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Review Article

L-Arginine in Restoring 'Immune Dysregulation' in Long COVID: It's the Therapeutic Role Beyond the Routine Dietary Supplement!

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Abstract: COVID-19 pandemic is over now and we are in great peace of relief after three years. This pandemic has observed significant impact on quality of life globally and the put unforgettable imprints on history of mankind. Reason for more havoc in this pandemic was less studied virus by medical scientists regarding its pathophysiology, available treatment options and lack of effective vaccine to tackle this dragon. COVID-19 is the first observed and reported pandemic of corona virus related global disease apart from its previous SARS and MERS. Fast track developments in medical treatment options due to this ultrafast digital and artificial intelligence techniques have curtailed mortality on large scale globally. Although mortality is significantly reduced, morbidity is documented on a large scale worldwide in this pandemic. Morbidity due to COVID-19 now called as 'Long COVID', which is underreported & half-heartedly evaluated globally. Long COVID is related to persistent immune dysregulation occurs during evolution of COVID-19 as natural trend of disease. Immune dysregulation has documented during course of active viremia, during recovery of viral illness and after post viral phase. Immune dysregulation occurs in 'selected group' of cases irrespective of disease severity and vaccination status and observed in cases with negligible illness to advanced one mandates further research. Thus, Immune dysregulation in COVID-19 is predominant cause for long covid and leading to brainstorming effect on medical scientists and researchers as of today. Globally, one third of recovered or affected cases of COVID-19 are facing long covid and needs prompt treatment options to tackle this dragon related long term effect on body. 'Immunomodulatory' or immunity modifying agents are the primary targets to curtail immune dysregulation and long covid. Some experts recommend 'disease modifying agents' to treat long covid cases. Still, many miles to go to reach to effective treatment options for long covid and we don't have effective options for this 'health issue of global concern'. L-Arginine is amino acid with multiple beneficial effects such as immunomodulatory effects which will regulates immunological response in inhibit dysregulated immune system additional to its universally known antioxidant, vasodilatory and regenerative and cellular proliferation effects on immune cells. These Immunomodulatory and or diseases modifying effects of L-Arginine makes it the future candidate with 'game changer' role for management of Long covid resulting from immune dysregulation as a core pathophysiologic pathway of this Dragon Pandemic.

Keywords: Immune dysregulation, COVID-19, Long COVID, Arginine, Immunomodulatory.

Inflammatory response and inflammatory markers in COVID-19 pneumonia

COVID-19 pandemic has been studied over last two and half years for its highly pathogenic nature of corona virus. Main hurdle for acquiring immunological memory after natural infection is genetic change in spike proteins of nucleocapsid of novel corona virus after certain interval resulting into different waves documented in different geographical settings. The immune response during acute illness contributes to both host defence and pathogenesis of severe COVID-19 [1-2]. Now the robust data is available for role of various inflammatory markers in initial assessment of cases which are associated with direct or indirect virus-related lung injury. This is first COVID-19 related global pandemic in history of mankind and more studied pandemic in all waves in all viral pandemics due to its rapid evolution and high mortality [3-5]. Apart from lung involvement, proportionate number of cases were shown systemic manifestations due to activation of

inflammatory pathway and inflammatory surge resulting in to pulmonary and extrapulmonary effects which have significant impact on final outcome. All these effects can be easily picked up by timely analysis of inflammatory markers. Now these markers are also called as 'inflammatory biomarkers.' Various inflammatory markers such as CRP, Ferritin, LDH, D-dimer and IL-6 were exuberantly used during workup of COVID-19 cases worldwide and reported their valuable role in initial assessment, predicting severity, guiding or triaging hospitalization, predicting need of interventions during hospitalization, analysing final outcome, predicting post recovery outcome and possibility of long covid manifestations and considered as 'composite index' [6-7]. Various treatment options used in COVID-19 pneumonia have showed significant impact on inflammatory markers during course of hospitalization [7-8]. Inflammatory markers has been studied for predicting antigenic cross-reactivity and antigenic mimicry which has resulted in autoimmune and rheumatological manifestations. During COVID-19 pandemic antigenic cross reactivity has documented with dengue fever [10-13]. Similarly, deregulated immune phenomenon has been documented after covid vaccination and transient autoimmune features have been reported in various studies [14-15]. COVID-19 related extrapulmonary manifestations have been reported secondary to dysregulated immune response and systemic effects on immunity & immunosuppression resulting into tuberculosis [16], central nervous system resulting into stroke [17] and endocrinal effects resulting into hyponatremia [18].

Immune dysregulation during COVID-19 as natural trends of disease

Although SARS-CoV-2 infection generally leads to a mild disease in a large proportion of infected individuals, 5-15% of COVID-19 patients develop a severe pathology that progresses to pneumonia and respiratory failure. Dysregulation in the immune system can lead to an unappropriated local and systemic immune responses and subsequently the rapid spread of the virus, leading to severe COVID-19 disease. Severity of illness increases with more lung parenchymal involvement as documented with chest imaging in proportion with inflammatory markers such as IL-6, CRP, Ferritin, LDH and D-dimer. Disease outcomes range from asymptomatic and mild to more severe and critical courses with pneumonia, acute respiratory distress syndrome (ARDS), multiorgan failure, and considerable risk of fatality. In this context, the immune cell landscape of severe COVID-19 patients is reported to be dysregulated and detailed insights on the cellular dynamics of severe COVID-19 patients are urgently needed to identify potential disease intervention points. [19] Previous studies have shown dysregulation of innate and adaptive immune cell compartments in patients with moderate, severe, and convalescent COVID-19 [19]. CRP is easily available, sensitive, reliable, cost effective, and universally acceptable inflammatory marker in COVID-19 pneumonia. CRP has very crucial role in COVID-19 pneumonia in predicting severity of illness, especially 'follow up titters' have significant role in step-up or step-down interventions in critical care setting. Correlating CRP with variables as duration of illness, oxygenation status and timing of BIPAP/NIV has important role in predicting outcome. CRP titer has significant association in predicting progression of pneumonia and we have documented that proportionate number of COVID-19 cases with mild variety on CT thorax with normal initial CRP has progressed to critical course. CRP follow-up titer can help in predicting progression of COVID pneumonia and assessing risk of post-COVID lung fibrosis [20-23].

