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Mini Review

Oral and Gut Health Can Play an Important Role in Psychosomatic Illness Associated with Coronavirus Disease 2019 Patients

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ABSTRACT

With physicians and patients fearful of coronavirus disease 2019 (COVID-19), this has a profound impact on the working and personal life and living style of individuals. In United States (U.S.), around 10.7% reported perceiving severe thoughts of hurting themselves and contemplating suicide as a reaction. There is a 3-4 times rise in the incidence of mental well-being disorders in the past year relative to the year prior as reported in the article in US. It was also confirmed that salivary glands of throats had affected by coronavirus and many patients infected have developed dysgeusia and anosmia which are also happened to be found in patients taking angiotensin-converting enzyme (ACE) inhibitors and angiotensin receptor blockers, thus pointing out the role of ACE receptors for entry of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). Reducing technologic use and addiction would be feasible by adequate sleep and preventing during work hours through reducing task triggering anxiety-related use of mobile phones. Consuming plenty of Vitamin C can protect against such viral infections. Study have also shown that sufficient vitamin D supplementation could boost humoral and cellular immune responses and reduce intestinal leakiness among COVID-19 infected population.

Keywords
COVID-19; SARS-CoV-2; Dental; Stress; HPA.

INTRODUCTION

Recent empirical research data suggest the role of alpha 7 nicotinic acetylcholine receptor (α7nAChR), vitamin D, intestinal dysbiosis/permeability, platelet activation, and autonomic nervous system, along with stresses and circadian rhythm imbalance due to melatonin provide biological implications in promoting of severe acute respiratory syndrome coronavirus 2 (SARS CoV-2) infection.[1]

Complex interactions within circadian, immune, and intestine and cardiovascular systems influence pathways of coronavirus disease 2019 (COVID-19) disease. The major characteristics COVID-19 research are vitamin D, platelets, thrombin, the blood brain barrier, gut's permeability and increased conversion of kynurenine pathway from tryptophan. Above important findings by various studies provides the important role of understanding the individual variation of signs, symptoms and disease severity/fatality. However, there are numerous manageable techniques that can be used to fix oral and gut issues from the root down.

In this study we review some of the above factors mainly stress, circadian rhythm and role of technology regulation that have been associated with the corona virus epidemy and their implication on health and quality of life. To start with the role of mental stress in viral infections are briefed.

EFFECT OF CORONAVIRUS DISEASE 2019 ON MENTAL HEALTH

The COVID-19 pandemic has impacted nearly all aspects of daily life events. In conjunction with the arrival of SARS-CoV-2

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and COVID-19, there has been a silent arrival of associated mental health conditions. The constant fear of contracting the COVID-19 infection, the fear of developing serious symptoms leading to hospitalization and fear of untimely death has resulted in a near complete breakdown of the professional and personal activities associated with life of human beings. In addition, the news of deaths of individuals known and unknown has caused a massive sense of interpersonal loss which is aggravated by the on-going societal disruption. The social distancing, quarantine, and the constant need to follow other safety measures has modified the social fabric which the individuals, families and communities would deal with stressors.

This has led the individuals to experience the disruption in multiple activities like closure of schools, places of employment, cancellation of public events, finance generation, restricted access to healthcare, absence of recreation opportunities and minimal occasions to engage in cultural and religious practices. In this scenario of altered functioning on-going for more than 10-months in domains of social, occupational, cultural, and social support systems, the mental health experts are predicting a high probability of increase in mental health conditions. During this period, there has been a rise in conditions such as depression, anxiety, isolation, drug use, technology addictions and domestic violence. In addition, it has also led to restricted ability to access support systems in times of untimely death to grieve and cope for the loss collectively. A recent survey in USA of 5412 adults found that 40.9% participants reported experiencing at least one adverse mental or behavioural health condition inclusive of depression, anxiety, post-traumatic stress, and substance use.[2] In addition, 10.7% individuals also reported considering self-harm as a response to the on-going COVID-19 pandemic. This indicates that there has been a 3 to 4 fold increase in the prevalence rates of mental health conditions in comparison to the previous year.[2] If the pandemic progresses without end, it poses the likelihood that more people may experience mental well-being disorders that will inflict damages to their neurological processes, which will contribute to irreparable harm.[3]

