Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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Review Article

Altered immunoemotional regulatory system in COVID-19: From the origins to opportunities

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ABSTRACT

The emergence of the novel coronavirus (SARS-CoV-2) and the worldwide spread of the coronavirus disease (COVID-19) have led to social regulations that caused substantial changes in manners of daily life. The subsequent loneliness and concerns of the pandemic during social distancing, quarantine, and lockdown are psychosocial stressors that negatively affect the immune system. These effects occur through mechanisms controlled by the sympathetic nervous system (SNS) and the hypothalamic-pituitary-adrenocortical (HPA) axis that alter immune regulation, namely the conserved transcriptional response to adversity (CTRA), which promotes inflammation and diminishes antiviral responses, leading to inadequate protection against viral disease. Unhealthy eating habits, physical inactivity, sleep disturbances, and mental health consequences of COVID-19 add on to the pathological effects of loneliness, making immunity against this ferocious virus an even tougher fight. Therefore, social isolation, with its unintended consequences, has inherently paradoxical effects on immunity in relation to viral disease. Though this paradox can present a challenge, its acknowledgment can serve as an opportunity to address the associated issues and find ways to mitigate the adverse effects. In this review, we aim to explore, in detail, the pathological effects of the new social norms on immunity and present suggested methods to improve our physical, psychological, and healthcare abilities to fight viral infection in the context of the COVID-19 pandemic.

1. Introduction

With the emergence of a novel coronavirus, currently termed severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), since late December 2019, and the World Health Organization (WHO) declaration of this outbreak as a "public health emergency of international concern" on January 30, 2020, and consequently characterizing it as a pandemic on March 11, 2020, we are now in the midst of an unparalleled global situation, with catastrophic casualties (Hanaei and Rezaei, 2020; Jabbari et al., 2020a). As of December 15, 2020, over 122 million coronavirus disease 2019 (COVID-19) cases and over 2.7 million deaths have been reported (Worldometers.info, 2020).

As there existed no effective preventative measure in the face of this virus (Hanaei et al., 2020; Lotfi et al., 2020; Mohamed et al., 2020a; Mohamed et al., 2020b; Momtazmanesh et al., 2020; Moradian et al., 2020a), such as a vaccine or other specific treatment (Basiri et al., 2020; Enriquez et al., 2019; Grant et al., 2020; Jahanshahlu and Rezaei, 2020a; Lotfi and Rezaei, 2020a; Mansourabadi et al., 2020; Mohamed et al., 2021; Mojtabavi et al., 2020; Mueller et al., 2020; Pourahmad et al., 2020; Rabiee et al., 2020; Raha et al., 2020; Rokni et al., 2020; Sadeghmousavi and Rezaei, 2020a; Saghazadeh and Rezaei, 2020a; Seyedpour, 2020; Sharifi et al., 2019; Torabi-Rahvar and Rezaei, 2020; Hassan et al., 2020; Lundstrom et al., 2020; Nejadghaderi et al., 2020; Saleki et al., 2020; Seyran et al., 2020; Sharifkashani et al., 2020; Shojaeefar et al., 2021; Pashaei and Rezaei, 2020; Rezaei, 2020a; Seyran et al., 2021; Shakerian et al., 2020), non-pharmacological interventions (Samieefar et al., 2020; Jabbari et al., 2020b) have been implemented to make the diagnosis of infection as early as possible (Rabiee et al., 2020;

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Basiri et al., 2021; Tantuoyir and Rezaei, 2021) and limit the spread of the infection (Prem et al., 2020). Namely, behavioral interventions aiming to separate people physically, generally referred to as "social distancing" (Galea et al., 2020), are executed so that the interpersonal transmission is interrupted. Using masks, self-isolation, and quarantine or lockdown of entire cities and communities are some of these strategies (Marais and Sorrell, 2020).

Quarantine is restricting people who are suspected of having had exposure to a contagious disease but are not showing illness as of yet, and isolation is separating those who are already ill (Cetron and Landwirth, 2005). Quarantine was successfully implemented during the severe acute respiratory syndrome (SARS) epidemic in 2003 (Goh et al., 2006) as a socially acceptable method (Cetron and Simone, 2004), and in the current pandemic, a community-wide quarantine was implemented in several countries; enforced to a magnitude unprecedented to mankind (Yousfi et al., 2020).

It is expected for these new social rules of conduct to come with consequences for people on communal and personal levels. The concerns grow from not knowing the future situation of our jobs (Schulte, 2020) to just wanting to be able to see the light of day outside the confinement of our homes (van Houwelingen-Snippe et al., 2020); but as the word itself entails, isolation and quarantine lead to being away from our communities, and one of the most devastating repercussions of that is a crushing feeling of loneliness (van Tilburg, 2020). This sense of disconnectedness (Gratz, 2020), together with the stresses and concerns during a pandemic (Whitehead and Torossian, 2021), can influence mental health (Tso and Park, 2020), and consequently health behaviors (Vanderbruggen et al., 2020), and overall physical well-being (Philip et al., 2020). The perception of loneliness can affect the function of multiple systems in the body, including the cardiovascular system (Cacioppo et al., 2002a). It can also be the precipitating factor for metabolic syndrome (Whisman, 2010), among other diseases, and can lead to increased death rates of all causes (Holt-Lunstad et al., 2015).