LDH is an easily available, sensitive & reliable, cost effective, and universally acceptable inflammatory marker in COVID-19 pandemic. Correlating LDH with variables like duration of illness, oxygenation status and timing of BIPAP/NIV at entry point is important to have satisfactory treatment outcome. LDH titer has significant associations with predicting progression of pneumonia, as proportionate number of pneumonia cases with mild variety on CT thorax and normal initial LDH has progressed to critical course which were documented with help of rising titers and we have documented follow-up rising titers has played crucial role with other inflammatory markers like LDH & ferritin [24-27]. IL-6 is easily available, sensitive, reliable, cost effective, and universally acceptable inflammatory marker in COVID-19 pneumonia. IL-6 has very crucial role in COVID-19 pneumonia in predicting severity of illness, especially 'follow up titers' have significant role in step-up or step-down interventions in critical care setting. Correlating IL-6 with variables as duration of illness, oxygenation status and timing of BIPAP/NIV has important role in predicting outcome. IL-6 follow-up titer can help in predicting progression of COVID pneumonia, and assessing risk of post covid lung fibrosis [28-31]. D-Dimer is easily available, and universally acceptable inflammatory marker, which has documented very crucial role in COVID-19 pneumonia in predicting severity of illness, and assessing response to treatment during hospitalization. D-Dimer has important role during interventions in intensive care unit, as follow up titers have significant role in step-up or step-down interventions in critical care setting. Correlating D-dimer with variables like duration of illness, oxygenation status and timing of BIPAP/NIV at entry point is important to have satisfactory treatment outcome [32-35].

Robust data of Ferritin is available in bacterial infection, and it can be utilized in this COVID-19 pneumonia pandemic for initial assessment before planning of treatment in indoor setting in comparison with other inflammatory markers and CT severity. Ferritin has very crucial role in covid-19 pneumonia in predicting severity of illness, especially follow up titers have significant role in step-up or step-down interventions in critical care setting. Correlating Ferritin with variables like duration of illness, oxygenation status and timing of BIPAP/NIV at entry point is important to have satisfactory treatment outcome. Ferritin titer can help in predicting progression of COVID pneumonia, and assessing risk of post covid lung fibrosis [36-39].

Basic Pathophysiology of Immune dysregulation during evolution of COVID-19:

Immune dysregulation in the context of the SARS-CoV-2 virus (COVID-19 disease) is complex. Early research in the COVID-19 disease pandemic identified a pathophysiology of cytokine storms leading to damaging hyperinflammation while additional research demonstrated profound long-term immune suppression [40-41]. Although COVID-19 patients may exhibit elevated levels of inflammatory cytokines compared to non-critically-ill patients, a study comparing the immune profiles of COVID-19 and influenza noted that while a 3–4% subset of COVID-19 patients exhibited hyperinflammation characteristic of a cytokine storm, they more commonly demonstrated immunosuppression [42]. COVID-19 associated lymphopenia is predictive of poor outcomes and is a risk factor for secondary hospital-acquired infections, accounting for 50% of estimated mortality secondary to COVID-19.

Innate immune system

Both the innate and adaptive immune systems experience dysregulation in COVID-19. Responsible for the initial antiviral activity, the innate system functions as a single defense mechanism, crucial for host response and illness protection. Pattern recognition receptors (PRRs) on innate immune cells detect pathogen-associated molecular patterns (PAMPs) from invading microbes and damage-associated molecular patterns (DAMPs) released from dying host cells [43]. In COVID-19, possible PAMPs include proteins from the SARS-CoV-2 viral envelope, spikes, and nucleoproteins (N) as well as single stranded RNA [6]. DAMPs may include S100A8/A9 and nucleic acids from dead cells [6]. This activation leads to NF-κB and AP-1 transcription of antiviral and inflammatory cytokines designed to induce apoptosis and inhibit viral replication [43]. Paradoxically, in COVID-19 pneumonia, the innate immune system fails to mount an effective antiviral response while also inducing potentially damaging inflammation. Severe cases are especially marked by decreased early production of type I and type III interferons (IFN) allowing for SARS-CoV-2 to replicate and cause severe cellular damage in the lungs [42-45]. Not only is this antiviral response of IFN delayed and reduced, but also accompanied by an unusually early and strong production of cytokines [9]. This overexaggerated and unregulated inflammatory response includes interleukin-6 (IL-6), interleukin-8 (IL-8), interleukin-10 (IL-10), and tumor necrosis factor-α (TNF-α), all of which predict disease severity and mortality [46-47]. Importantly, the ensuing hyperinflammation is believed to induce edema, fibrosis, and thrombosis in the lungs leading to hypoxia, acute respiratory distress syndrome (ARDS), and death [46]. However, hyperstimulation by inflammatory cytokines of cell surface receptors on adaptive immune cells such as lymphocytes and monocytes may cause a paradoxical immunosuppressive effect, a concept that will be explored in more detail in subsequent sections.

