

# Sex, sleep, steroids, and lifestyle: Unraveling the coronavirus disease 2019 conundrum

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## ABSTRACT

Coronavirus disease 2019 (COVID-19) has wreaked havoc and distressed economies worldwide. Countries have gone on lockdown of their economies to prevent the spread of the disease. This obviously led to collateral damage in the form of worsening healthcare for non-COVID-related conditions and is playing havoc with the world economy. Herein, we suggest novel strategies to prevent COVID-19 related complications, keeping in view the pathophysiology of the disease.

**Key words:** COVID-19, coronavirus, economy, dexamethasone, remdesivir

## INTRODUCTION

The coronavirus (CoV) belongs to the Coronaviridae family. It is an RNA virus closely related to SARS-CoV. The disease entity was named coronavirus disease 2019 (COVID-19) on 11 February 2020 by the World Health Organization (WHO). The International Virus Classification Commission named it Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2).

Mutation rates of RNA viruses are greater than DNA viruses, which makes them more adaptive to any vaccination. The virus has four main structural proteins: spike (S), membrane (M), envelope (E), and nucleocapsid (N). The SARS-CoV-2 spike (S) protein plays a key role in viral attachment, fusion, and entry. Structural and non-structural proteins Orf3, Orf8, and Orf10 likely enhance the pathogenicity of the virus and make it mount the cytokine storm that is the key to fatal complications of the virus.

CoVs mainly affect birds and mammals including humans. There are six CoVs that can infect humans: HCoV-229E, HCoV-OC43, HCoV-NL63, HKU1, SARS-CoV, and MERS-CoV. The 2019 new coronavirus (2019-nCoV) was identified

through genomic sequencing when cluster pneumonias were noted in Wuhan, China. The origin of the virus was traced to a wet market in Wuhan, China. Thereafter, despite the WHO declaring it as a global pandemic and worldwide shutting down of economies, the virus has continued to spread.

## CLINICAL MANIFESTATIONS OF COVID-19

COVID-19 is rather selective in infecting elderly much more than children. The answer may lie in the way the immune system evolves. As we progress from an immune-suppressed state in utero to a gradual buildup of the immune system, we get exposed to the world of viruses and bacteria, which may be microbiota of the gut or the newly mutated CoV.<sup>[1]</sup>

Once infected, viral shedding is the highest in the first 3 days of the patient being symptomatic. The pre-symptomatic transmission phase is 1–3 days before people become symptomatic. This adds to the conundrum in the management of COVID-19 and poses a challenge for public health strategists. The focus is on diagnosis and prevention of the spread.<sup>[2]</sup>

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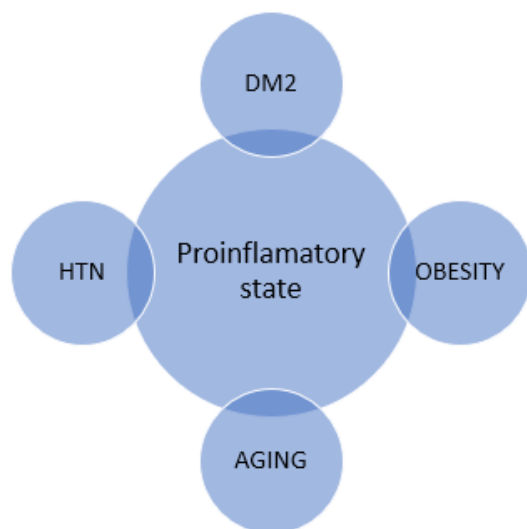
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COVID-19 is highly infectious, but pathologic manifestations could be myriad. It could vary from very mild, which could be asymptomatic, to acute respiratory failure and death. So, what defines the fulminant course of the disease and is there a way to define which set of population would need aggressive management. The data so far points to comorbidities as the defining factor for the severity of clinical manifestations.

## COMORBIDITIES AS A DEFINING FACTOR IN MORBIDITY AND MORTALITY ASSOCIATED WITH COVID-19

The course of the disease process in COVID-19 is defined by the inflammatory versus anti-inflammatory process in the body. Proinflammatory states (Figure 1) have been strongly associated with a bad prognosis.<sup>[3-5]</sup> There is a clear link with the metabolic state and the immune system.<sup>[6]</sup> Obesity being a state of chronic inflammation has been known to induce the alteration of the immune system with proinflammatory M1 macrophages being activated and anti-inflammatory M2 macrophages being suppressed. With obesity, we see a decrease in adiponectin and that corresponds to an increased incidence of type 2 diabetes mellitus (DM2).<sup>[7]</sup>



**Figure 1:** Proinflammatory states that predispose the body to COVID-19 related complications. DM2: type 2 diabetes mellitus; HTN: hypertension.

Aging of the immune system is accompanied by a proinflammatory state with a marked increase in cytokines, namely IL-1, IL-6, IL-18, and tumor necrosis factor (TNF).<sup>[5]</sup> As we age, immune senescence sets in and there is increase in cytokines and sometimes erratic immune

modulation. This leads to accentuation of inflammatory disorders.<sup>[8]</sup> This might explain the increased cytokine storm that we see in COVID-19 patients.