The ways that loneliness can lead to all these poor health outcomes are rather complex (Hawkley and Cacioppo, 2003); health behaviors, increased stress reaction, and faulty physiological repairing functions are the three main suggested pathways to pathology (Cacioppo et al., 2015). An interesting way that loneliness affects us is in how it changes the activities of the immune system. Loneliness can alter adaptive and innate immune responses (Matthai and Black, 1993). Perceived loneliness can cause a conserved transcriptional response to adversity (CTRA), which promotes inflammation through the increased transcription of related genes (Uchida et al., 2018), eliciting an inflammatory response through the actions of the sympathetic nervous system (SNS) (Irwin and Cole, 2011), and diminishes antiviral responses by decreasing the expression of the genes associated with them, leading to inadequate protection against viral disease (Uchida et al., 2018).

Therefore isolation, with its unintended consequences, has inherently paradoxical effects on immunity in relation to viral disease, which is very much in line with the pandemic we are currently living through; and though this paradox can present a challenge, its acknowledgment can nonetheless serve as an opportunity for us to become conscious of how the lockdown affects us (Yousfi et al., 2020), and to develop preventative and therapeutic measures in order to boost the immune system and keep it intact (Ranasinghe et al., 2020); by reducing the feeling of loneliness and mitigating any adverse effects of it (Razai et al., 2020).

In this review, we aim to explore, in detail, the pathological effects of the lockdown on immunity and present suggested methods to improve our physical, psychological, and healthcare abilities to fight viral infection in the context of the COVID-19 pandemic.

2. Origins

2.1. Emotional aspects of lockdown

It is human nature to be scared of anything that could potentially threaten our survival (Steimer, 2002). There is also an instinctive fear of the unknown instilled in all of us (Carleton, 2016), so the emergence of a novel, potentially fatal virus left us collectively feeling afraid and anxious. The concerns grew more extensive with daily and weekly reports of the newly diagnosed cases and mortalities, and when the lockdown was finally enforced (Kumar, 2020), it affected almost every aspect of our lives, creating a social situation that was unsettling to all of us.

Months later, now that lockdown has turned into social distancing, things still are not back to normal. Our most basic forms of social conduct and self-expression have drastically changed. We cannot even see each other's faces with the masks we need to wear, covering more than half of our facial expressions, and as a result, masking our emotions (Nestor et al., 2020). All of this "distance" is making us feel separated and lonely; as if the viral pandemic is ferally molding itself into a loneliness epidemic (Hwang et al., 2020; Jeste et al., 2020).

With the spreading news that older age and underlying diseases led to a higher chance of contraction and poorer outcomes (Mueller et al., 2020), groups that were marginalized in this pandemic, e.g., the elderly (Lichtenstein, 2021), had a more challenging time coping, feeling even lonelier (Monahan, 2020). Those with chronic illnesses, such as cancer and diabetes, also had additional sources of worry, namely the infection overly affecting them, being marginalized as a high-risk group, and doubting their ability to manage diabetes if they got infected (Joensen et al., 2020; Razavi et al., 2021).

2.2. Psychosocial aspects of immune regulation

With these emerging physical and social conditions comes the challenging need to adapt, and this arising challenge matches the exact definition of a "psychosocial stressor"; those are situations that put our adaptive abilities to the test (Monroe and Slavich, 2016). A psychological stressor can be studied from two aspects; one, the quality and quantity of the exposure to it, and two, the individual perception of the experienced stress (Irwin and Cole, 2011). The latter can often overpower the former, meaning one's subjective cognition of a situation, regardless of its objective magnitude, gives it meaning, and consequently determines the person's response to the stressor; thus, people react distinctively to psychological stressors (Hawkley and Cacioppo, 2003).

This difference in the perception of events and subsequent decision making is very much under the influence of the individual's emotional and psychological state (Lerner et al., 2015), and this is exactly where the destructive effects of the quarantine unfold, mediated by loneliness. Loneliness affects perception in such a way that ordinary events, considered regular by most, are more likely to be viewed as stressful (Cacioppo, 1994). Therefore loneliness, in and of itself, can be a generating source of acute, as well as chronic psychosocial stress (Mushtaq et al., 2014). Furthermore, different types of psychosocial stressors, such as separation, defeat, loss, rejection, or evaluation in a social context, can lead to inflammation, as shown in animal and human studies (Eisenberger et al., 2017).

This consequent psychological and inflammatory response in the lonely (Cacioppo, 1994) is evident in their higher increase of pro-inflammatory cytokines in the face of social stressors, causing an elevated inflammatory response (Audet et al., 2014). This inflammation, activated by psychosocial stressors, is caused through two pathways, namely the sympathetic nervous system (SNS) and the hypothalamic-pituitary-adrenocortical (HPA) axis, which can be activated by central neural mechanisms; hence the observed psychological influence (Irwin and Cole, 2011).