In addition to PRR pathways in COVID-19, dysregulation occurs in other sensors of cellular stress including the transcription factors, nuclear factor, erythroid 2-related factor (Nrf2) and hypoxia-inducible factor 1a (HIF-1a). Nrfr2 activation inhibits SARS-CoV-2 replication through type 1 IFN signaling and inhibits inflammatory cytokine release [48-49]. However, lungs of COVID-19 patients exhibit Nrf2 suppression, possibly contributing to decreased antiviral action and increased cytokine levels [13]. Conversely, HIF-1α activation is increased in severe COVID-19. HIF-1α is correlated with mortality in elderly COVID-19 patients and may contribute to the induction of inflammatory organ damage [50]. Hyperinflammatory damage with additionally immune paralyzing effects to host innate responses provide a complex sequence of dysregulation creating specific cell type chaos that leads to altering degrees of disease severity, and varies during the course of the disease.

Adaptive immune system

Cellular and humoral activity of the adaptive immune system is critical for developing a balanced and efficient host response to invading pathogens while also conferring immunologic memory for future infections with similar coronaviruses. Additionally, the activation of this process demonstrates particular importance in terms of vaccination efficacy and longevity [51]. Conversion from the innate immune response to the adaptive arm of the immune system is a critical function in acute COVID-19, and therefore, quantitative analysis of this response could maintain prognostic value. Early antibody production is associated with disease severity, and T cell production of IFN- ɣ is correlated with disease moderation [52]. Unfortunately, the adaptive immune system demonstrates significant dysregulation in COVID-19 as well.

B cells

Many COVID-19 patients demonstrate a robust memory B cell and antibody-secreting B cell plasmablast response early in infection. However, research on B cell levels over the course of illness is conflicting with some studies identifying an increase of plasmablasts and another identifying a decrease in B cell frequency. Additionally, an imbalance of IL-6 and IL-10 production by B cells has been observed in COVID-19. However, most B cell alterations experienced in acute COVID-19 are recovered in convalescent patients [53-54].

T cells

CD4+ helper T cells and CD8+ cytotoxic T cells have been identified as crucial in the immunologic response to SARS-CoV-2 infection. CD4+ T cells are responsive to the virus's spike protein, and the presence of CD8+ T cell expansion in bronchoalveolar lavage is correlated with illness moderation [55]. However, one of the most remarkable characteristics

of immune dysregulation in COVID-19 is an immense depletion of CD4+ and CD8+ T cells associated with disease severity. While lymphopenia is observed in other respiratory viral illnesses such as influenza A H3N2 viral infection, COVID-19 induced lymphocytic depletion is distinctive for its magnitude and longevity. Additionally, CD8+ T cells, crucial for their cytotoxic activity against virally infected cells, may experience the more stark reduction. While CD8+ T cell have some cellular markers of activity indicating specificity to SARS-CoV-2, markers of exhaustion indicate dysregulated function. This lymphopenia has been identified as an important risk factor in the development of secondary infections in hospitalized COVID-19 patients [55-56]. The lack of intense lymphocytic infiltration found in the lungs of critical COVID-19 patients demonstrates that the peripherally observed lymphopenia may be occurring through a mechanism beyond simply recruitment to the infection site. Using an enzyme-linked immune absorbent spot (ELISpot) assay as a tool to quantitate peripheral immune cell function in patients with COVID-19, researchers not only confirmed T cell lymphopenia, but also identified functional suppression of T cells as measured by IFN-ɣ. Decreased production of IFN-ɣ by CD4+ T cells correlates with COVID-19 severity. T cell counts in COVID-19 patients are inversely proportional to IL-6, IL-10, and TNF-α concentrations and shown to express elevated levels of PD-1. These cytokines and signalling pathways have been identified as possible mechanisms for the observed immune exhaustion and dysregulation in COVID-19 [56-58].

Immune dysregulation as frontline mechanism of long covid

Long COVID is an often-debilitating illness that occurs in at least 10% of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infections. More than 200 symptoms have been identified with impacts on multiple organ systems. At least 65 million individuals worldwide are estimated to have long COVID, with cases increasing daily [59]. Biomedical research has made substantial progress in identifying various pathophysiological changes and risk factors and in characterizing the illness; further, similarities with other viral-onset illnesses such as myalgic encephalomyelitis/chronic fatigue syndrome and postural orthostatic tachycardia syndrome have laid the groundwork for research in the field [60-69]. There are likely multiple, potentially overlapping, causes of long COVID. Several hypotheses for its pathogenesis have been suggested, including persisting reservoirs of SARS-CoV-2 in tissues; immune dysregulation with or without reactivation of underlying pathogens, including herpesviruses such as Epstein–Barr virus (EBV) and human herpesvirus 6 (HHV-6) among others; impacts of SARS-CoV-2 on the microbiota, including the virome; autoimmunity and priming of the immune system from molecular mimicry; microvascular blood clotting with endothelial dysfunction; and dysfunctional signalling in the brainstem and/or vagus nerve [59-69].