DM2 is the result of chronic underlying inflammation and could worsen the generalized inflammation in the body.<sup>[9-11]</sup>

Primary hypertension (HTN) is the clinical manifestation of chronic inflammation accompanied by oxidative stress over years. Current evidence suggests that inflammation can lead to the development of hypertension and endothelial dysfunction. Controlled hypertension also does not totally negate the cardiovascular effects related to HTN likely because underlying inflammation remains intact.<sup>[12]</sup>

In fact, individuals with any proinflammatory state would potentially be at risk for COVID-19 related complications. The proinflammatory state may be related to hypothyroidism,<sup>[13]</sup> hyperthyroidism,<sup>[14]</sup> or any common chronic autoimmune pathology like rheumatoid arthritis, inflammatory bowel disease, or gout.<sup>[15,16]</sup>

## POTENTIAL PREVENTIVE MODALITIES TO PREVENT COVID-19 RELATED MORBIDITIES AND MORTALITY

First, we would expound on the potential therapeutic options to extol and blush up the innate immune system of the body, which could potentially prevent or cure the infection with an appropriate immunological response. The five areas of focus would be diet, exercise, healthy sex, sleep, and mindfulness meditation (Figure 2).

Diet rich in antioxidants as seen in the Mediterranean diet attenuates the inflammatory process as shown by decreased C-reactive protein (CRP) in the body in the long run.<sup>[17]</sup> An improper dietary pattern predisposes the body to a proinflammatory and prothrombotic state due to endothelial dysfunction. The state gets accentuated if COVID-19 related infection gets interwoven in the complex scenario.

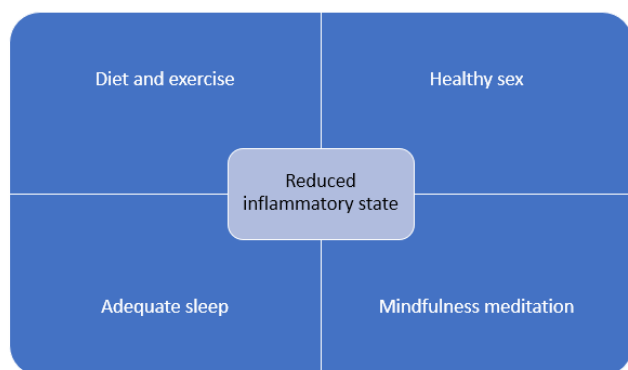
Mild-to-moderate physical exercise leads to a decreased inflammatory state in the body as manifested by decreased CRP.<sup>[18]</sup> The same is not true for intense physical activity.

Healthy regular sex is an epitome of a metabolically healthy adult. It adds to the sparks of immunity with decreased markers of inflammation.<sup>[19]</sup>

Sleep is the biggest healer of the endocrine system. Partial sleep deprivation leads to a marked increase in markers of inflammation especially interleukin-1 and TNF.<sup>[20]</sup>

A metaanalysis of 20 randomized controlled trials reported that mindfulness meditation is associated with reduced inflammation as shown by reduced CRP, improved CD4+ T-cell count, and increased telomerase activity.<sup>[21]</sup> Increased telomerase activity is seen as a boost to immunity and the ability of the body to mount an appropriate immune response.

Furthermore, there are gender differences in metabolic response to inflammation.<sup>[22,23]</sup> There are increased markers of inflammation with low estrogenic state in mice.<sup>[24]</sup>



**Figure 2: Potential modalities to reduce proinflammatory state in the body.**

## REDUCING MORTALITY RELATED TO COVID-19

Once patients are sick enough to be hospitalized, there are a few options that are emerging besides supportive therapy. The anti-viral drug remdesivir currently stands out. Therapeutic plasma exchange also helps. Other modalities like dexamethasone and anti-inflammatory monoclonal antibodies like tocilizumab, sarilumab, and siltuximab primarily aim to modulate proinflammatory immune response.

Remdesivir is an inhibitor of the viral RNA-dependent, RNA polymerase. It was shown to reduce the time to recovery, but mortality remained high despite the treatment.<sup>[25]</sup> This reinforced the need for added therapy for COVID-19 treatment.

Humoral immunity plays a key role in eliminating COVID-19 from the body. Thus as an adjunctive treatment, therapeutic plasma exchange works for the treatment of COVID-19 infection.<sup>[26]</sup>

A recent trial in England (RECOVERY) by Horby *et al.* with dexamethasone has shown mortality benefit with the

use of low-dose dexamethasone in critically ill patients admitted in critical settings with COVID-19 related complications. For patients who were on ventilators, the risk of death was cut down by one-third and for those on oxygen, the risk of death was cut down by one-fifth. On the other hand, for people who were not on respiratory support, it did more harm than good. Therefore, the drug essentially works in suppressing the cytokine storm or a state of excessive inflammation. But in the initial phase of the disease when there is relative immunosuppression, the drug could be counterproductive as there are increased complications relating to COVID-19. This is likely because of accentuated immunosuppression.

The anti-inflammatory monoclonal antibodies work by predominantly limiting the proinflammatory state and potentially reducing the cytokine storm, which could be fatal.<sup>[27]</sup>

## CONCLUSION

The CoV related pandemic is a wakeup call for humans. It is survival of the fittest in action as elucidated by Charles Darwin. The definition of fittest remains the one who could adapt the most. The adaptive skills in the current scenario are the people with a reduced proinflammatory state in the body. The need of the hour is to put in action the strategies to reduce the proinflammatory state. This would help the human race in the years ahead with not only COVID-19 but also with other ongoing infectious and lifestyle-related insults.

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None.

## Conflict of Interests

None declared.

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