2.3. Conserved transcriptional response to adversity (CTRA)

Functional activation of the human genome is significantly altered in different social circumstances (Gibson, 2008). This was first studied in

the gene expression of leukocytes (Idaghdour et al., 2010). As touched upon earlier, both the physiological and psychological processes in any given social situation amount to its total effect, and each of these aspects activates different gene modules, along with a conserved generalized response to adverse life conditions (Cole, 2013). Of these adverse conditions, social isolation has been thoroughly studied in this regard (Cole et al., 2007). More than 200 genes are expressed at significantly different levels in chronic social isolation compared to social integration (Cole et al., 2011).

As observed in studies, there was a lower expression of genes related to antibody synthesis in objective isolation, which could be due to less contact with socially spread microbes, whereas subjective isolation was associated with a decreased expression of specific transcripts in immunoglobulin G1 (IgG1) synthesis and type I interferon (IFN) genes, and an elevated expression of pro-inflammatory genes (Irwin and Cole, 2011; Cole, 2013). This socially regulated pattern, called the conserved transcriptional response to adversity (CTRA), involves the β-adrenergic receptors, the SNS, the HPA axis, and the glucocorticoid response (Holmes et al., 2019).

CTRA and its different implications are of evolutionary advantage (Cole et al., 2007). Isolation puts us at a higher risk of getting harmed, i.e., attacked or wounded, where we do not have the protective circle of others around us (Moieni et al., 2015), and the resulting inflammation is the evolutionarily chosen shield of protection, adapted for times of loneliness and isolation (Leschak and Eisenberger, 2019). Taken in the context of the today world, inflammation heightens trait sensitivity to negative social experiences, shifting their perception into the psychological model of "threat", and therefore helping the individual avoid potentially harmful situations by further favoring isolation (Leschak and Eisenberger, 2019). In other words, CTRA itself can lead to self-perceived isolation, meaning inflammation, and perceived social stress are interconnected, each leading to the other, mediated by CTRA in both directions (Cole et al., 2015).

The diminished socially spread pathogen exposure in isolation reduces the need for robust antiviral immunity. Moreover, as potential wounding is more likely to occur and possibly more threatening to immediate survival in the context of social isolation, inflammation is prioritized at the expense of antiviral response (Leschak and Eisenberger, 2019).

2.3.1. Inflammatory cytokines and immune dysregulation

When reviewing the COVID-19 pandemic and its accompanying social issues and psychiatric outcomes with relation to each other, inflammatory cytokines and their interaction with neuroendocrine components are commonly remarked (Raony et al., 2020). Furthermore, loneliness and inflammation have been found correlated (Leschak and Eisenberger, 2019; Moieni and Eisenberger, 2018; Brown et al., 2020), such that loneliness enhances inflammatory responses to an acutely stressful event (Brown et al., 2018), such as biological challenges, e.g., endotoxin (Jaremka et al., 2013a). Stress and troubled interpersonal connections could possibly heighten inflammatory responses synergistically (Jaremka et al., 2013a). Pro-inflammatory cytokines such as TNF-α (Moieni et al., 2015; Jaremka et al., 2013b), IL-6 (Moieni et al., 2015; Jaremka et al., 2013b; Smith et al., 2020a; Hackett et al., 2012; Theeke et al., 2016; Nersesian et al., 2018; Balter et al., 2019; Loucks et al., 2006) and acute-phase reactants such as CRP (Nersesian et al., 2018; Loucks et al., 2006; Vingeliene et al., 2019), fibrinogen (Nersesian et al., 2018; Steptoe et al., 2004; Mezuk et al., 2016) and IL-1RA (Hackett et al., 2012) levels have been found significantly affected by loneliness.

Social isolation as a form of prolonged and chronic stress leads to sustained activation of the HPA axis, resulting in a reduced allostatic negative feedback through the elaboration of cortisol. This allostatic overload results in a down-regulation of the glucocorticoid receptor gene, namely NR3C1 (Cole et al., 2012). This phenomenon is referred to as functional glucocorticoid desensitization (Cole et al., 2015) and has been implicated in the context of CTRA gene expression (Holmes et al., 2019).

2.3.2. Antiviral immune response

With the evolutionary explanation mentioned earlier, antiviral activity is diminished both in loneliness and social isolation (Leschak and Eisenberger, 2019), with the down-regulation of type I and II IFNs (Cole et al., 2015). This inadequate antiviral immunity has been studied with regard to the immune response to different viruses, which has been found impaired in infection with simian immunodeficiency virus (SIV) (Cole et al., 2015). Elevated antibody titers against some ubiquitous or latent viruses (Hodel and Grob, 1993), such as higher CMV antibody titers (Glaser et al., 1985) have been associated with a more severe symptom cluster of depression, fatigue, and pain (Jaremka et al., 2013c), and higher EBV (Glaser et al., 1985) and HSV-1 antibody titers (Glaser et al., 1985; Jaremka et al., 2018) have also been observed in lonelier individuals.

With loneliness causing a poorer subjective adaptation to stressful challenges, another observed aspect of immune dysregulation, rather than suppression, is that the balance between type 1 (IFN-gamma) and type 2 (IL-10) cytokines shifts toward type 2 in stress, and this could be a potential explanation for the higher observed type 2 mediated immune reactions in times of elevated stress, such as viral infection, expression of latent viruses, autoimmunity and allergic or asthmatic reactions (Marshall Jr et al., 1998).