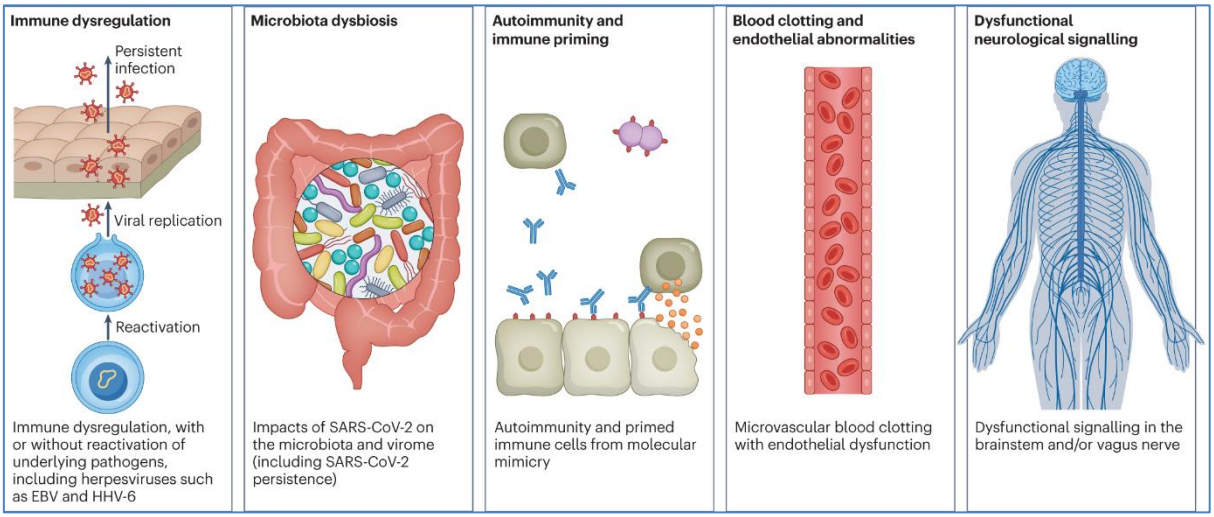

Figure 1: Hypothesized mechanisms of long COVID pathogenesis [59]

There are several hypothesized mechanisms for long COVID pathogenesis, including immune dysregulation, microbiota disruption, autoimmunity, clotting and endothelial abnormality, and dysfunctional neurological signalling. EBV, Epstein–Barr virus; HHV-6, human herpesvirus 6; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

1. Studies looking at immune dysregulation in individuals with long COVID who had mild acute COVID-19 have found T cell alterations, including exhausted T cells, reduced CD4+ and CD8+ effector memory cell numbers and elevated PD1 expression on central memory cells, persisting for at least 13 months [70].
2. Studies have also reported highly activated innate immune cells, a lack of naive T and B cells and elevated expression of type I and type III interferons (interferon-β (IFNβ) and IFNλ1), persisting for at least 8 months [71]
3. A comprehensive study comparing patients with long COVID with uninfected individuals and infected individuals without long COVID found increases in the numbers of non-classical monocytes, activated B cells, double-negative B cells, and IL-4- and IL-6-secreting CD4+ T cells and decreases in the numbers of conventional dendritic cells and

exhausted T cells and low cortisol levels in individuals with long COVID at a median of 14 months after infection [72].

4. The expansion of cytotoxic T cells has been found to be associated with the gastrointestinal presentation of long COVID. Additional studies have found elevated levels of cytokines, particularly IL-1β, IL-6, TNF and IP10, and a recent preprint has reported persistent elevation of the level of CCL11, which is associated with cognitive dysfunction. It remains to be seen whether the pattern of cytokines in myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS), where the levels of certain cytokines are elevated in the first 2–3 years of illness but decrease over time without a corresponding decrease in symptoms, is similar in long COVID [73-74].
5. Multiple studies have found elevated levels of autoantibodies in long COVID27, including autoantibodies to ACE2 (the receptor for SARS-CoV-2 entry), β2-adrenoceptor, muscarinic M2 receptor, angiotensin II AT1 receptor and the angiotensin 1–7 MAS receptor. High levels of other autoantibodies have been found in some patients with COVID-19 more generally, including autoantibodies that target the tissue (such as connective tissue, extracellular matrix components, vascular endothelium, coagulation factors and platelets), organ systems (including the lung, central nervous system, skin and gastrointestinal tract), immunomodulatory proteins (cytokines, chemokines, complement components and cell-surface proteins). A major comprehensive study, however, did not find autoantibodies to be a major component of long COVID [75-76].
6. Reactivated viruses, including EBV and HHV-6, have been found in patients with long COVID (and have been identified in ME/CFS45), and lead to mitochondrial fragmentation and severely affect energy metabolism46. A recent preprint has reported that EBV reactivation is associated with fatigue and neurocognitive dysfunction in patients with long COVID [72].
7. Several studies have shown low or no SARS-CoV-2 antibody production and other insufficient immune responses in the acute stage of COVID-19 to be predictive of long COVID at 6–7 months, in both hospitalized patients and non-hospitalized patients. These insufficient immune responses include a low baseline level of IgG, low levels of receptor-binding domain and spike-specific memory B cells, low levels of nucleocapsid IgG and low peaks of spike-specific IgG. In a recent preprint, low or absent CD4+ T cell and CD8+ T cell responses were noted in patients with severe long COVID, and a separate study found lower levels of CD8+ T cells expressing CD107a and a decline in nucleocapsid-specific interferon-γ-producing CD8+ T cells in patients with long COVID compared with infected controls without long COVID. High levels of autoantibodies in long COVID have been found to be inversely correlated with protective COVID-19 antibodies, suggesting that patients with high autoantibody levels may be more likely to have breakthrough infections. SARS-CoV-2 viral rebound in the gut, possibly resulting from viral persistence, has also been associated with lower levels and slower production of receptor-binding domain IgA and IgG antibodies51. There are major differences in antibody creation, seroreversion and antibody titre levels across the sexes, with women being less likely to seroconvert, being more likely to serorevert and having lower antibody levels overall, even affecting antibody waning after vaccination [77-79].
8. Several reports have pointed towards possible viral persistence as a driver of long COVID symptoms; viral proteins and/or RNA has been found in the reproductive system, cardiovascular system, brain, muscles, eyes, lymph nodes, appendix, breast tissue, hepatic tissue, lung tissue, plasma, stool and urine [80-81]. In one study, circulating SARS-CoV-2 spike antigen was found in 60% of a cohort of 37 patients with long COVID up to 12 months after diagnosis compared with 0% of 26 SARS-CoV-2-infected individuals, likely implying a reservoir of active virus or components of the virus. Indeed, multiple reports following gastrointestinal biopsies have indicated the presence of virus, suggestive of a persistent reservoir in some patients [83].

