

Role of Melatonin as a Biomarker and Therapeutic agent in modulating the circadian rhythm in Covid-19

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Abstract

Calling Covid-19 a viral disease would be an understatement. The worldwide impact this pandemic has caused in every sphere of human life is remarkable and so is the pace at which treatment modalities and immunisation agents were formulated for it. More so, the severe complications of this disease can be devastating and fatal, therefore a number of pharmaceutical agents have been studied that have shown response in the critically ill. This article throws light upon how melatonin can be a safe and effective adjuvant pharmaceutical agent against Covid-19. Melatonin is one of the hormones that controls the bodily clock, which in turn has a crucial role to play in the pathogenesis of Covid-19. Yoga asanas can also aid in suppressing the aggravated immune response and inflammatory process in this disease. Anxiety due to the disease itself and other social factors related to it, is another reason for disturbed sleep and hence poor immune response in alleviating the effects of Covid-19.

Keywords: Chronomics, Melatonin, Yoga, Circadian rhythm, Covid-19

INTRODUCTION

The Covid-19 pandemic has largely effected the sleep-wake cycle and circadian clock of the body, primarily due to social distancing restrictions and hence disruption in work timings, isolation norms, and also increased frequency of night duties among the essential workers [1]. Also, the diseased individuals experience a lack of good quality sleep especially the ones who require a prolonged ICU stay, due to limited exposure to environmental zeitgebers, non-cycling or weakly cycling light environments, excessive noise due to equipment alarms, therapeutic sedation and intravenous or continuous feeding [2]. The circadian clock plays a role in the processes of adaptive and innate immunity, and disruption of this rhythm can lead to increased pathogen replication and dissemination [3]. A similar concept was described as chronobiology, which identifies mechanisms underlying diversity in time, its impact on health and disease and its mapping called chronomics. Chronobiology considers predictable variability within physiological range and it consists of a multi-frequency spectrum of rhythms. In a worldwide project BISCOS (BIOsphere and COSmos), blood chemistry was measured, repetitive and predictable changes which would allow treatment as per time, known as chornotherapy, were found out. This part of chronomics aids in primary prevention of disease. Chronomics has been most widely studied in the context of cardiovascular diseases and mental health, but the methodology remains same for other types of diseases too. The human body has shown daily, weekly, monthly as well as yearly variations in the prevalence of disease;

laboratory test results and also how the body reacts to pharmacological agents [4]. A number of systems in our body have their biological rhythm which coordinates with the central clock and run in harmony with the environment as well [58]. The circadian rhythm has a genetic basis described by a 'chronotype' which refers to the timing of behaviours that manifest from the functioning of the central rhythm [59].

Cortisol and melatonin are two hormones that regulate the 24-hour pattern of bodily functions [5]. Melatonin is centrally secreted by the pineal gland and exhibits a secretory rhythm with well-defined onset and offset phases in both animals and humans with circulating concentrations high at night and lower during the day [6]. The major function of melatonin in the body is to maintain the variations in the biological rhythm, and its release is also affected by the presence of light [56].

We aimed to comprehensively observe the available data related to our review. The research team acquired published data extracted from various journals by the search method TIAB (Title / Abstract). Research and review articles with information on circadian rhythm, melatonin and Covid-19 were searched with no time limit and the recent reports relevant to our review were selected. 59 abstracts as well as full texts were individually reviewed for inclusion.

Chronomics and Covid-19

Resistance to cellular injury due to physical agents such as noise and bacterial endotoxins has been studied to be related to circadian rhythms in mammals, by Franz

Halberg, the father of Chronobiology [55]. Circadian regulation has been reported in the pathogenesis of other viral diseases such as Influenza A, Herpes virus, flavivirus and vesicular stomatitis virus [7]. The underlying molecular mechanisms of Covid-19 related complications like respiratory failure, micro coagulation events and cytokine storm are regulated by the circadian clock [2]. The human respiratory mechanics, ventilator response to hypercapnia, airway response to inhaled allergens, cellular oxygenation effect of Hypoxia inducible factor 1 alpha (HIF1a) all show clock regulation [2]. Covid-19 respiratory failure like other acute lung injuries have shown to alter clock related gene expression in the lungs [2,8]. Along with this, Acute Kidney Injury (AKI) which has been a common complication of Covid-19 disease, also shows circadian rhythmicity through the RAAS [9,10,11]. Merve M et al have precisely explained the genesis of AKI due to circadian rhythm disruption in Covid-19. SARS-CovV-2 increases the levels of Angiotensin-II which acts through AT₁ receptor and mediates severe inflammation by the NF- κ B pathway [12].