It is rather unfortunate that infection with viruses of social stigma, such as HIV or HCV, consequently leads to further isolation and loneliness. The mere diagnosis of HCV has been associated with feelings of loneliness and social isolation (Montague et al., 2019), and it is much the same when living with HIV through the years (Brown et al., 2019). The internalized stigma of HIV infection and subsequent suboptimal adherence to antiretroviral therapy is another studied situation in this context (Enriquez et al., 2019; Turan et al., 2016; Rendina et al., 2019). The same phenomenon with the stigma has been happening with a COVID-19 diagnosis (Sotgiu and Dobler, 2020). Loneliness has been found related to lower preventative behaviors toward infection during COVID-19 (Stickley et al., 2021), which leads us to believe that the relation between antiviral immunity and loneliness, although controlled differently in each direction through distinct mechanisms of immunity and behavior, is nonetheless reciprocal.

2.3.3. Innate and adaptive immunity

Loneliness can affect the proper activity of innate immunity through reduced natural killer cell functionality (Kiecolt-Glaser et al., 1984), and cellular and humoral immunity, through decreased plasma IgG, IgM (Dénes, 1980), and IgA (Dénes, 1980) levels and diminished lymphocyte activity such as decreased mitogen stimulation (Hodel and Grob, 1993).

Focusing again on CTRA, another way it affects immunity is through transcriptome shifts that are primarily mediated by myeloid lineage immune cells, e.g., dendritic cells and monocytes (Cole et al., 2011), and it has been confirmed, through studies on isolated subpopulations of leukocytes, that changes in transcription in response to human social adversity are mediated by monocytes (Miller et al., 2008; O'Donovan et al., 2011). In addition, animal models have shown an up-regulation in the production of distinct, immature, pro-inflammatory monocytes by the SNS through changing hematopoietic mechanisms, mediated by β-adrenergic signals that enhance the differentiation and development of monocytes through increased transcription of the myelopoietic growth factor, granulocyte-macrophage colony-stimulating factor (GM-CSF) (Powell et al., 2013). GM-CSF has been associated with loneliness in other studies as well (Henneghan et al., 2020).

2.4. Lifestyle, health behaviors, and the psychodynamics of social distancing

Along with the aforementioned immunological adaptations to the newly set social circumstances, it is vital to take consequent behavioral

and environmental changes into account when analyzing the COVID-19 situation (Emerson, 2020).

2.4.1. Eating habits

Keeping a healthy diet has proven to be exceedingly difficult during the pandemic (Jayawardena and Misra, 2020). The main changes in diet have been a lower intake of fresh fruits, vegetables, and protein-rich foods of high quality, e.g., fish or meat, and higher consumption of snacks and sugary, high-fat foods, making the diet progressively imbalanced. These changes can possibly affect immunity and the management of chronic underlying diseases, subsequent to inadequate content of micronutrients and the resultant disproportionate calorie intake (Jayawardena and Misra, 2020), eventually leading to a lack of sufficient nutrients to support the immune system (Nieman and Bishop, 2006) and causing weight gain (Zachary et al., 2020), respectively.

The use of food as a defective coping mechanism to re-establish a sense of control over the uncertain circumstances we are currently living through is possible and should be carefully considered regarding those with eating disorders (Schlegl, 2020).

2.4.2. Sedentary lifestyle and inactivity

The catastrophic lifestyle changes in the settings of COVID-19 have led to increased sedentary behavior and decreased levels of physical activity (Zheng et al., 2020), and resultant weight gain (Zachary et al., 2020). These behaviors come with consequences for the immune system, causing immunosuppression through a heightened inflammatory state, oxidative stress, and other processes (Booth et al., 2017), thus making the individual more susceptible to viral infection (Luzi and Radaelli, 2020). In contrast, increased levels of physical activity have been shown to improve markers of immunity, leading to lower levels of inflammatory markers, namely CRP, IL-6, IL-18, and TNF-α, along with decreased leukocyte counts (Wedell-Neergaard et al., 2018).

A mediator for the effects of sedentarism on immunity, especially during a viral pandemic, is obesity (Luzi and Radaelli, 2020). In an article on influenza and influenza-like viruses, a reciprocal connection between viral infection and obesity was observed, meaning the illness would lead to obesity, and obesity, in turn, through prolonged viral shedding, increased viral load in a breath, and higher viral variability, caused greater spread of the infection (Luzi and Radaelli, 2020).

2.4.3. Sleep disturbances

Sleep disturbances and insomnia are of the common consequences of quarantine, experienced by many (Kokou-Kpolou et al., 2020). Loneliness due to COVID-19 is associated with more troubles around sleep (Grossman et al., 2021). Higher scores of insomnia have been reported among people with concerns of having themselves or a loved one been infected. Other predictors of insomnia are loneliness, heightened intolerance to uncertainty, worries of COVID-19, and higher severity of depression (Voitsidis et al., 2020). As sleeping is arguably the most basic behavior of restorative value, the resultant sleep deprivation, as seen in the times of COVID-19 and loneliness (Cacioppo et al., 2002b), can impair immune functions through decreased cytokine release (Bryant et al., 2004).

Moreover, increased duration of sleep has been observed in a study on nursing students. This is concurrent with a longer time spent in bed and increased sleep latency, meaning it takes longer for them to fall asleep; therefore, sleep efficiency, which is the ratio between time spent asleep and time spent in bed, is lower in lockdown (Romero-Blanco et al., 2020).

