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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Linking COVID-19 and Parkinson's disease: Targeting the role of Vitamin-D

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ABSTRACT

COVID-19 pandemic has a major effect on world health, particularly on individuals suffering from severe diseases or old aged persons. Various case studies revealed that COVID-19 might increase the progression of Parkinson's disease (PD). Coxsackievirus, dengue virus Epstein-Barr virus, hepatitis C virus, Japanese encephalitis, Western equine encephalomyelitis virus, West Nile virus, and human immunodeficiency virus have all been linked to the development of transient or permanent parkinsonism, owing to the induction of neuroinflammation/hypoxic brain injury with structural/functional damage within the basal ganglia. Coronavirus mainly infects the alveolar cells and may lead to acute respiratory distress syndrome. SARS-CoV-2 invades cells via the ACE2 receptor, which is widely expressed in the central nervous system, where the virus may precipitate or accelerate dementia. SARS-CoV-2 could enter the central nervous system directly by the olfactory/vagus nerves or through the bloodstream. Here, we talked about the importance of this viral infection in terms of the CNS as well as its implications for people with Parkinson's disease; anosmia & olfaction-related impairments in COVID-19 & PD patients. And, also discussed the role of vitamin D to sustain the progression of Parkinson's disease and the COVID-19; regular vitamin D_3 consumption of 2000–5000 IU/day may reduce the risk and severity of COVID-19 in parkinsonian patients.

1. Introduction

According to WHO, the COVID-19 pandemic significantly impacts world health, with 178,202,610 confirmed cases and 3,865,738 deaths as of June 21, 2021. Moreover, even after the virus remains undetectable, several survivors of COVID-19 experience long-term sickness and persistent symptoms [1]. We need to see if COVID-19 is associated with a higher incidence of Parkinson's disease (PD), either right after infection or over time. PD is a progressive neurodegenerative condition that manifests itself in various motor and non-motor symptoms [2]. The process of PD is associated with a distinctive prodrome before the development of main motor symptoms [3]. The loss of the dopaminergic neurons in the midbrain, neuroinflammation, and the development of aggregates of protein such as Lewy bodies, α-synuclein riched in various brain locations are all symptoms of PD [98]. According to genetic studies, familial PD cases are approximately 5%, while roughly 25% of sporadic cases are heritable. Ageing is the most critical risk factor for PD, and studies of genes linked to the disease have revealed a number of cellular dysfunctions [4]. In addition, biomarker studies show that PD patients have chronic systemic inflammation and immunity problems linked to an increased risk of PD. In contrast, the cause(s) of sporadic PD is mostly unclear, bacterial and viral infections linked in some cases [5].

Abbreviations: ACE2R, receptor of angiotensin-converting enzyme 2; ACE2, angiotensin-converting enzyme 2; ARDS, acute respiratory distress syndrome; CSF, cerebrospinal fluid; HBD2, human beta-defensin 2; PD, Parkinson's disease.

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The reproductive number (R_0) indicates the virus's rate of transmission, which is between 3.6 and 4 for SARS-CoV-2, showing strong contamination away from influenza, which has an R_0 of 1.4–1.6 [6,7]. Throughout the infection's pre-symptomatic phase as well as after it has resolved, transmission can occur. This happens as viral shedding peaks early, generally during the commencement of signs, and persists several days after recovery [7–9]. These viruses are 32 KB type genome RNA with up to 25% recombination rate and a glycoprotein crown that can also mutate rapidly [11]. These qualities could explain the virus's adaptability and fluctuations in infectivity throughout time. The virus's glycoprotein attaches to ACE2R (receptor of angiotensin-converting enzyme 2), which are widely expressed in the lungs, causing infection [12,13]. As a result, SARS viruses infect pulmonary alveolar cells, triggering severe widespread alveolar injury, oedema, and inflammation, progressing to acute respiratory distress syndrome (ARDS) in young persons [14]. In children and young adults, the condition is asymptomatic or lesser. Adult symptomatic forms become more severe as they get older. Symptoms can appear between day 2 and day 14 after infection. However, there have been examples of symptoms appearing later. COVID-19 can have symptoms comparable to influenza, such as lethargy, fever, and an unproductive cough [15,16]. Diarrhoea, one of the first symptoms in a smaller number of instances, indicating an infection that started in the gastrointestinal system. Headache and nausea are examples of neurological complaints. Patients may also have a loss of taste and smell that is sporadic or transitory. The majority of infected people (about 80%) have a mild clinical form and recover without problems [17]. Some patients require special care due to respiratory failure and pneumonia, which normally develop within 10–14 days and necessitate a lengthy stay in the hospital. The most important risk factor for presenting a necessary form is age, which begins to rise at 50 [1].

