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Long COVID-19: Psychological symptoms in COVID-19 and probiotics as an adjunct therapy

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Abstract: There is an increase in mental health sequelae following COVID-19 infection, with some studies showing a higher prevalence rate of psychiatric sequelae in post-COVID-19 survivors than in the general population. This review discusses the possible causes, prevalence, and risk factors of COVID-19 associated psychological manifestations, namely anxiety, depression, and post-traumatic stress disorder (PTSD). Although the exact cause is yet to be determined, it is likely multifactorial involving environmental, biological, and psychological factors due to the pandemic. Variation exists for risk factors and prevalence, but the female gender and psychiatric disorder history seem to be consistent risk factors across several studies. While conventional psychotropic medications are the common therapeutic intervention, probiotics could be a potential adjunct treatment to prevent and treat COVID-19 and its associated psychological manifestations. Their anti-inflammatory effects have been seen directly via reducing plasma concentration of proinflammatory cytokines or indirectly via the suppression within the kynurenine pathway and restoration of gut permeability. Additionally, short-chain fatty acids (SCFAs) are crucial gut microbial metabolites with essential roles, including signaling along the microbiota-gut-brain (MGB) axis, maintaining blood-brain barrier's (BBB) integrity, neuronal functions, neurotransmitters, and neurotrophic factors modulation.

Keywords: mental health; COVID-19; anxiety; depression; probiotics

1. Introduction

The world has been suffering and fighting against the deadly COVID-19 pandemic since the end of 2019 [1-3]. The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) from the family *Coronaviridae*, has claimed many lives and still spreading stronger with

the emergence of new variants such as the Beta and Omicron [4-8]. Coronavirus has caused not just the current COVID-19 pandemic but also past outbreaks-severe acute respiratory syndrome (SARS) and middle east respiratory syndrome (MERS) [9, 10]. When this review went to press, over 400 million confirmed cases and 6 million deaths were reported worldwide [11]. Vaccines were developed and approved for emergency use by World Health Organization (WHO) to protect against severe symptoms, hospitalization, and death [12-15]. Many countries took drastic measures by closing their international borders, implementing lockdown, mass screening and testing, contact tracing, and educating the public on using face masks and RTK test kits [16-20].

Recently, many studies have reported the clinical characteristics, pathogenesis, epidemiology, and complications of acute COVID-19 [21, 22]. However, the long-term consequences of COVID-19 remain unclear [23]. The viral infections' post-infectious sequelae often involve damage to different organs, particularly the brain [24]. Furthermore, recognition of mental health consequences of infection rises as COVID-19 cases increase [25-27]. A similar trend is seen with previous SARS and MERS outbreaks that have been associated with long-term neuropsychiatric consequences [28, 29]. Given the phylogenetic similarities between the coronavirus subtypes, we use SARS and MERS data to predict the psychological implications of COVID-19 [30]. This review is based on a recently published paper titled "Psychological Symptoms in COVID-19 patients: Insights into Pathophysiology and Risk Factors of Long COVID-19" [9]. This review provides an understanding of the cause, prevalence, and risk factors of COVID-19 associated psychological effects, the psychiatric sequelae of COVID-19, and probiotics as a possible adjunctive therapy. Given the impact of this pandemic, we must understand COVID-19's psychological implications so that appropriate and effective health care plans and psychological rehabilitation can be made available to improve the individual functioning of COVID-19 survivors [9].

2. Incidence and Risk Factors of COVID-19 on Psychological Effects

Although results associated with the psychological symptoms post-COVID-19 from many studies are available and increasing, they are mainly from surveys or self-reported by patients. Nonetheless, the results are significant and may provide an insight into some of the possible explanations for COVID-19's psychological symptoms [9].

There are many potential causes of COVID-19 associated psychological manifestations. They may be associated with virus-infected individuals who are worried about the stigma [31], the outcome of the illness [25], the psychological reactions after COVID-19 infection, the medical interventions [10], and traumatic memories of severe disease and amnesias [32]. However, the pandemic consequently also affects uninfected individuals. Risk factors affecting individuals regardless of infectivity include social isolation [33], anxiety [34], stress in both health care workers and essential workers [35], unemployment, and financial

difficulties [36]. Notably, the COVID-19 associated psychological effects are likely multifactorial due to the pandemic's biological, environmental, and psychological factors.