2.4.4. Mental health

As with the stresses of contagion and stay-at-home orders, daily life took on a completely different look in lockdown (Tull et al., 2020), with the isolation consequently affecting mental health (Ustun, 2020). Poor mental health outcomes have been thoroughly studied in the context of COVID-19, from loneliness, anxiety, and depression (Gorenko, 2021) to suicidal ideation (Lewis, 2020). Self-reported alcohol and substance use increased significantly in lockdown due to boredom, loneliness, a lack of social contact, or loss of daily structure (Vanderbruggen et al., 2020). Lack of movement and long hours of sitting were associated with worse depression, stress, and loneliness, as self-reported physical activity among previously active people was significantly lower after the pandemic (Meyer et al., 2020). A higher screen time had the same mental health outcomes (Meyer et al., 2020).

Social adversity, with its resultant inflammatory response through CTRA, as discussed earlier in the case of loneliness, could also be a cause for the development of anxiety and consequent depression, and has been studied as an etiological theory for depression (Slavich and Irwin, 2014). This theory can explain the emergence of depression and anxiety in the settings of COVID-19. However, it also signifies the shared underlying pathology and resultant compromise of the immune system in social isolation, anxiety, and depression, portraying them as conjoined phenomena in mental health outcomes of COVID-19.

It is worth noting that self-isolation and quarantine lead to more severe depression and anxiety in comparison with social distancing (Meyer et al., 2020), which could also be explained by the theory mentioned above, with regard to levels of social adversity and human connection in each of those settings. Furthermore, social platforms also play a major role in people's emotional response to the pandemic, as one might feel fear by obtaining fake news about the disease (Jain et al., 2020; Fernández-Torres et al., 2021), and so the *infodemic* has further worsened the fears of the *pandemic* , and appears to be immensely detrimental to mental health.

2.5. COVID-19 and immune dysregulation

When investigating immunity against COVID-19, the very nature of the disease should also be taken into consideration. The virus attacks the immune system in such a way that results in a systemic inflammatory response, with disproportionately high levels of inflammatory cytokines, often referred to as a "cytokine storm," which is one of the most prominent features of the disease and can ultimately lead to severe COVID-19 outcomes like the acute respiratory distress syndrome (ARDS) (Coperchini et al., 2020). In severe cases of COVID-19, macrophage activation syndrome, along with NK cell and CD4 cell lymphopenia, are also present, ultimately leading to a major dysregulation of the immune system (Giamarellos-Bourboulis et al., 2020).

This pro-inflammatory profile, along with the impaired immunity, is also present in people with certain conditions like obesity, which is associated with chronic low-grade systemic inflammation and consequently poorer COVID-19 outcomes (Chiappetta et al., 2020), or in times of social isolation or loneliness (Leschak and Eisenberger, 2019; Moieni and Eisenberger, 2018; Brown et al., 2020), which are all prevalent observations in times of COVID-19.

The cytokine storm in COVID-19 almost imitates an exaggerated image of the aforementioned pro-inflammatory profile. This shared pathology of the immune system, present in different magnitudes, makes the impaired immune profile in the social settings of COVID-19 almost look like an invitation to a more drastic progression of symptoms in the case of contraction, given that a basic level of dysregulation is already present and is more likely to be exacerbated. Likewise, the virus itself and its social consequences compound each other's negative effects.

Taken together, the aforementioned psychosocial factors lead to an altered immunoemotional regulatory system (IMMERS, (Saghazadeh and Rezaei, 2019)) in times of COVID-19, making the achievement of immunity against this ferocious virus an even tougher fight.

3. Therapeutic opportunities

3.1. Nutraceuticals, functional foods, and dietary recommendations

3.1.1. Micronutrients and nutraceuticals

Nutrients are essential to the immune system, as they are needed in cell division and cytokine and antibody production and release (Nieman and Bishop, 2006). The importance of micronutrients is evident in their necessary presence for many enzymes to function properly. Select vitamins and minerals have been known for their roles in maintaining the functionality of the immune system, of which are zinc, iron, selenium, copper (Raha et al., 2020), and vitamins A, B2, B6, B12, C, D, and E (Calder and Kew, 2002; Gulhane and Hiware, 2020). Therefore, a diet that provides the necessary nutrients is recommended to boost immunity against viral infection (Calder et al., 2020).

Viral and bacterial infections cause an immune response marked by the production of inflammatory cytokines. This is also the case in COVID-19 patients who often display increased pro- and anti-inflammatory cytokines (Huang et al., 2020). It becomes even more vital in those with a severe disease who require intensive care unit (ICU) admission and nutritional interventions via enteral tubes, and therefore guidelines and recommendations have emerged for this purpose (Minnelli et al., 2020).