1.1. History: Parkinson's disease and viruses

Stanley Fahn and colleagues revealed a link among the existence of antibodies to OC43 and 229E coronaviruses (causes flu) in the CSF and PD nearly two decades before the current pandemic [18]. Previously coronaviruses were already found to cause neurological symptoms and CSF invasion in children on rare occasions [19,20]. Medical information reveals evidence of a relationship between viral infections and PD [21]. The most recognised case is post-encephalitic PD, which occurred in the course of the encephalitic lethargica wave in 1918, which coincided with the influenza A virus H1N1 (Spanish Flu epidemic) [22]. The cause of encephalitis lethargica, however, is still unknown after more than a century. While a causative function for the influenza A virus H1N1 in the progress of PD after encephalitic lethargica has yet to be shown, there is evidence of a link between virus influenza A infection and the temporary PD development [23,24]. Many people who survived the avian flu developed PD [25]. New research suggests that the hepatitis C virus is neurotropic and can replicate in the CNS. Parkinsonism is infrequently seen in HCV patients. Patients with hepatitis C virus had a considerably increased chance of getting PD, according to Tsai et al., who conducted a large countrywide population-based study [26]. Cognitive impairment, tiredness, and sadness are all common symptoms of chronic hepatitis C virus infection. Recent findings suggest a molecular mimicry pathway between herpes simplex virus 1 and α-synuclein in the membranes of SnPc dopaminergic neurons. When PD patients were compared to healthy controls, there was a difference in the level of autoantibodies that recognised herpes simplex virus 1. The antibodies were able to cross-react with the homologous α-synuclein epitope, suggesting that they could promote α-synuclein aggregation [25]. These findings imply that herpes simplex virus 1 may have a role in activating an immunological response in PD, leading to the death of dopaminergic neurons. The dengue virus is a single-stranded enclosed RNA virus that belongs to the flavivirus family. The disease is spread by Aedes mosquitoes. The symptoms of dengue infection can range from a moderate viral fever to dengue hemorrhagic fever and shock. It is also a multisystem disease with a wide range of unusual symptoms [27]. One example is neurological symptoms. Meningoencephalitis, Acute Disseminated Encephalomyelitis, Transverse Myelitis, and Guillain–Barre Syndrome are a few of them.

Coxsackie, human immunodeficiency, Western equine encephalomyelitis, and Japanese encephalitis virus are linked to the progress of temporary or permanent PD, mostly due to neuroinflammation induction or brain damage due to hypoxia (Table 1). Furthermore, conflicting research advises that previous Epstein-Barr, hepatitis C, herpes simplex 1, influenza A, and varicella-zoster viral infections can raise the likelihood of getting PD in the long run (Fig. 1). After finding the genetic variants associated with the pathogenesis of PD, the involvement of “environmental” aspects serving as extrinsic stimulators towards the neurodegeneration in vulnerable persons has become more recognised [28,29].

2. Covid-19 impact on Parkinson's disease

The world appears to have come to a virtual halt in recent months. Several nations have made strenuous efforts to decline the spread of the virus SARS-CoV-2 as it remains spreading worldwide. Social alienation is one of them, as is a complete social and economic lockdown in some countries. The impact of the COVID-19 catastrophe on the existence of the most vulnerable peoples, medical services, and the global economy is palpable. Here, special worries about the elevated susceptibility of people with prolonged diseases include neurological illnesses like PD [30]. Undoubtedly, PD is common in older, and it may wreak havoc on respiration, as evidenced by the greater risk of pneumonia seen in individuals with severe PD. A PD diagnosis may contribute to greater breathing problems or an adverse consequence following a COVID-19 infection. The “instant” effects of SARS-CoV-2 infection on parkinsonian persons have been widely discussed, including in webinars and educational webpages produced by patient organisations all around the world. COVID-19, on the other hand, has the potential to have far-reaching consequences for PD patients [31]. Here, we will look at some of the less visible but possibly deadly effects of the COVID-19 epidemic on PD patients. More particularly, how preventive social actions to reduce the danger of infection have radically altered the lifestyle of many victims. We also discuss how this situation is already resulting in new programs that provide encouragement and guidance to patients and their families. The SARS-CoV-2 outbreak has drastically altered patients' daily activities in a relatively short period. Such sudden change necessitates a dynamic adjustment to the changed situations, a psychological operation that relies on adequate dopaminergic function. Many parkinsonian patients exhibit cognitive and motor inconsistency in response to the depletion of dopamine in the nigrostriatal region, which is the disease's pathophysiological substrate [32,33]. Moreover, the adaptation dependent on dopamine is a need for effective coping. Its absence gives rise to loss of self-control & a greater risk of psychological problems such as anxiety [34]. This could clarify why stress-linked psychological problems like anxiety & depression are widespread in parkinsonian patients, affecting patients up to 30–40%, even when they are not in crisis [35]. As a result, the parkinsonian pathophysiology sets patients at higher risk of extreme stress. Progression of this condition might be a part of the COVID-19 pandemic's many hidden miseries. Notably, higher