A study showed that>15% of SARS and MERS survivors experienced long-term neuropsychiatric effects [28]. Another study showed 42.5% of SARS survivors experienced ≥ 1 active psychiatric illness, 54.5% experienced PTSD, 39% had depression, 36.4% had a pain disorder, 32.5% had a panic disorder, and 15.6% had OCD, a sharp increase from the 3.3.% pre-infection prevalence of any psychiatric diagnoses [37]. Seeing the similarities between COVID-19, SARS, and MERS infections, we may be able to speculate on the psychological symptoms following COVID-19 conditions [9]. With regards to COVID-19, according to studies, the prevalence of post-infection anxiety ranges between 6.5-63% [38], while in a study involving hospitalized and non-hospitalized patients, the prevalence rate of depression ranges between 12-48% [39, 40] and for PTSD, at 1-3 months post COVID-19, its prevalence rate ranges from 12.1- 46.9% [38].

In terms of risk factors, there is variation in profile for different psychiatric manifestations linked with COVID-19 [9]. Some of the anxiety risk factors include illness severity [23, 41], female gender [42], medical comorbidities [43], the stigma of COVID-19 infection, history of psychiatric illness [44, 45], perceived discrimination, death of a family member and living with children [41], and poor social support [46]. For depression, some reported risk factors are female gender [23, 47-49], illness severity [23, 41, 50], stigma of COVID-19 infection, history of psychiatric illness [45], perceived discrimination, living with children, more significant total number of symptoms after discharge [41], and poor social support [46]. In contrast, some risk factors of PTSD include a history of psychiatric illness, total duration of isolation, the stigma of COVID-19 infection [45], death of a family member, living with children, illness severity, and perceived discrimination [41]. To sum up, there seem to be similarities and associations between risk factors of anxiety, depression, and PTSD with an individuals' disease severity, the level of social support, and mental health. One study from China found lower perceived social support, adverse media reports, and trauma exposure to be consistent risk factors for anxiety, depression, and PTSD [51]. The risk factor for social support is in line with an Israel study that found feeling socially disconnected predicted the presence of PTSD a month post-hospitalization [52].

Besides the similarities observed in terms of an individuals' mental health, a risk factor that seems consistent for various psychological disorders is the female gender, with few studies showing females have 2.2.-2.5 times greater chance of developing psychiatric morbidity after COVID-19 infection [38, 53-56]. A study also found that women were more represented among dead COVID-19 patients with the common mental disorder than men [57]. This is somewhat consistent with a SARS study showing female survivors have a higher risk of anxiety, depression, and stress levels [58]. Besides the female gender, COVID-19 studies found females with a psychiatric diagnosis history [42, 59-62] and those with psychological symptoms a month post-discharge suffered more in all psychopathological domains [62].

Nonetheless, although an increased severity of post-COVID-19 psychiatric symptoms seems to be associated with individuals having a history of the psychiatric disorder [48], even individuals without any history of mental health morbidity (74%) did report symptoms of depression and anxiety post-COVID-19 [54]. This is somewhat in agreement with previous SARS and MERS studies [28, 63], showing a third of patients reporting ≥1 psychological impairment (anxiety, depression, PTSD) > six months post-discharge [63].

3. Psychiatric Sequelae of COVID-19

The long-term psychiatric manifestation of COVID-19 is unclear. However, their prolonged effects could be speculated by understanding COVID-19's effects on the central nervous system (CNS) and looking at evidence from previous SARS and MERS [10]. Some SARS survivors continued having persistent mental issues at 1-year follow-up, despite improving their physical conditions [58, 64]. In one study, a quarter of the SARS survivors experienced significant PTSD symptoms after 30 months [65]. Additionally, some had persistent mental consequences that were clinically significant at up to 4 years of follow-up [37]. Notably, some studies have demonstrated the presence of psychiatric manifestations post-COVID-19 infection. Several prospective studies have shown that symptoms of long COVID-19 can persist up to 3 months [66], 5 months [67], 6 months [68, 69], and even up to 12 months [70, 71] post-hospitalization. This review will focus on post-COVID-19 anxiety, depression, and PTSD.

