Journal of Medical Research and Health Sciences
Received 12 Jan 2021 | Revised 15 Feb 2021 | Accepted 28 Feb 2021 | Published Online 15 Mar 2021

DOI: https://doi.org/10.15520/jmrhs.v4i3.319
JOURNAL 4 (3), 1204–1211 (2021)

ISSN (O) 2589-9031 | (P) 2589-9023

RESEARCH ARTICLE

Melatonin as a potential adjunctive therapy for COVID-19

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Abstract
The global pandemic of COVID-19 has created historic and devastating impact. The pathophysiology and adverse clinical effects, are attributed to the uncontrolled inflammatory cascades and immune responses attributed to a "cytokine storm". Melatonin has shown its role in anti-inflammation, antioxidant, and immunomodulation and proposes potential therapeutic tool against COVID-19. The clinical data and safety profile of melatonin in COVID-19 are currently under prospective evaluation, however, its efficacy in diseases with chronic inflammation and other viral infections propose potential current benefits of melatonin for COVID-19 infection and sequelae

Keywords: COVID-19, SARS-CoV-2, melatonin, N-acetyl-5-methoxy-tryptamine, anti-inflammatory, antioxidant, immunomodulatory

1 | INTRODUCTION

The World Health Organization identified COVID-19 as a global pandemic in March 2020. (1) To date, there have been over 111 million cases and over 2.4 million deaths worldwide. (2) COVID-19 is caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and posed a challenge for modern medicine as the pathophysiology of the virus and time-course of disease was not initially understood. Progressively, much has been learned about the pathophysiologic mechanisms specifically related to the inflammatory cascades and related disease complications, leading to newer proposed therapeutic agents and adjunctive therapies. (3) , (4) Major therapy considerations for COVID-19 have included corticosteroids, antivi-

Supplementary information The online version of this article (https://doi.org/10.15520/jmrhs.v4i3.319) contains supplementary material, which is avail-able to authorized users.

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rals, antibiotics, and supportive mechanical ventilation. (5) A recent data supports melatonin as an adjuvant treatment for COVID-19 due to its anti-inflammatory, anti-oxidative, and immune-system enhancing properties. (6) (7) (8) (9) Our article will briefly review the pathogenesis of COVID-19 and expand upon the potential role of melatonin therapy in the disease process.

2 | COVID-19 PATHOGENESIS :

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), known as the COVID-19 virus, is an enveloped single stranded positive sense RNA virus. (10) (11) COVID-19 infection and the course of disease has been described to occur in three stages: an early viral infectious phase, a pulmonary mixed phase, and a hyper-inflammation phase. (3) (4)

In the early viral infection phase, the virus enters host cells by attaching to angiotensin converting enzyme 2 (ACE2) receptor using its spike protein. (10) , (11) , (12) The binding of the protein is primed by transmembrane protease serine 2 (TMPRSS2) and another protease- furin. (10) , (12) , (13) The ACE2 receptors are mainly found within the pulmonary, intestinal, and vascular endothelial cells. (3) , (4) , (12) , (13) , (14) Once the virus enters the cell it can start forming proteins using its genome to replicate itself. (14) Subsequently, the initial inflammation causes the immune response of influx of T-cells which leads to initial symptoms in patients. (14) , (15) Most patients tend to be asymptomatic, or can have minor flu-like symptoms such as cough-ing, sneezing, fever, fatigue, myalgias, headache and anosmia. (14) Treatment during this stage is pre-dominantly supportive, symptomatic management as studies looking into antiviral treatments such as with remdesivir have not shown significant mortality benefit. (16)

In the second phase, the virus continues to replicate and there is an increased inflammation throughout the lungs. (14) These patients often develop a viral pneumonia, having worsening cough, fever, and hypoxia. (4) Symptoms such as nausea, anorexia, vomiting, diarrhea can also occur as intestinal cells tend to be affected as well. (17) , (18) It is during this stage that patients begin having elevated inflammatory markers such as C-reactive protein (CRP), ferritin, IL-6, IL-1, and D-dimer. (14) , (15) , (19) Treatment during this stage varies with patient presentation as more hypoxic patients in respiratory failure may begin requiring respiratory support in the form of high-flow nasal cannula and non-invasive ventilation. (20) As the inflammatory response heightens, anti-inflammatory therapies have been utilized such as dexamethasone, which has shown mortality benefit for hospitalized patients requiring respiratory assistance. (21)