Treatment options for immune dysregulation during acute COVID-19:

The immune dysregulation observed in COVID-19 has strong implications for its treatment. Due to the widely-held belief that COVID-19 is characterized predominantly by a hyperinflammatory cytokine storm, many medications aiming to suppress the immune system have been considered, including anti-IL-6 receptor antibodies, IL-1 receptor antagonists, and JAK/STAT inhibitors. However, in the context of significant immunosuppression explored in this review, anti-inflammatory therapies may be harmful and further diminish innate and adaptive immune responses necessary for viral control and illness moderation. Instead, treatments that suppress the immune system may only be appropriate in the smaller subset of patients who are experiencing cytokine storms. A randomized control trial found that the administration of dexamethasone reduced mortality in COVID, but only for critical patients needing respiratory support [84]. In theory, such treatments may be even more effective when targeted exclusively to patients with hyperinflammatory phenotypes [40].

Impact of vaccines, variants and reinfections on long COVID:

The impact of vaccination on the incidence of long COVID differs across studies, in part because of differing study methods, time since vaccination and definitions of long COVID. One study indicated no significant difference in the development of long COVID between vaccinated individuals and unvaccinated individuals [85]; other studies indicate that vaccines provide partial protection, with a reduced risk of long COVID between 15% and 41%4,5, with long COVID continuing to impact 9% of people with COVID-19 [86]. The different SARS-CoV-2 variants and level of (and time since)

vaccination may impact the development of long COVID. The UK's Office for National Statistics found that long COVID was 50% less common in double-vaccinated participants with Omicron BA.1 than in double-vaccinated participants Delta, but that there was no significant difference between triple-vaccinated participants; it also found long COVID was more common after Omicron BA.2 infection than after BA.1 infection in triple-vaccinated participants, with 9.3% developing long COVID from infection with the BA.2 variant [87]. The impact of vaccination on long COVID symptoms in people who had already developed long COVID differs among patients, with 16.7% of patients experiencing a relief of symptoms, 21.4% experiencing a worsening of symptoms and the remainder experiencing unchanged symptoms [88].

Reinfections are increasingly common. The impact of multiple instances of COVID-19, including the rate of long COVID in those who recovered from a first infection but developed long COVID following reinfection, and the impact of reinfection on those with pre-existing long COVID is crucial to understand to inform future policy decisions. Early research shows an increasing risk of long COVID sequelae after the second and third infection, even in double-vaccinated and triple-vaccinated people [89]. Existing literature suggests multiple infections may cause additional harm or susceptibility to the ME/CFS-type presentation [90]. There is also early evidence that certain immune responses in people with long COVID, including low levels of protective antibodies and elevated levels of autoantibodies, may suggest an increased susceptibility to reinfection [74]. One study on the success of vaccinations in mice identified that memory $CD4^+$ and $CD8^+$ T cells were crucial for limiting disease severity during exposure to the beta variant. Memory T cells are believed to be key in responding to VOCs because they recognize more viral epitopes that may be conserved compared to antibodies that only recognize spike proteins. This evidence supports that establishing a functional adaptive immune response to COVID-19 is not only important in controlling a patient's initial infection but also in terms of vaccination efficacy and reinfection [40].

Treatment options for immune dysregulation during acute COVID-19:

Although there are currently no broadly effective treatments for Immune dysregulation in long COVID, treatments for certain components have been effective for subsets of populations.

Basic aspects of L-Arginine

Arginine (R) is considered a non-essential amino acid for healthy adult humans since it is endogenously synthesized from the amino acid citrulline as an immediate precursor in virtually all cell types. The small intestine is the major source of citrulline for arginine synthesis by the proximal tubules of the kidneys, known as the intestinal–renal axis for arginine synthesis. However, arginine is generally classified as a semi or conditionally essential amino acid owing to the fact that arginine must be supplied in the diet in some pathological conditions, including sepsis, trauma, and cancer [91]. l-Arginine is a semi-essential amino acid involved in numerous biological processes. It is a substrate for different enzymatic reactions and is metabolized using three major known pathways in the body: (1) Arginase metabolizes l-Arginine to l-ornithine, (2) l-Arginine decarboxylase metabolizes l-Arginine to agmatine, and (3) nitric oxide (NO) synthase (NOS) uses l-Arginine to form NO and citrulline. Three isoforms of NOS have been identified; two of them (endothelial NOS and neuronal NOS) are expressed constitutively, while the last one is inducible and is mainly involved in the inflammatory/immune response [92].

Versatile molecule: Arginine

l-Arginine is the substrate used for NO production by NOS [5]; due to its ability to cause NO generation, which has been shown to be a major endothelial relaxation factor (able to increase vasodilation and reduce arterial blood pressure), l-Arginine has considerable potential in becoming a tool to tackle cardiovascular issues. For instance, in patients with known endothelial dysfunction, l-Arginine supplementation (6–8 g per day) has been shown to improve endothelial function and ultimately lower blood pressure [93]. Three isoforms of NOS have been identified; two of them (endothelial NOS and neuronal NOS) are expressed constitutively, while the last one is inducible and is mainly involved in the inflammatory/immune response [94]. NO is considered a signaling molecule involved in a number of processes, including inflammatory responses. It is also essential in mediating vasodilation and bronchodilation, in addition to regulating neuronal function, signal transmission, and intraocular pressure. NO acts as an antithrombotic and cytoprotective agent that impedes platelet adhesion, smooth muscle cell growth, and expression of adhesion molecules. A reduction in NO levels triggers a dysregulated control of vascular tone as well as increased thickness and adhesiveness of the vascular wall. NO can also prevent endothelial cells from undergoing programmed death [94-95].