The rates of anxiety, depression, and PTSD in COVID-19 survivors have surged [72]. A Chinese cohort study showed a significant number of COVID-19 patients six months post-hospitalization had anxiety/depression (23%) and sleep abnormalities (26%) [23]. Another study also showed that 41.3% of patients in Iran and a third of patients in Italy experienced anxiety and depression post-discharge [73, 74]. A Korean study also identified long-term psychological sequelae, accounting for ≥20% of all sequelae [75]. A prospective cohort study in Milan with a sample size of 402 found that at 1-month post-COVID-19, 55.7% of participants scored ≥1 psychopathological dimension (depression, anxiety, PTSD, and OCD), 36.8% in two, 20.6% in three, and 10% in four [48]. Additionally, a single-center study in Spain on COVID-19 survivors found that, out of 179 patients, some had anxiety, depression, and PTSD at 29.6%, 26.8%, and 25.1%, respectively, two months post-COVID-19 [55].

The prevalence of COVID-19 associated psychological manifestations ranges between studies and the various psychological symptoms. For instance, studies are reporting higher rates of PTSD (96.2%) [76], depression (60.2%), and anxiety (55.3%) among hospitalized COVID-19 patients that are clinically stable than normal controls [77]. However, another China study found that the prevalence rate of clinically significant anxiety, depression, and PTSD symptoms for COVID-19 patients post-hospitalization were 10.4%, 19%, and 12.4%, respectively [50, 78]. The difference in rates could be a result of variations in assessment methods and the instruments used to measure these outcomes, time frames for

follow-ups, and the different samples or differences among countries in the implications of cultural or spiritual beliefs to manage the psychological consequences of coronavirus disease [72, 79, 80]. Hence, these findings should not be generalized, and study designs with larger-scale sizes and more comprehensive should be conducted. However, according to a study, the prevalence rate of anxiety and depression is much higher compared to the average general adult population in China [81]. This is in agreement with an Ethiopian study that showed anxiety and depression rates were higher (61.8%, 55.7%) than before (32%,5.73%) the COVID-19 pandemic [46].

4. Probiotics as an Adjunct Treatment

Probiotics belonging to the microbial genera are commonly present in the intestinal tract. It has anti-inflammatory properties, helps maintain gut barrier integrity, and restores intestinal homeostasis and microbial balance [9]. Research studying probiotics' application to prevent and treat COVID-19 is available [82]. Probiotics have been recommended by the guidance (version 5) established by China's National Health Commission and National Administration of Traditional Chinese Medicine to treat severe COVID-19 infections, maintain the balance of intestinal microecology, and prevent secondary bacterial infection. This suggests that first-line medical staff and the Chinese government trust the importance of gut microbiota in COVID-19 disease [83-85].

Regarding COVID-19's psychiatric sequelae, probiotics could be an adjunctive treatment compared to conventional psychotropic medications [9]. Many research and clinical trials have been conducted within the last decade, determining probiotics' effects on mental health, and their efficacy in improving mental illness has been proven in clinical trials [86]. Clinical studies showed that probiotic intervention alleviates anxiety and stress, and improves depressed patients' mental status [87-89]. A survey by Büttiker et al. hypothesized that the homeostatic relationship between host, microbiome, and virome, could be decisive in determining the efficiency of subsequent disease susceptibility, immunological responses, and long-term psychopathological effects impact the CNS, for instance, COVID-19 [90].

The local and systemic production of chemokines, cytokines, and other inflammatory mediators are induced [91]. Coronavirus binds directly to angiotensin-converting enzyme 2 (ACE-2) receptors in the respiratory epithelial cells, potentially resulting in a cytokine storm that causes widespread inflammation, multi-organ damage, and immune-mediated encephalopathy exhibits convulsions and delirium [10, 92]. This cytokine storm results in asurge in T-helper (Th)-1 cytokines, including Tumor Necrosis Factor (TNF)-α, Interleukin (IL)-1β, CCL2, CXCL10, IL-6, and Interferon (IFN)-γ, and Th-2 cytokines, including IL-10, IL-4, and IL-1 receptor antagonists in the serum of COVID-19 patients [62, 93]. Significantly, cytokine dysregulation (notably transforming growth factor-β (TGF-β), TNF-α, IL-1β, IFN-γ, IL-6, and IL-10) are associated with psychiatric disorders [48, 94-99] and are increased in COVID-19 patients [9]. Probiotics possibly reduce inflammation as it has anti-inflammatory

effects that have been shown either via the direct observation of reduced plasma concentration of proinflammatory cytokines or indirectly via the suppression within the kynurenine pathway and restoration of gut permeability, which have been associated with the etiopathology of depression [86]. Kynurenine and its metabolites have essential roles in mediating inflammatory effects relevant to anxiety, mood, and psychotic disorder [100]. A recent meta-analysis revealed that probiotic intervention could decrease the expression of indoleamine 2,3-dioxygenase 1 (IDO); an important enzyme that metabolizes tryptophan to kynurenine in the immune cells and plasma of patients [101]. It is fair to say probiotics could reduce inflammation-induced CNS pathology [9].