Biochemical basis of the physiological and therapeutic role of Melatonin

Melatonin, chemically N-acetyl-5-methoxytryptamine is a hormone produced by the pineal gland. Melatonin is synthesized on demand by immune-competent cells and constitutively by resident macrophages such as alveolar macrophages based on the duration, and magnitude of innate immune responses [13,14]. Previous research and data related to disruption of melatonin secretion rhythm has been a part of many disorders [15]. It has been used to treat Circadian rhythm sleep disorders like Delayed Sleep phase syndrome (DSPPS), jet lag, displaced sleep in shift workers, non-24 hour sleep-wake cycle and age related sleep disorder [16,17,18]. Furthermore, melatonin use has been reported in perimenopausal and postmenopausal women to improve thyroid function, increase gonadotropin levels and has a possible anti-depressive role, in Angleman's syndrome in children (in which melatonin not only improves sleep quality and duration but also plays an anti-seizure role), in breast cancer, and in neurodegenerative and cardiovascular diseases [16,17,18,19]. The oncostatic effects of melatonin have been described in various tumours including breast cancer, ovarian and endometrial carcinoma [20]. Melatonin possesses anti-oxidative, anti-inflammatory, anti-excitatory and immunoregulatory properties along with indirect antiviral ones [21,22]. The antiviral role of melatonin has been studied in Respiratory Syncytial Virus (RSV), Equine Encephalitis Virus (EEV), viral hepatitis, viral myocarditis and Ebola virus disease [21]. The rationale of melatonin use in SARS-CoV-2 has been described by Zhang R et al, melatonin modulates inflammatory response in Covid-19 through its above mentioned properties [5]. Serum or saliva melatonin assays can allow medical professionals to monitor endogenous melatonin secretion. Melatonin samples have to be collected half hourly for 5-6 hours starting

approximately 4 hours prior to the usual bedtime of the patient, so salivary sample is preferred [18]. Urinary aMT6s reflect the amount of circulating melatonin related to the period between the prior urine void and the subsequent urine sample [23]. The aMT6s level is stable over time and measured via well-proven and reliable techniques [24]. It has a greater reliability in measuring circadian phase position over other circadian markers (ie, core body temperature and cortisol) because the melatonin concentration remains relatively uninfluenced by external factors such as stress, physical activity, and excessive carbohydrate intake. In contrast, these factors can mask the cortisol and core body temperature [25,26]. Patients with low melatonin levels can be candidates for melatonin therapy. Melatonin is a primary circadian pacemaker quantifiable by measuring 6-sulfatoxymelatonin (aMT6s), which is its major metabolite excreted in urine. Actually, melatonin acts as a chemical code of the biological clock and can be a biomarker to comprehend the impact of circadian disruption on neurophysiological, behavioural, and metabolic processes.

Melatonin acts via membrane specific receptors- high affinity ML1 receptors and low affinity ML2 receptors [27,28]. ML1 receptors have two subtypes Mella and Mellb [29]. The ML1 type are GPC receptors [30] and their activations leads to inhibition of adenylate cyclase in the cells [20]. Mella (now known as MT1) subtype is found in the *pars tuberalis* of anterior pituitary, the SCN of hypothalamus, cortex, thalamus, substantianigra, nucleus accubens, amygdala, hippocampus, cerebellum, cornea and retina [31]. Mellb or MT2 is distributed in the retina primarily and also in hippocampus, cortex, paraventricular nucleus and cerebellum [32]. The activation of ML2 receptors leads to hydrolysis of Pi [33]. Melatonin has a short distribution half-life after intravenous administration (0.5-5.6 minutes) [34], and about 60 minutes after oral administration [35]. The plasma concentration shows a biohasic pattern with a half life of 2 and 20 minutes [36]. Oral bioavailability was studied to be between 10-56 % [37]. Melatonin is quickly metabolised after an oral or intravenous dose mainly in the liver but hepatic first pass metabolism is not significant [33]. Melatonin in Covid-19 acts by various mechanisms, as an anti-inflammatory, by suppressing NF- κ B [38,39], up regulation of NF-E2 related factor (NFr2) and activating sirtuin-1 [40,41]. Melatonin exerts its anti oxidative effects by down regulating pro-oxidative enzymes and upregulating anti-oxidative enzymes and may also act as a free radical scavenger [42,43]. The anti-oxidant property of melatonin is by virtue of its chemical structure which has the ability to donate an electron or a hydrogen atom [57]. In addition to this, Melatonin also stimulates immune response by enhancing the proliferation of NK cells, T and B lymphocytes, granulocytes, monocytes and up-regulating complement receptor 3, suppresses VEGF which increases in severe inflammation and immune responses and induces edema [44,45,46].