Focusing on its action on viral infections, NO is known to have either indirect or direct antiviral activity. A direct effect of NO can lead to inhibition of viruses, and in fact, NO is considered one of the earliest antiviral responses of the host, whereas indirect effects include the regulation of inflammation and immune response. NO also plays a key role in the generation of oxidized phospholipids, which can operate as potent immunomodulatory signals. NO is necessary for the formation of several reactive oxygen and nitrogen species, including peryoxynitrite, dinitrogen trioxide, and nitrogen dioxide, which all can have an antiviral effect. However, these free radicals can also cause oxidative stress that can lead to severe cytotoxic effects. NO is known to act as a pro-apoptotic inducer in some cells or as an anti-apoptotic modulator in

other cell types [94-96] In summary, NO has antiviral effects that can be very useful from an immunologic standpoint; however, an excess of NO can also lead to cytotoxic effects shown in figure 2.

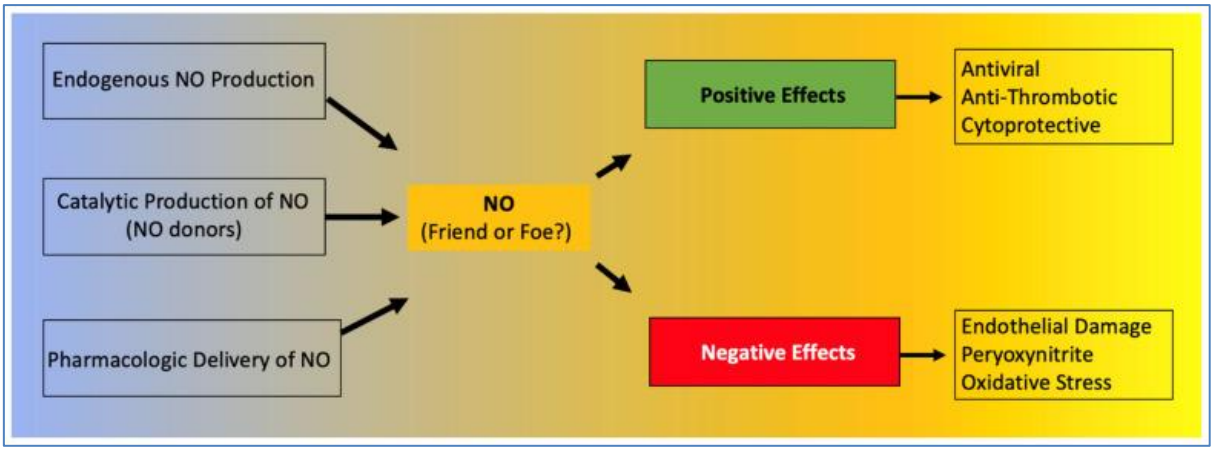

Figure 2: Positive and negative effects of nitric oxide (NO)

A clinical study conducted on 14 patients during the first outbreak of the severe acute respiratory syndrome coronavirus (SARS-CoV) in 2003 concluded that inhaled NO treatment for severely sick patients with SARS resulted in improvement of arterial oxygenation and allowed non-invasive pressure support to be discontinued [97]. SARS-CoV is a positive-sense RNA virus that has a genome of approximately thirty kilobases. There are some structural proteins that are common among all forms of coronaviruses; these proteins include a nucleocapsid, membrane, envelope protein, and spike (S protein). The S protein of SARS-CoV interacts with angiotensin-converting enzyme 2 (ACE2) on the host cells; it has two domains: S1, which is used in receptor binding, and S2, involved in membrane fusion [98]. Akerstrom and colleagues demonstrated that NO inhibits certain steps of the SARS-CoV replication cycle in a concentration-dependent manner, although the exact underlying mechanism was not clarified. In a follow-up study, the same authors proposed two specific mechanisms that NO uses to inhibit the replication of SARS-CoV. The first mechanism involved the disruption of palmitoylating the S protein (depalmytoilation). Such disruption affects the ability of the S protein to interact with ACE2. The second mechanism involved NO reducing the amount of viral RNA replication early on in the replication cycle due to an effect of the cysteine proteases encoded by SARS-CoV; indeed, when Vero E6 cells were treated with S-nitroso-*N*-acetyl penicillamine, a significant decrease in viral RNA production was detected three hours post-infection [99].

Effects of l-Arginine on the Immune System [94]

A large part of a normal immune system depends on the amount of l-Arginine available in the body. Arginase is known to represent an integral part of certain granulocyte subsets, which can be released locally or systematically once there is an immune response. In addition, there is an accumulation of immature myeloid cells that express arginase, which is released when fighting off specific illnesses. These myeloid cells that express arginase can decrease the amount of l-Arginine [100] T cell function has been shown to depend on l-Arginine levels. A decreased ability of lymphocytes to proliferate has been reported in critically ill septic patients and correlated to reduced availability of l-Arginine. Moreover, l-Arginine administration has been found to be beneficial to maintain immune homeostasis (Figure 2), especially in terms of T cell and macrophage function. In fact, l-Arginine is essential in the macrophage M1-to-M2 switch [101].