There is a pronounced oxidative component seen throughout the first and second stage of disease as the virus creates conditions favorable for further viral replication by causing an excess of reactive oxygen species (ROS). (22) , (23) There also appears to be an underlying mechanism specific to COVID involving the ROS oxidizing the cysteine residues on the peptidase domain of ACE2 receptor and increasing the affinity for SARS-CoV-2 proteins, thus increasing binding and severity of the COVID-19 infection. Antioxidant therapy such as vitamin C has been proposed for treatment, but more studies are needed to indicate direct benefit for COVID-19. (23) , (24)

The third stage of the disease manifests as extrapulmonary systemic hyperinflammation. (17) In comparison to the first stage, where T-helper cells were recruited to the area of localized inflammation, there seems to be an increased immune-dysregulation associated with this severe stage of the disease, whereby the number of T helper, suppressor, and regulatory T cell counts are significantly decreased. (15) The down regulation of this immune system regulatory response in combination with the increase in inflammatory cytokines throughout the progression of this disease leads to what has been termed the "cytokine storm," a phenomenon also seen in severe acute respiratory syndrome (SARS) and the middle eastern respiratory syndrome (MERS). (25) , (26) The consequences of lethal cytokine storm include diffuse alveolar damage, collateral tissue damage, and systemic organ failure. (24) Increased degradation of fibrin, consumption of coagulation factors and thrombocytopenia can also be present. (5) Beyond the dexamethasone described above, additional

therapies to either indirectly reduce viral burden or reduce the inflammatory response are needed for these patients. Additional medications can be required depending on the constellation of symptoms and organs affected.

3 | ROLE OF MELATONIN :

N-acetyl-5-methoxy-tryptamine (melatonin) is a neurohormone secreted by the pineal gland and many peripheral sites and acts to regulate sleep through action in the suprachiasmatic nucleus. Beyond the role in sleep, there are notable additional effects linked to immune function and inflammatory response regulation.

Metabolites of melatonin, including N(1)-acetyl-N(2)-formyl-5-methoxykynuramine (AFMK) and N(1)-acetyl-5-methoxykynuramine (AMK), act to both directly scavenge free radicals, particularly reactive oxygen species (ROS) and reactive nitrogen species, (27) , (28) and indirectly through changes in enzymatic free radical generation, including upregulating superoxide dismutase degradation of ROS and inhibiting NADPH oxidase production of ROS. (29) , (30)

In addition to antioxidant function, melatonin demonstrates both pro- and anti-inflammatory systemic effects. It increases proliferation of T cells, B cells, natural killer (NK) cells, polymorphonuclear neutrophils, and monocytes. (31) Notably, it promotes differentiation to CD4+ T (Th)cells. Inhibition of systemic melatonin expression through pinealec-tomy inhibits Th cell production and subsequently B cell activation, though this effect is reversible with melatonin supplementation. (32)

Conversely, melatonin suppresses the systemic inflammatory response through inhibition of macrophage NOD-like receptor 3 (NLRP3) inflammasome activation and toll-like receptor 4 signaling. (33) , (34) , (35) It also inhibits production of pro-inflammatory transcription factors such as nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) and stimulates production of anti-inflammatory factors, including nuclear factor erythroid 2-related factor 2 (NRF2). (36) , (37) One mechanism may be through activation of sirtuin-1, a NAD+ dependent histone deacetylase, which has varying immunomodulatory functions, including inhibition of tight junction function and downregulation of high mobility group box 1 protein (HMGB1). (37) , (38)

4 | CLINICAL DATA ON MELATONIN AND COVID-19 :

Melatonin and its anti-inflammatory and antioxidant role in humans have been well described in multiple studies. The benefits of melatonin can be seen in diseases with chronic inflammation such as obesity, type 2 diabetes mellitus (T2DM), and periodontitis. (39) , (40) The earlier study by Alamdari et al conducted a double blind, placebo-controlled trial on obese women. (39) The subjects were assigned to either a daily oral dose of 6mg melatonin or placebo. The inflammatory markers (TNF-a and IL-6) of the daily melatonin group were significantly reduced ($p=0.02$ and $p=0.03$, respectively). (39) Bazyar et al also conducted a double-blind, randomized control study involving 50 patients with T2DM and chronic periodontitis. (40) The intervention group received 6mg of melatonin daily for 8 weeks and the results demonstrated that inflammatory markers including IL-6 and high sensitivity-C reactive protein were significantly reduced ($p =0.008$ and $p=0.017$, respectively). (40) The study showed that melatonin improves the level of inflammation which concurrently benefits periodontal disease status represented by decreases in pocket depth (PD) and clinical attachment loss (CAL). (40)