The production of pro-inflammatory cytokines, namely TNF-α and IL-1, has been found inhibited by vitamin D (Sharifi et al., 2019), in addition to its other anti-inflammatory effects (Topilski et al., 2004). Vitamin D can also help maintain pulmonary arterial blood pressure and inhibit cystic fibrosis and emphysema (Roselin and Parameshwari, 2020), through regulating the renin-angiotensin system (Li, 2003), thus strengthening the lungs (Roselin and Parameshwari, 2020). Deficiency of vitamin D could lead to an increased risk of infection, especially in the respiratory system (Laaksi et al., 2007; Karatekin et al., 2009); therefore, vitamin D has been suggested as a preventative factor in the face of COVID-19 (Grant et al., 2020) and also in mitigating the potentially deleterious outcomes (Razdan et al., 2020), so sun exposure in times of quarantine or taking vitamin D supplements should be considered (Yousfi et al., 2020). The recommended guideline for people at risk of infection is rapidly raising vitamin D concentrations by taking 10,000 IU/d of vitamin D3, reduced to 5000 IU/d after a few weeks, with the goal concentration being above 40–60 ng/mL (100–150 nmol/L) (Grant et al., 2020).

Vitamin C, present in citrus fruits, acts as an antioxidant and is also well-known for its therapeutic effects on upper respiratory tract infections (URTIs), reducing both the severity of symptoms and duration of the illness (Aldrin Joshua et al., 2020).

Melatonin has also been studied in this regard. Melatonin can rejuvenate the glutathione redox system and restore the function of neutrophils in times of heightened oxidative stress, and therefore has been hypothetically suggested as a potential immune booster in the face of COVID-19 (NaveenKumar et al., 2020).

3.1.2. Functional foods

In the pursuit of an intact host defense against COVID-19, dietary recommendations other than micronutrient supplementation have also been studied.

Functional foods are foods with biologically active ingredients. They are physiologically beneficial to health and can help prevent chronic diseases, namely, type 2 diabetes mellitus (Alkhatib et al., 2017). Some functional foods have been associated with anti-inflammatory and anti-oxidative properties, such as polyphenol-rich herbs, e.g., coffee and green or black tea (Alkhatib et al., 2017), or antimicrobial properties such as bioactive peptides in natural food proteins, which are also available as nutraceuticals (Acquah et al., 2020). These properties could potentially be protective against COVID-19.

Of the functional foods that have been studied in light of the immune system and used as immune boosters are spices and herbs. Higher ginger, turmeric, garlic, curcumin, and cloves consumption have been found associated with fewer COVID-19 cases per million population (Elsayed and Khan, 2020). Curcumin was studied both when used with zinc, as an immunity booster (Roy, 2020), and alone, showing additional anti-depressant properties (Soni et al., 2020). Garlic has been recommended in times of COVID-19 for having antimicrobial, anti-inflammatory, and all-around immunomodulatory properties (Donma and Donma, 2020).

Items of traditional herbal medicine have also been studied as immune boosters in the fight against COVID-19, namely propolis, which is the resinous substance that bees make from botanical exudates (Berretta et al., 2020).

3.1.3. Recommended eating patterns

Eating patterns such as intermittent fasting (IF) and calorie restriction (CR), have been suggested as methods to boost immunity. IF was found to affect immunity in multiple regards, affecting inflammation and oxidative stress, metabolic rate, and body weight, as well as composition (Faris et al., 2020). Inflammation, for example, was depressed with IF, as shown in reduced CRP and IL-6 levels in prolonged (Aksungar et al., 2007) and short-term IF (Brannon et al., 2009). Other markers of inflammation (TNF-α), along with oxidative stress biomarkers such as nitrotyrosine, 8-isoprostane and protein carbonyls, and metabolic markers such as serum cholesterol and triglycerides, were also reduced with an alternate-day pattern of CR, which led to better medical outcomes in patients with asthma (Johnson et al., 2007).

IF can activate immune responses (Cheng et al., 2014) and induce autophagy, which is the elimination of dysfunctional organelles and proteins, as well as invading pathogens (Bagherniya et al., 2018), and through distinct mechanisms, stimulates the immune system and primes host defense; therefore, along with the other aforementioned effects, IF could be a potential preventative approach to COVID-19 (Hannan et al., 2020). However, this is not recommended for everyone, as spontaneous fasting could have adverse effects even among healthy individuals. Moreover, the CR that happens in IF can be detrimental to the condition of underlying diseases and it is strongly advised for COVID-19 patients not to fast, as there is a risk of inadequate nutrient supply (Hannan et al., 2020). The net benefits of IF in prevention of COVID-19 should be further studied appropriately.

3.2. Adapting to the new manner of living

3.2.1. Exercise and physical activity

The previously mentioned immune consequences of obesity due to physical inactivity can be mitigated by moderate physical exercise and drugs commonly used in the treatment of obesity-related diabetes, namely metformin and pioglitazone (Luzi and Radaelli, 2020). Although any physical exercise can be considered favorable compared to inactivity in times of COVID-19 (Alkhatib, 2020), it is vital to keep a certain level of physical activity to mitigate the immune consequences of inactivity and isolation (Simpson and Katsanis, 2020).

In terms of exercise recommendations in these conditions, a mild to moderate intensity has been suggested, as excessive exercise may negatively affect immunity through subsequent higher cortisol levels (Codella et al., 2015) and an increased risk of infection (Simpson et al., 2020). It is advisable to exercise at home, not to put oneself at the risk of exposure to the airborne virus. Targeting balance, strength, control, stretching, or a mix of these, some of the activities achievable at home are those using own body weight, such as sit-ups, push-ups, chair squats, climbing the stairs, lunges, or just walking around the house. One could also choose to walk to necessary places like the store and carry the groceries as a weight-bearing exercise (Chen et al., 2020). To keep the recommended moderate intensity, the exercise should use 64-76% of the maximum heart rate, which can be calculated individually by subtracting one's age from 220 (American College of Sports et al., 2018).

