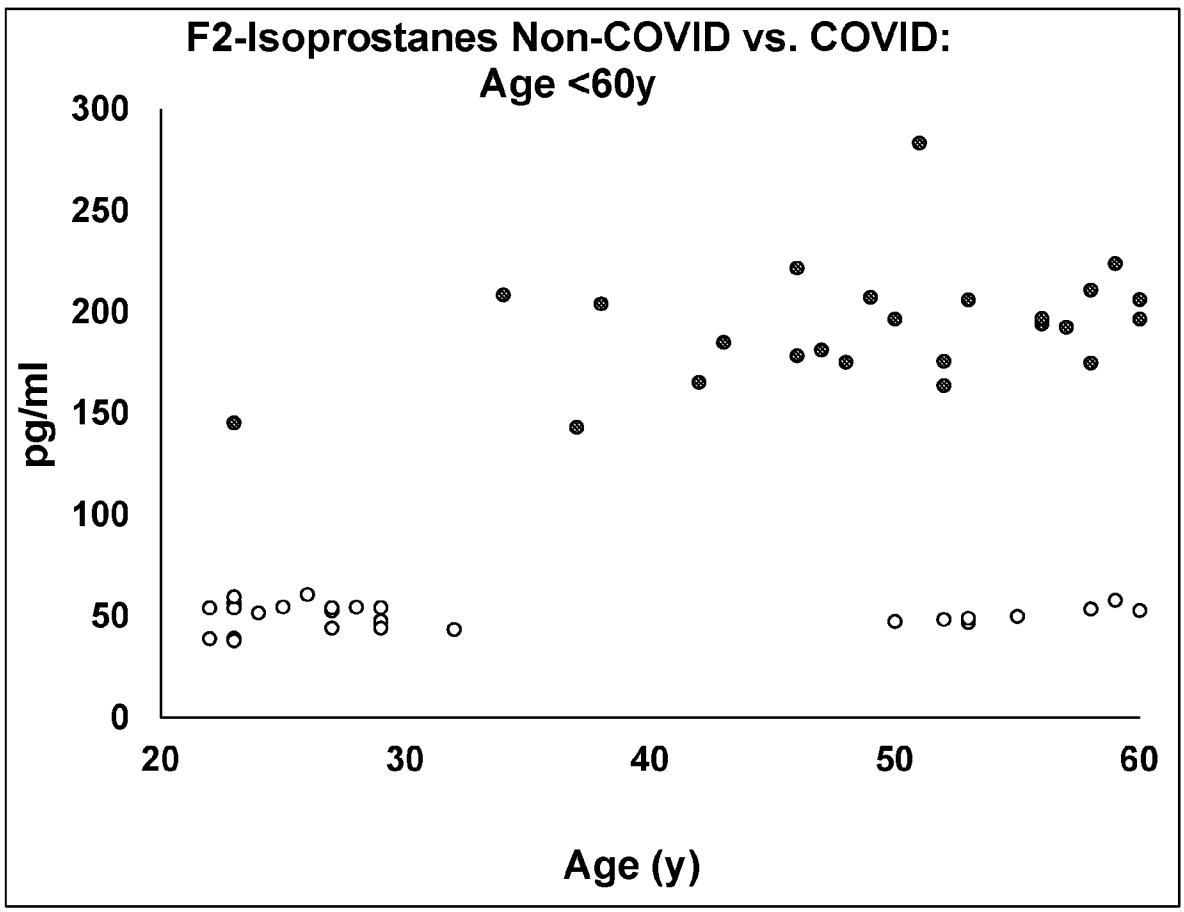
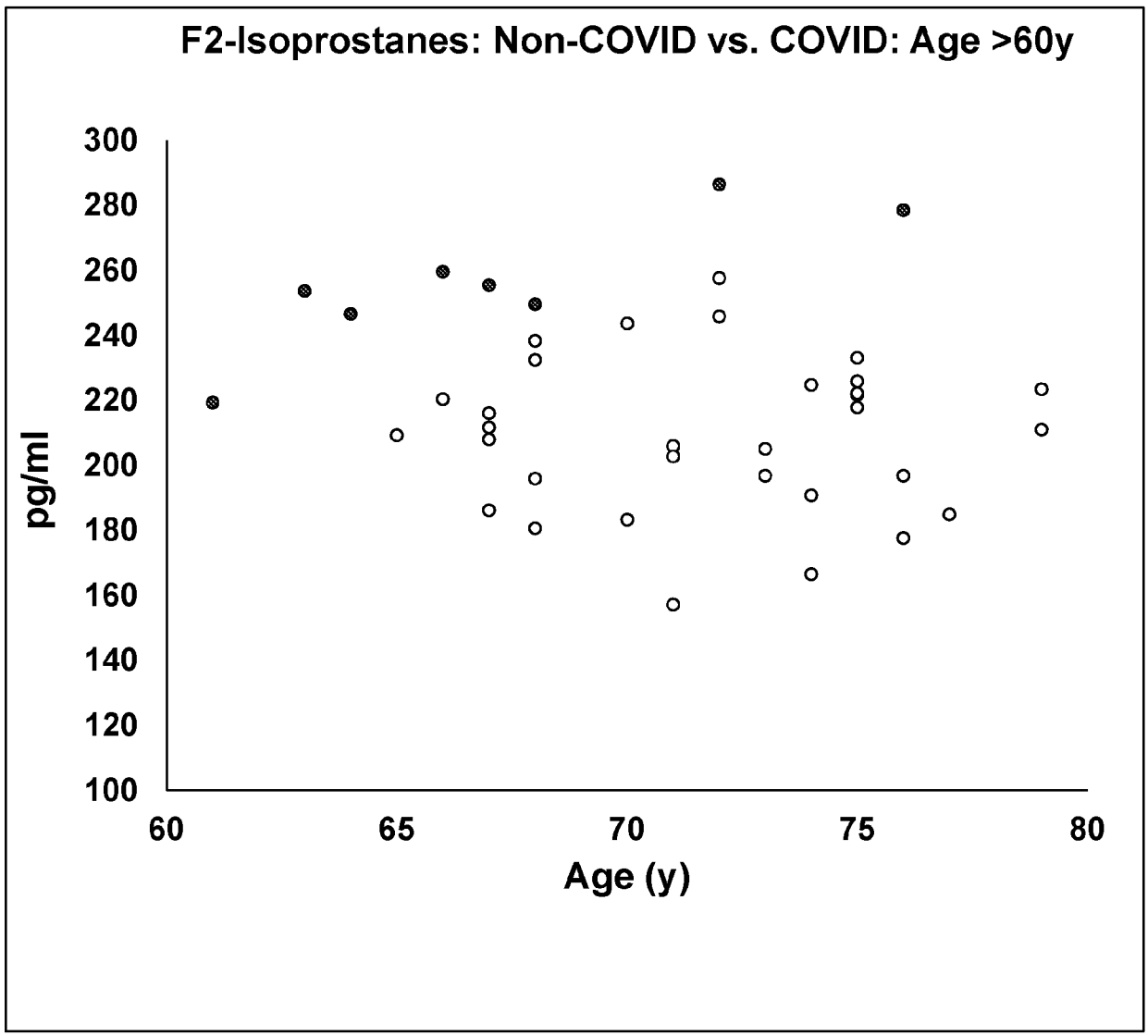