Additionally, a recent meta-analysis of 22 randomized control trials studied melatonin supplementation and inflammatory markers in patients with obesity, T2DM, non-alcoholic fatty liver disease (NAFLD), steatohepatitis, rheumatoid arthritis (RA), ulcerative colitis (UC), coronary artery bypass surgery candidates, metastases, multiple sclerosis, methadone maintenance treatment, or atopic dermatitis. (41) The meta-analysis demonstrated that melatonin supplementation significantly reduces the level of TNF-a and IL-6 ($p<0.001$). The study also suggested a longer course of melatonin ($\geq$ 12 weeks) with $\geq$ 10mg

of melatonin per day has greater efficacy in anti-inflammatory roles. (41) The multiple studies as well as the recent meta-analysis demonstrates the benefits of melatonin in cytokine downregulation and most notably repeatable in different disease states.

Although the potential therapeutic adjunctive role of melatonin in prevention and treatment of COVID-19 infection are underway, there are a number of *in vitro* and *in vivo* data in other viral infections which can potentially translate to clinical data. Melatonin demonstrable anti-inflammatory, antioxidant, and immunomodulatory effects treatment of a number of viral infections including: respiratory syncytial virus, (42) , (43) Venezuelan equine encephalitis virus, (44) viral hepatitis, (45) and viral myocarditis. (46) Given the favorable effects of melatonin in these viral mediated disease, it appears likely there may be a similar utility in COVID-19. Currently, there are trials such as NCT04568863 looking at intravenous melatonin on patients admitted to intensive care unit with COVID-19, NCT04530539 studying the effect of melatonin and vitamin C on COVID-19, and NCT04353128 evaluating the efficacy of melatonin as prophylaxis of COVID-19 in healthcare workers.

5 | SAFETY OF MELATONIN

The importance of medication safety profile cannot be undermined. Melatonin has been studied in infants to elderly population with various dosages and administration routes (oral or intravenous). (47) The dosing variability from 0.5mg oral tablets to a high dose of 1g intravenous administration has shown very little adverse effects, albeit typically mild and include headache, nausea, dizziness, and sleepiness. (47) Although the safety of melatonin has not been specifically studied in COVID-19, this general safety profile proposes a great utility of melatonin with minimal risks. Use of melatonin has been associated with more rare reports of vivid dreams and even more rarely with nightmares (48) . These reported effects are particularly unusual for doses <5 mg/night. (48) It is our practice to routinely mention this to patients and to dose reduce or stop if problematic. Our preference is to use a sustained release melatonin product and to begin using 4-5 mg at bedtime.

6 | Conclusion

COVID-19 has a complex disease course that progresses from a predominantly viral replication stage to a more inflammation-based disease course. Investigation into therapies have largely revolved around anti-viral, antioxidant, anti-inflammatory, and immunosuppressive agents. Melatonin has emerged as an adjuvant treatment for COVID-19, having been strongly supported by studies in viral infectious as well as inflammatory mediated chronic diseases. The potential value of melatonin is evidence based, given the has been demonstrable anti-inflammatory, anti-oxidation, and immune-enhancing effects. The related anti-inflammatory would conceivably decrease systemic inflammation and downregulate activation of T-cells within lung tissue. The antioxidant effect should decrease the number of free radicals produced from alveolar macrophages activating their inflammatory response. Given the apparent beneficial anti-inflammatory and immune modulating effects, coupled with a strong safety profile, widespread availability and minimal cost, we strongly recommend melatonin as a logical adjunct to optimize the evolving treatment paradigms for COVID-19 management.

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How to cite this article: B.S.Y.M.D., S.D.S.M.D., K.H.M.S., A.P.M.S., P.J.P.M.D.F.A.C.P., D.J.M.D. Melatonin as a potential adjunctive therapy for COVID-19. Journal of Medical Research and Health Sciences. 2021;1187−1194. https://doi.org/10.15520/jmrhs.v4i3.319