MOLECULAR MECHANISMS OF FEAR, ANXIETY AND STRESS IN CORONAVIRUS DISEASE 2019

Psychological stress modulates the vulnerability, seriousness and recurrence of viral infections.[3] Discrimination stress that correlates with epidemic illness symptoms are usually associated with lack of sleep and disrupted melatonin metabolism. This matter can influence general state of well-being in terms of psychological factors and can impact sleep. Reduced melatonin seen in ageing, type 2 diabetes, obesity, essential hypertension and cerebrovascular disorder, thereby pointing out role of melatonin (sleep) in susceptibility and severity of COVID-19 disease.[4] Recent work suggests that psychological stress can also result in increased synthesis and release of corticotropin-releasing hormone (CRH) from hypothalamus and amygdala. CRH can function independently of the activation of the hypothalamic-pituitary-adrenal (HPA) axis, even by activating mucosal mast cells, contributing to the upregulation of the pro-inflammatory cytokine necrosis factor tumor necrosis factor alpha (TNF-α). TNF-α acts on intestine epithelial cells to weakens tight junctions of gut, contributing to intestinal permeability.[5] This disorder of intestinal flora because of stress will indirectly affect multiple processes in the body. Hence, the guts are a major contributor to how stress will cause signs of illness during the SARS-CoV-2 pandemic.[6] Immune system is closely associated with central nervous system (CNS) for physiological homeostasis during cytokine release and inflammatory response to an infection.[7]

ROLE OF AUTONOMIC NERVOUS SYSTEM IN CORONAVIRUS DISEASE 2019

Vagal nerve stimulation releases acetylcholine, thereby activates α7nAchR, which is known to protection against many viral infections by regulation of immune cell responses. Studies have also shown the role of melatonin in increasing vagal acetylcholine thereby regulation of immune cells responses, Vagal release of acetylcholine improves the gut permeability thereby regulation of viral entry into system. Thus, such studies can be important pathophysiological aspects of COVID-19 regulation by explaining the alteration of balance between melatonin effects *via* vagal nerve dysregulation, altered levels α7nAChR, thereby dysregulation immune system. The shift of sympathetic/parasympathetic nervous system is found in COVID-19 disease condition, which is the pathophysiology of stress and has a huge impact on severity and fatality.[8]

SALIVARY GLANDS AND CORONAVIRUS DISEASE 2019

The studies have reported that salivary glands as potential sources of COVID-19 and many patients infected have developed dysgeusia and anosmia which are also happened to be found in patients taking angiotensin-converting enzyme (ACE) inhibitors and angiotensin receptor blockers, thus pointing out the role of ACE receptors for entry of SARS-CoV-2.[9] Human saliva is a distinct secretion to the body. It consists mostly of water (94-99%), organic molecules (0.5%) and inorganic molecules (0.2%). Saliva also contains dietary toxins, serum components, oral and metabolite microorganisms, exfoliated epithelial cells and white blood cells. So far, more than 700 microbial species, many of which are related to oral and systemic diseases, have been identified in saliva. Saliva not only creates an ecological niche for invasion and development of oral microorganisms, but also prevents over-growth of specific pathogens to preserve oral cavity homeostasis.[10]

In the oral cavity, predominately ACE-2 enzymes are located on the tongue relative to gingival or oral mucosa, which converts Angiotensin to Angiotensin-2, as the ACE-2 enzymes effected due to COVID-19 resulting increase in Angiotensin-2 and thus leads to dysgeusia.[7] World Health Organization (WHO) has launched solidarity trail of drugs with a possible treatment for COVID-19 disorder, comprising of remdesivir, chloroquine, lopinavir, ritonavir and interferons. Many of these antivirals, antibacterials and immune boosters are associated with loss of taste or dysgeusia. However, no proven effective therapeutics have been documented.[11] According to a previous report on vesicular stomatitis virus, this pathogen has a high aggregating capacity in the presence of saliva and certain host factors, such as fibrinogen,

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could facilitate this aggregation mechanism, indicating that saliva plays an important role in the biological action of this virus.[12] The biochemical components of saliva are closely correlated with the presence of similar type of pathogen Zika virus (ZIKV), suggesting complex virus-saliva interactions.[13] There are systemic drugs and several immune associated problems that cause mismatch in oral microbiota. This is the implication of COVID-19 disease, therefore need prompt medical and dental advice and guidance to support vulnerable patients.[14]