A gradually increased exercise volume during lockdown can cause a

higher maximal oxygen consumption ($V\ O_{2max}$) (Alkhatib, 2020). This can be particularly beneficial in individuals who have had low-grade inflammation for a long time, with more inflammasomes and higher pro-inflammatory cytokine levels, and are susceptible to higher risks of infection and poorer outcomes, i.e., those with obesity, diabetes, and metabolic syndrome (Zbinden-Foncea et al., 2020).

3.2.2. Sleep recommendations

With the previously mentioned immune advantages of adequate sleep and the observed sleep disturbances in times of COVID-19 (Cacioppo et al., 2002b), maintaining a healthy sleep pattern should be prioritized. The recommended sleep duration for adults is usually 7–9 h per night, though this depends on age, gender, and physical activity and should be individualized (Hirshkowitz et al., 2015).

3.3. Suggestions for better mental health and reducing the feeling of loneliness

The current circumstances demand different strategies for different groups of people to cope (Hiremath et al., 2020). WHO has shared mental health considerations for the general population, advising to minimize their exposure to outbreak news to reduce anxiety, and for healthcare workers, recommending them to take care of themselves and rest between shifts, along with considerations for other groups (Organization, 2020).

Certain groups of people, namely adults who live alone, those with lower income, and young adults (18–30 years old), are known to be more likely to experience loneliness, and these groups are even more at risk of loneliness during the COVID-19 pandemic. In addition, other groups, e.g., students, also felt lonelier during lockdown than before the pandemic. It has been suggested that interventions to mitigate loneliness should first target these groups of people (Slavich and Irwin, 2014). The COVID-19 pandemic has made feelings of loneliness and social isolation more prominent, and various interventions in this regard have been studied, namely social prescription by medical professionals, individual and group-oriented therapy, and different strategies involving information and communication technologies (ICT). However, there is still uncertainty about which of these methods works best for each target group (Smith and Lim, 2020). Nonetheless, the stressors present in the context of COVID-19 implicate the urgent need to focus on resilience, both on an individual and a societal level (Vinkers et al., 2020).

3.3.1. Social prescribing

Social prescribing is incorporating non-medical interventions, e.g., physical activities, the arts, or other forms of engaging with the community, in the course of therapy, to tackle more extensive determinants of health while turning to resources that are already present in communities, and thus improving well-being (Razai et al., 2020).

A study suggests turning to poetry to combat loneliness in these times of solitude (Xiang and Yi, 2020). Singing was also utilized in the COVID-19 lockdown, as the silence of Italian cities was broken by people singing together, apart, each at their own windows, bringing people together at heart and improving the feeling of social cohesion (Corvo and De Caro, 2020). Along with these social suggestions, dog ownership was also found to be protective against loneliness for people living alone in times of COVID-19 (Oliva and Johnston, 2020).

3.4. Telemedicine

Telemedicine can be defined as the act of health care professionals providing health care services through the use of ICT, so that valid information is being exchanged, where there is distance between the provider and the recipient of the care (eHealthe, 2010). The distancing nature of the new social norms demanded new ways of health care delivery, as those not infected with the virus, and even more so people at higher risks of infection, like people with underlying diseases, still required care from their medical professionals without risking exposure in hospitals (Smith et al., 2020b); thus remotely-delivered interventions were necessary during the COVID-19 lockdown (Gorenko, 2021; Moazzami et al., 2020).

The remote management of people with chronic diseases through telemedicine has been studied prior to this situation (Bashshur et al., 2014), and has been brought to attention in times of COVID-19 for the management of type 1, type 2, and gestational diabetes (Torlone et al., 2020), and in programs to decrease anxiety in at-risk patients with scleroderma (Thombs et al., 2020).

3.4.1. Telepsychiatry

With the strain of COVID-19 on mental health and the lack of immediate access to necessary psychiatric care, the use of telemedicine in the context of psychiatry, referred to as telepsychiatry, has been studied. However, it is still underused and can be potentially promoted in current circumstances (Di Carlo, 2020). The emotional, interpersonal, and economic burden of the current living conditions has led to neglect and thus worsening of mental health and ultimately a higher risk of suicide, as mentioned earlier. Therefore, proper follow-up is vital in the face of psychiatric disorders, and telemedicine can be a useful platform in ensuring this aim in times of COVID-19 (Wasserman et al., 2020).

Brief 30-min phone calls with clinicians were studied as a connection plan to provide care during social distancing restrictions, thus reducing the risk of suicide (Van Orden, 2020). As regular visits are also required in patients with psychosis for their treatment and preventing relapse, an intervention called “Phone Pal” was studied to provide communication between patients and volunteers, as these patients are particularly isolated in their daily lives and face social stigma. However, the intervention can be implemented for other disorders as well (Pinto da Costa, 2020). Dialectical behavior therapy, a type of cognitive-behavioral therapy, was also studied among patients with borderline personality disorder, before and during confinement. During the confinement period of 8 weeks, video and phone calls were used, and patients felt decreased levels of fear and tension and had lower addictive or compulsive behaviors like alcohol consumption or binge-eating, along with an increased feeling of distress, which could be associated with loneliness (Salamin, 2021).