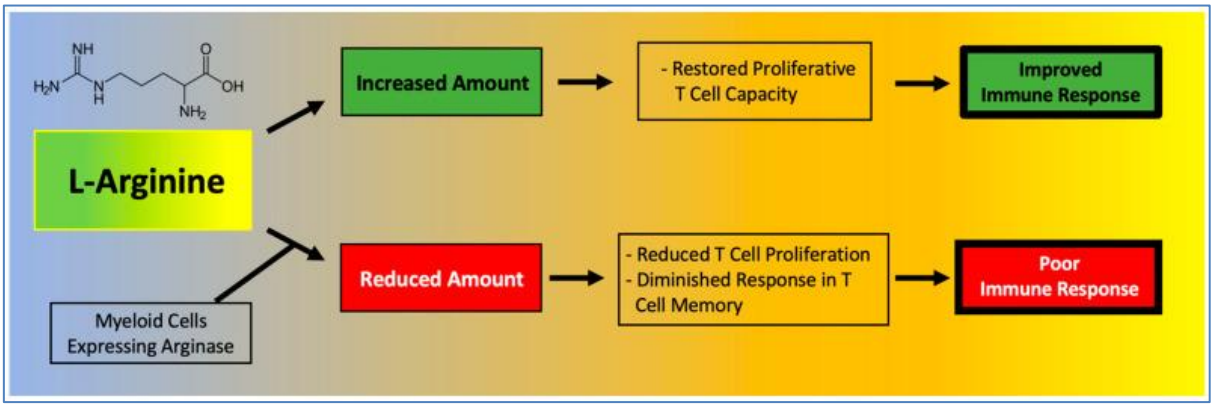

Figure 3: Main effects of l-Arginine on the immune system

A deficiency in l-Arginine has been shown to lead to a reduction in T cell proliferation and to cause a diminished response in T cell-mediated memory. In vitro assays have validated that L-Arginine can restore the function of T cells [102]. Mechanistically, the immunosuppressive effects of myeloid-derived suppressor cells (MDSCs) due to l-Arginine depletion and lymphocyte mitochondrial dysfunction have been demonstrated in models of cancer [103]. The expansion of MDSCs observed in COVID-19 has been directly correlated to enhanced arginase activity and lymphopenia. Monocytic MDSCs were significantly expanded in the blood of COVID-19 patients and were strongly associated with disease severity; MDSCs were shown to suppress T cell proliferation and IFNγ production, at least in part through an arginase-dependent mechanism, strongly indicating a role for these cells in the dysregulated COVID-19 immune response. Indeed, MDSCs express high levels of arginase, which metabolizes l-Arginine to ornithine and urea, effectively depleting this amino acid from the microenvironment. l-Arginine depletion is known to inhibit T cell receptor signaling, eventually resulting in T cell dysfunction and to increase the generation of reactive oxygen species (ROS), thereby exacerbating inflammation [104-106].

In a recent study focused on COVID-19, Dr. Claudia Morris and colleagues were able to determine the bioavailability of L-Arginine in three cohorts: asymptomatic healthy adults, adults hospitalized with COVID-19, and children hospitalized with COVID-19; they found that both adults and children affected by COVID-19 display significantly lower levels of plasma L-Arginine (as well as L-Arginine bioavailability) compared to controls [107]. Additionally, a low L-Arginine-to-ornithine ratio observed in COVID-19 patients [107] indicates an elevation of arginase activity in these patients. In another study, plasmatic L-Arginine levels were shown to inversely correlate with the severity of COVID-19 [108]. This study also revealed that the expression of the activated GPIIb/IIIa complex (PAC-1), known to be involved in platelet activation and thromboembolic events, is higher on platelets of patients with severe COVID-19 compared to healthy controls and inversely correlated with the plasmatic concentration of L-Arginine [108]. These pieces of evidence seem to go against the recently proposed strategy of l-Arginine depletion in COVID-19, based on the assumption that some steps in the viral lifecycle of SARS-CoV-2 could depend on l-Arginine residues (for instance, the nucleocapsid protein has a 6.9% l-Arginine content) [109].

In fact, a decrease in the bioavailability of l-Arginine has been shown to cause a diminished T cell response and function, eventually leading to an increased susceptibility to infections. Twelve weeks of continuous l-Arginine supplementation significantly decreased the level of IL-21 [110], while NO has been shown to suppress the proliferation and function of human Th17 cells [111], which have been implied in the pathogenesis of the cytokine storm and of hyperinflammatory phenomena observed in COVID-19 patients. Higher l-Arginine levels are associated with lower levels of CCL-20, a ligand for CCR6, a part of the chemotaxis system that is induced in response to coronavirus infections. In vitro assays have demonstrated that the proliferative capacity of T cells is significantly reduced in COVID-19 patients and can be restored through l-Arginine supplementation. Corroborating these findings, recent metabolomics data indicates that l-Arginine pathways are altered in COVID-19 patients and an increased mRNA expression of arginase has also been found in the peripheral blood mononuclear cells (PBMCs) of COVID-19 patients [94].

Potential role of L-Arginine in immune dysregulation in long COVID

Immune dysregulation has been documented in long covid cases especially those cases required long term hospitalization, those required ventilatory support or oxygen supplementation, those required oxygen or ventilatory support at home. These classes of patients were having post covid lung sequel as long COVID manifestations [111-115]. These cases can be picked up during hospitalization by analysing CT severity and typical radiological phenotypes. Radiological phenotyping is natural trend of evolution of COVID-19 pneumonia at entry point. Presence or absence of GGOs, consolidations and crazy paving with necrosis were key radiological markers in categorizing these phenotypes. Radiological phenotyping should be correlated with clinical and laboratory parameters for accurate analysis of severity assessment, duration illness prediction and inflammatory markers workup. Phenotyping will also help in monitoring of COVID-19 pneumonia cases and guide for necessary timely interventions in indoor units to have successful treatment outcome. Post covid fibrosis is reversible and should be labelled as sequalae due to near total reversible nature [116-119]. These can be earliest predicted by performing composite assessment [120-121].