VITAMIN D AND CORONAVIRUS DISEASE 2019

Vitamin D and melatonin have been implicated in promoting of SARS CoV-2 infection.[1] Many factors are linked to this. Frist the emergence of COVID-19 during winter months in north hemisphere, time where Vitamin D levels are found lowest in these communities. However, in south hemisphere fatalities are less. Reduction in Vitamin D are also commonly found in aged population, and higher fatalities seen among elderly people both in home and home care facilities, especially under conditions of lockdown, where the exposure to sunlight is exceedingly small. It is also established by recent studies on the role of Vitamin D in increasing the gut permeability regulation of immune cells and epigenetic role.[15] Cathelicidin gene is known to be influenced by Vitamin D. Butyrate is a gut derived short chain fatty acid, its dietary form sodium butyrate have been shown to increase cathelicidin gene which helps in histone deacetylation inhibition, hence inhibiting the entry of influenza virus.[16]

It is important to know that melatonin plays a major role in Vitamin D synthesis and eventual melatonin release, based on melatonin mediated Vitamin D action.[17] Absence of Vitamin D results in malnutrition, reduced sunlight exposure during COVID-19 lockdown which might lead to Vitamin D deficiency and risk of mortality due to elevated risk of comorbid disease condition.

MELATONIN IN CORONAVIRUS DISEASE 2019 ILLNESS

The complexity of various body systems and their interactions, including circadian, intestinal, circulatory, and immune systems will contribute to the considerable variations evident in SARS-CoV-2 symptomatology.[1] There would seem to be a powerful role for pineal and local melatonin in the regulation of SARS-CoV-2, including *via* melatonin's circadian regulation of the α7nAChR. Stress, mainly discrimination stress due to co-morbid disease condition such as diabetes, hypertension, neurodegenerative disorders plays an important role in sleep dysregulation and reduced melatonin production. Discrimination stress is found to be associated with increase gut dysbiosis or permeability, where there is elevation of Lipopolysaccharides and reduction of gut derived butyrate, which are known to increase and activate toll-like receptor 4 (TRL4) of immune cells, which reduces melatonin levels. Reduce butyrate as mentioned earlier leads to increase in pro inflammatory immune response and reduction in the anti viral cytotoxicity of natural killer cells. α7nACh receptor is one of essential mediator of melatonin, it is known to provide protection to lipopolysaccharides (LPS) and also known to increase nitric oxide synthase functions, which known to reduce the COVID-19 viral replication by reducing the palmitoylation of nascently expressed spike (S) protein thereby impacting on the fusion between the S protein and ACE-2 receptor; and reduction in the early steps of viral replication *via* effecting the cysteine proteases.[18] Thus, overall reduction in melatonin leads to loss of anti-inflammatory, anti-oxidant, immune regulatory effects. The α7nAChR in pulmonary epithelial cells is important to the susceptibility as well as symptom severity/fatality in SARS-CoV-2 patients. Both melatonin and the α7nAChR have treatment implications, both as prophylactics and in symptom management of SARS-CoV-2.[19] stress, Vitamin D, platelets, thrombin, blood-brain barrier (BBB) permeability, gut dysbiosis/permeability are affected features of SARS-CoV-2 and it is alterations in such factors that increases SARS-CoV-2 induced fatality in high-risk conditions.[6] Thus, there may be therapies and preventive ideas that come from the study of the relationship between these above pathways.

CONCLUSION

Besides proper rest and prophylactic usage of vitamins in COVID-19 pandemic, scientists have found ways to help patients deal with insomnia and problems linked to exhaustion by preventing electronic exposure to digital gadgets at night. Adequate nutrition which helps in maintaining gut barrier i.e role of sodium butyrate as a nutraceutical. Vitamin D supplements which benefits in immune response as well gut dysbiosis/permeability. Newer drugs targeting α7nAChR like nicotine gums and patches although requires investigations like how safely it can be provided. Greater beneficial effects of controlling co-morbidities like diabetes, cerebrovascular diseases (CVDs), hypertension would benefit in reducing the severity and fatalities of COVID-19 disease.

CONFLICTS OF INTEREST

The authors declare that they have no conflicts of interest.

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