3.5. Interventions aimed at the elderly

Among people aged 60 and older, COVID-19 has been observed to have substantially higher infection rates, symptom severity, and mortality (Tian et al., 2020). Comorbidity is the main cause of this observation. However, it could also be attributed to immunosenescence, which is the decline in the immune system of the elderly and the overall consequences of aging such as lower fitness and general functionality along with the resultant frailty and weakness. Immunosenescence can also affect response to vaccination and the outcome of infectious diseases (Zhavoronkov, 2020).

Moreover, an individual’s subjective age can affect the association between perceived feelings of isolation or loneliness, and the observed psychiatric symptoms during the COVID-19 pandemic; meaning, compared to their actual age, those who felt younger showed a weaker correlation between loneliness and psychiatric symptoms, and those feeling older showed a stronger association. In other words, those with an older age identity are at higher risk of loneliness affecting their mental health. Therefore, higher subjective, as well as objective, age can be risk factors for adverse effects of loneliness in times of COVID-19 (Shrira, 2020).

This explains the need for interventions aimed at the elderly, to mitigate the increased feeling of loneliness during the pandemic in this population; many of whom live in nursing homes and may therefore be feeling even lonelier. To fight this feeling of isolation, self-guided therapy sessions, along with interventions involving phone calls and video calls, have been suggested (Gorenko, 2021). To name a few, “The

Telephone Outreach in the COVID-19 Outbreak Program" implemented weekly phone calls for the elders at nursing homes to talk with volunteer students, which resulted in the senior residents looking forward to phone calls every week and feeling more socially connected (van Dyck et al., 2020). "TOVID" (**T**elephony **O**r **V**ideophony for **I**solated el**D**erly) provided the same aim. Compared to video calls, telephone calls proved easier to handle independently and were used more frequently among the elderly in hospitals, long-term care, and nursing homes. Both modalities were equally satisfying overall, though video calls were even more favored by the nursing home and long-term care residents, when given help with establishing the call (Sacco et al., 2020).

There is also the need for social workers to be trained in practices involving the elderly, regarding subjects that were highlighted in times of COVID-19, namely ageism, loneliness, the use of technology, and the required collaborative practice between those of different professions (Berg-Weger and Schroepfer, 2020).

4. Conclusion

COVID-19 can severely affect immune regulation (Mohamed et al., 2020a; Torabi-Rahvar and Rezaei, 2020; Lundstrom et al., 2020; Nejadghaderi et al., 2020; Shojaeefar et al., 2021; Delavari et al., 2020; Nasab et al., 2020; Sahu et al., 2020; Bahrami, 2020; Fathi and Rezaei, 2020; Jenab, 2020; Saghazadeh and Rezaei, 2020b; Sarzaeim and Rezaei, 2020; Yazdanpanah et al., 2020a; Yazdanpanah et al., 2020b; Darbeheshti and Rezaei, 2020; Ahanchian, 2020; Goudarzi, 2020; Heidarpour et al., 2020; Khosroshahi and Rezaei, 2020; Yousefzadegan and Rezaei, 2020; Aleebrahim-Dehkordi et al., 2020; Babaha and Rezaei, 2020; Rezaei, 2020b; Darbeheshti, 2021; Khanmohammadi and Rezaei, 2021; Moradian et al., 2020b), as it involves multiple organs (Nejadghaderi et al., 2020; Goudarzi, 2020; Heidarpour et al., 2020; Hessami, 2020; Vakhshoori et al., 2020; Jahanshahlu and Rezaei, 2020b; Lotfi and Rezaei, 2020b; Jabalameli et al., 2021; Safdarian et al., 2020; Torabi et al., 2020), namely the central nervous system (Amanat et al., 2021; Sadeghmousavi and Rezaei, 2020b; Saghazadeh and Rezaei, 2021). During the pandemic, health polices at both national and international levels (Nejadghaderi et al., 2021; Kafieh et al., 2021) and related social consequences have changed almost every aspect of our lives, leading to feelings of anxiety, loneliness, isolation (van Tilburg, 2020), and stress (Salehi et al., 2021). Altogether, the pandemic of COVID-19 has become a live enemy to our IMMERS (Saghazadeh and Rezaei, 2019). The present review concluded that the adverse effects of isolation could be mitigated through health behaviors. Armed with the capacity to utilize the suggested methods, we can aim for a robust immune system and fight this battle (Mohamed and Rezaei, 2020), which has persisted for a year now (Jabbari and Rezaei, 2020). Pro-sensing biomaterials are of emerging interest that can accelerate the early immune responses (Saghazadeh and Rezaei, 2021), while testing the clinical efficacy of a variety of ancient and modern therapies that selectively modulate inflammation remains under investigation (Pezeshki and Rezaei, 2021; Zarandi et al., 2021; Palit, 2021; Peymani et al., 2021).

Ethics approval and consent to participate

Not applicable.

Consent for publication

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Availability of data and materials

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Competing interests

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