As a critical driver of inflammation and oxidative stress, endothelial dysfunction has also been involved in the pathophysiology of the neurological symptoms of COVID-19 and Long-COVID. Fatigue is a prevailing symptom in Long-COVID patients, and previous trials have evidenced a significant decrease in fatigue in subjects treated with Vitamin C, fully consistent with our present results. Supporting our strategy to combine L-Arginine to Vitamin C, previous investigations have shown that ascorbic acid can synergistically improve the effects of other agents: for example, if added to glucagon-like peptide 1 (GLP-1) agonists, it reduces ROS generation in diabetic patients, in combination with metformin, it reduces macro- and microvascular diabetic complications [122]. In the survey-based study conducted by Raffaele Izzo et al. [122] showed the beneficial effects of the combination of L-Arginine and Vitamin C in Long-COVID. Their investigation was based on a robust rationale, *i.e.,* targeting endothelial dysfunction in Long-COVID. Indeed, endothelial cell infection with consecutive inflammatory cell recruitment and endothelial dysfunction could explain the

impaired microcirculation observed across vascular beds in COVID-19, triggering vasoconstriction, ischemia, and a pro-coagulant state. Consistent with our view, several investigators had proposed that endotheliitis could be a critical mechanism underlying systemic impaired microcirculatory function observed in different vascular beds in patients experiencing Long-COVID symptoms [122-124].

A recent clinical study has demonstrated that COVID-19 patients develop endothelial dysfunction, which remains significantly impaired compared to healthy controls subjects at a 6-month follow-up [125], implicating that endothelial dysfunction is a main player in both acute COVID-19 and Long-COVID. Interestingly, increased numbers of circulating endothelial cells, a biomarker of vascular injury, most likely detached from the vessel wall due to pathological insults, were found to significantly correlate with the severity of COVID-19 outcome [126]. Strikingly, elevated levels of circulating endothelial cells persisted in recovered COVID-19 convalescent patients [127], denoting long-term detrimental effects of SARS-CoV-2 infection on endothelial function. Actual signs of endothelial dysfunction (denoted by glycocalyx damage) have been reported in convalescent COVID-19 patients after mild disease progression without hospitalization [128]. Other studies evidenced that sustained endotheliopathy is common in convalescent COVID-19 subjects [129], and that Long-COVID symptoms, specifically non-respiratory symptoms, are mainly due to persistent endothelial dysfunction [130].

Published data have actually demonstrated that reduced levels of L-Arginine increase the generation of reactive oxygen species (ROS), aggravating inflammation [131]. Besides, in vitro assays revealed that the T cell proliferative capacity is significantly reduced among COVID-19 patients and can be restored through L-Arginine supplementation [132]. COVID-19 patients with severe symptoms present an increased level of myeloid-derived suppressor cells, directly correlated to an enhanced activity of arginase – the enzyme responsible for metabolizing L-Arginine to ornithine and urea [132]. Another recent investigation has demonstrated an inverse correlation between L-Arginine level and platelet activation [133], a major contributor to thromboembolic complications of COVID-19. While eNOS produces physiological levels of NO, the inducible NO synthase (iNOS) is mainly expressed under inflammatory stimuli in parenchymal cells and leucocytes, producing much larger amounts of NO, and its exact role in COVID-19 remains to be fully clarified [134-135]. Recommended daily dose of L-arginine in therapeutic effect is 1.5 gram one to two times daily for 3-6 months.

CONCLUSIONS

Immune dysregulation is documented during evolution of COVID-19 illness and observed in post covid care settings in those facing long covid manifestations. Robust data is available regarding the potential role of immune dysregulation in long covid pathophysiology. As of today, we don't have an answer to management of Immune dysregulation in the long covid. Definite treatment options for long covid are still underway and many experimental drugs have shown some benefit in small studies. Researchers have documented some relief of Immune dysregulation and long covid after vaccination, but we are not sure whether vaccination or patients own immune switch between TH1 and Th2 has played a role restoring immunity. Vaccination has resulted in immune dysregulation related rheumatological and autoimmune manifestations, hence the full proof protective role of the vaccine in restoring immunity after natural COVID-19 related immune dysregulation is the real question. Even after three years of COVID-19 pandemic, we have no effective treatment for long covid. Initially we thought a great breath of relief as this pandemic has weaned off but real danger is immune dysregulation which is persisting even after complete clinical recovery irrespective of severity and hospitalization. Effect of treatment options used during ongoing COVID-19 illness during hospitalization have not shown any benefit in curtailing immune dysregulation in post covid care settings. Immune dysregulation has been documented irrespective of use of medicines during evolution of illness in outdoor or indoor setting and irrespective of use of the medicines which has shown benefit in curtailing inflammatory surge or burst during the course of natural disease. Thus, immune dysregulation is not related to the outcome of disease but it is the part of COVID-19 disease which has persisted and we don't have a 'Reboot system' to tackle this immune dysregulation.

Robust data is available regarding the potential role of L-arginine in immune regulation and its trends during immune dysregulation. L-Arginine is cost effective, easily available, potent and preferred therapeutic option to treat immune dysregulation. Although L-arginine is present in food its concentration is not therapeutic. L-Arginine has shown significant relief in long covid manifestation by reverting immune dysregulation. L-arginine has been widely studied for immune regulation and its pleiotropic effects such as reverting 'endothelial dysfunction' and restoring 'Th1 and Th2' interplay which is a crucial pathway of long covid pathophysiology. L-Arginine is the 'Ray of hope' in darkness of the huge burden of Long covid globally and considered as 'best option' to tackle immune dysregulation in post covid care setting with long covid manifestations. Thus L-arginine should be considered as frontline to restore 'immune dysregulation' in long COVID and used for its therapeutic role and benefit beyond the routine dietary supplement.

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