Beasg FMC et al assessed the evidence for adverse effects associated with short and long term use of melatonin [47]. No life threatening adverse events were found, however the safety of continuous therapy for long term could not be concluded because of lack of evidence from long term RCTs. The adverse effects are limited to occasional dizziness, headache and nausea with short term use of melatonin even at high doses [48].

Potential effects of meditation and yoga on melatonin

Covid-19 disease and its consequences are due to an exaggerated immune and inflammatory response. Alveolar macrophages that compose up to 90% of total macrophages in healthy human lungs lead to immune suppression and mucous production after phagocytosing airborne microorganisms and particulate material[49]. Several studies have found that meditation and yoga can reduce this kind of inflammation in the body, along with offering other benefits, including:

- In a study, healthy men who did yoga asanas, pranayama, and meditation for three months had higher levels of melatonin, compared to people who did flexibility exercises, slow running, and playing games. The group which performed yoga also saw improvements in their cardiovascular and mental health[50].
- Six weeks of mindfulness meditation for 20 minutes a day reduced proinflammatory gene activity and inflammatory signaling, and increased anti-inflammatory chemicals in the body. This study involved women diagnosed with early-stage breast cancer[51].
- A 90-minute asana practice increased the expression of two molecules with antimicrobial properties in healthy adults [52].
- Six days of a combined practice of mantra-based meditation and asanas regulated the levels of a pro inflammatory molecule (cytokine) and reduced the activity of pro-inflammatory genes. This study involved women who attended a yoga/meditation retreat; researchers compared them to women who stayed at the centre but didn't participate in the retreat [53].

Melatonin also has pro inflammatory and anti-inflammatory properties. The proinflammatory activity is thought to help the body fight invading pathogens such as viruses and bacteria. The anti-inflammatory actions of melatonin involve many chemical pathways in the body, including reducing the level of molecules that promote inflammation and increasing the level of cytokines that reduce inflammation.

DISCUSSION

While SARS-CoV-2, the virus that causes COVID-19, infects the lungs and causes respiratory symptoms like cough and difficulty breathing, it can also damage a number of other organs, including the heart, kidneys, stomach and intestines, and blood vessels. This damage is not all caused by the virus directly, but by the body's excessive inflammatory response to the virus, what's

known as a "cytokine storm," named after one of the molecules involved in causing inflammation. Inflammation is a normal response of the body to injury or infection, which aids in healing tissues. But chronic inflammation has been linked to a number of diseases such as stroke, heart disease, cancer, obesity, and diabetes. The circadian clock and inflammatory response have been correlated.

With respect to the nature of transmission of this disease, telemedicine came into practice for a number of medical professionals across India. Several patients who had a mild disease took video consultations managed by specialists and general practitioners of Doon Hospital located in Dehradun, Uttarakhand, India. This method, adopted by the government proved to be convenient for patients as well as doctors. During these consultations it was observed by many doctors that patients who had recovered from Covid-19 or were in the recovery phase or had lost a close family member due to Covid-19 related complications, experienced symptomatic anxiety which had to be treated with low dose short acting benzodiazepines. Both anxiety and insomnia have been observed in patients who survived Covid-19, due to the disturbance in immune system which might as well contribute in the worsening of symptoms of Covid-19 [54]. Melatonin could be used for Covid-19 related insomnia and thus contribute in controlling the progression of disease as well as development of anxiety.

CONCLUSION

The pandemic dissemination of the SARS-CoV-2 led, on the one hand, to a worldwide effort to develop mechanistic-based therapeutics and vaccines, and on the other hand, the searching for determining the spreaders and the mechanisms of transmission, also look for other biomarkers for patient treatment and management. The pathogenic mechanisms underlying inflammatory response is related to the circadian clock and thus melatonin could play a therapeutic role. Melatonin, a multitask molecule, orchestrates defence responses by allowing the proper mounting. Some studies in rats and mice have shown that melatonin can relieve the acute respiratory stress caused by infection with certain viruses and bacteria. Melatonin can be a safe treatment option as an adjuvant to currently accepted first line therapy for Covid-19. It can also be used as biomarker for quantifying the severity of disease. It might be efficacious especially in patients with critical disease admitted in ICUs and patients with underlying sleep disorders. Also, yoga asanas as mentioned can be of great help to isolated patients with mild disease and in patients where drugs are not tolerated. Both of these treatment modalities could be of use in Covid-19 related sleep disturbance and anxiety.

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Authors' Contribution

RK Singh, Rajeev Singh Kushwaha and Kanika Kakkar wrote the article. Sandeep Dabral and Rachit Garg helped in the write up of the article.

Conflicts of Interest

There are no financial or non-financial conflicts directly or indirectly pertaining to any points.

Ethical Approval

This is a review article; no study was performed on an individual, group or animal by any of the authors.

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