Furthermore, there is a possible link between probiotics and their metabolites- short-chain fatty acids (SCFAs)- with COVID-19 and its psychological manifestations. SCFAs are a crucial gut microbial metabolite that is important in signaling along the microbiota-gut-brain (MGB) axis. The MGB axis concept is defined as the bidirectional communication between the gut microbiota and brain, has been verified in both animal and numerous preclinical and clinical studies, underscoring the involvement of MGB in maintaining health and contributing to various neuropsychiatric disorders [86]. Anxiety and depression are some of the neuropsychiatric disorders that have been associated with the MGB axis caused by gut dysbiosis [102-105]. Interestingly, there seem to be gut dysbiosis and a few other similarities when comparing the gut microbiota composition of COVID-19 individuals and individuals with neuropsychiatric disorders. The similarities include increased opportunistic pathogens, decreased bacterial richness and diversity, depletion of beneficial anti-inflammatory symbiotic bacteria, and particularly SCFAs producing bacteria [104]. This is consistent with several studies demonstrating alterations in gut microbiome composition in a few neuropsychiatric disorders [104, 106-112].

SCFAs have several important roles. They maintain the integrity of the blood-brain barrier (BBB) by enhancing the expression of tight-junction proteins [113]. SCFAs deficiency can increase gut permeability of the gut-blood barrier (GBB), leading to the translocation of bacterial products, increasing cytokine levels, and impacting the BBB integrity [104]. Additionally, SCFAs influence neuronal functions and contribute to microglial maturation as they modulate neuronal activity directly via receptors expressed on neurons, interact with microglia, and function in brain immunity [104, 114]. They have an essential role in reducing inflammation in the brain by downregulating microglial activation and hence, the secretion of the proinflammatory cytokines [115]. Besides that, SCFAs modulate the level of neurotransmitters and neurotrophic factors [116]. Neurotransmitters, for instance, serotonin and gamma-aminobutyric acid (GABA), have significant roles in orchestrating the brain's normal functioning; imbalances in these neurotransmitters trigger stress, anxiety, depression, and impaired cognition [9]. The findings of SCFAs depleting are worrying and may significantly impact the brain as their deficiency is associated with chronic brain inflammation related to behavioral and cognitive dysfunctions and many brain pathologies

[104]. With that, probiotics may have the potential to be an adjunct treatment of not just COVID-19 but along with its associated psychological manifestations as it restores and maintains intestinal homeostasis and microbial balance.

5. Conclusion

Although COVID-19 primary vaccination and booster vaccination have been implemented in many countries [12], the psychological manifestations associated with COVID-19 are soaring, and so is its attention gained from the public, clinical, and research sectors. The exact mechanisms driving these physiological manifestations and how long they would last are still unclear. However, the effects are possibly significant, given that some COVID-19 survivors still experience these symptoms months after hospital discharge. The cause has yet to be determined, but it seems to be multifactorial. It could be due to the direct action of coronavirus on the brain and CNS, the indirect effects via systemic inflammatory responses to the virus, or a result of psychological stressors such as being infected, stigma, and the experience of being in the ICU [9]. The female gender and a history of psychiatric disorders seem to be consistent risk factors across several studies. However, huge variation exists. COVID-19 associated neuropsychiatric disorders have been connected to brain inflammation, changes in the MGB axis, and gut microbiota alteration [104]. Therefore, with this connection and the knowledge regarding probiotics, probiotics could be a potential adjunct therapy for preventing and alleviating not just COVID-19 but its associated psychological manifestations [9]. Nonetheless, more comprehensive research is needed to understand the link between psychosocial, biological-physiological, and immunological aspects of COVID-19 and its subsequent psychological manifestations.

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