F2-Isoprostanes Non-COVID vs. COVID:
Age <60y
300
250
200
150
100
50
0
pg/ml
20
30
40
50
60
Age (y)

FIG. 10


F2-Isoprostanes: Non-COVID vs. COVID: Age >60y
pg/ml
300
280
260
240
220
200
180
160
140
120
100
60
65
70
75
80
Age (y)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2021/070523

A. CLASSIFICATION OF SUBJECT MATTER
IPC(8) - A61K 31/19; A61K 31/198; A61P 31/14 (2021.01)
CPC - A61K 31/19; A61K 31/198; A61P 31/14 (2021.05)

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
see Search History document

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
see Search History document

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
see Search History document

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	US 8,106,170 B2 (TER MEULEN et al) 31 January 2012 (31.01.2012) entire document	1-3, 50
Y	WO 2020/064946 A2 (SOCIÉTÉ DES PRODUITS NESTLÉ S A) 02 April 2020 (02.04.2020) entire document	1-3, 48-50
Y	US 2004/0234457 A1 (RENNIE et al) 25 November 2004 (25.11.2004) entire document	48-50

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"D" document cited by the applicant in the international application
"E" earlier application or patent but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
29 June 2021	JUL 29 2021
Name and mailing address of the ISA/US Mail Stop PCT, Attn: ISA/US, Commissioner for Patents P.O. Box 1450, Alexandria, VA 22313-1450 Facsimile No. 571-273-8300	Authorized officer Harry Kim Telephone No. PCT Helpdesk: 571-272-4300

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2021/070523

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☒ Claims Nos.: 4-47, 51-96
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying additional fees, this Authority did not invite payment of additional fees.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.

☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.

☐ No protest accompanied the payment of additional search fees.