Table 1
Pathways linked with virus-induced PD pathogenesis.

Injury type	Pathways involved
Direct neuronal injury Indirect neuronal injury	• Virus affinity towards ganglia, multiplication, and lysis of neurons • Stimulation of microglia; T cell reaction • Hypoxia • Hypercytokinemia and vascular integrity decline

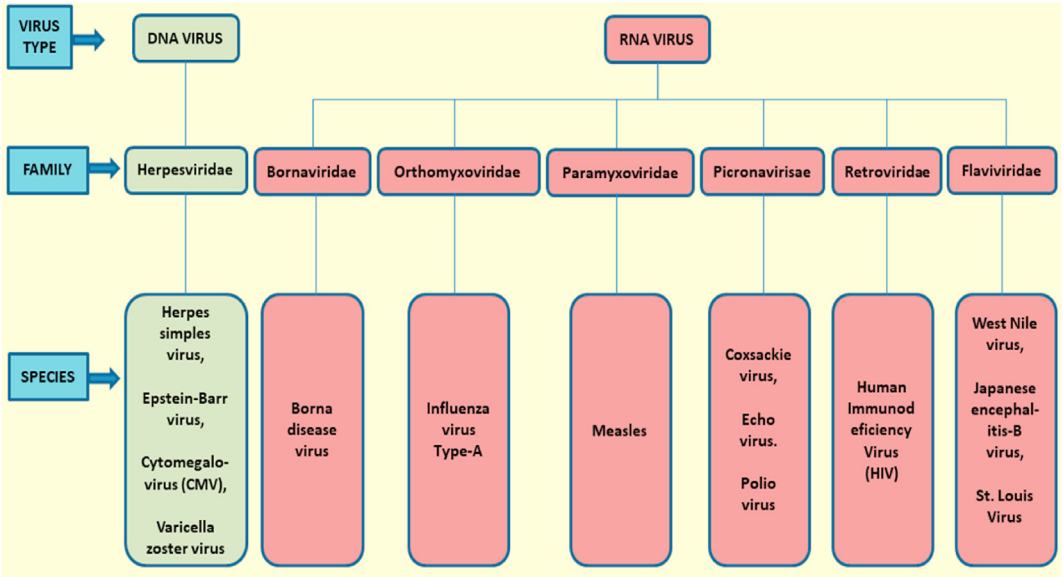

Fig. 1. Parkinson's disease associated viruses.

stressful situations during the COVID-19 pandemic might have many short- and long-term negative repercussions for people with PD. Firstly, increasing psychological stress can exacerbate numerous motor functions such as tremors, dyskinesias, and gait freezing while decreasing the efficiency of the dopaminergic medicaments [36–38]. Second, greater stress has the potential to reveal a hidden hypokinetic stiff condition by diminishing compensating processes [39,40]. During the pandemic, this might contribute to an increment in the number of diagnoses of PD. In a year's time, it could be interesting to compare the incidence of PD amidst the epidemic to the previous year. Third, experiments on animals have found that extended bouts of prolonged stress can hasten the death of dopaminergic cells due to toxins [41]. Because there is no similar research in human patients, it is currently unknown if persistent stress can increase the progression of PD. Surprisingly, some variables defend against stress's negative consequences. This is referred to as "resilience," which is defined as the capability to preserve or rapidly regain mental health in the face of difficulty. Personal attributes like creativity, optimism, intelligence, and a sense of social care and the environmental connection, are all linked to resilience [42]. The present situation provides an opportunity to examine who copes better with the present circumstances versus those who have the most difficulty and the factors that influence these variations. It is also worth noting that particular treatments for stress reduction, such as mindfulness-based programmes, are available. Mindfulness has been found in many recent studies to decrease anxiety and depression and enhance motor functions [43]. These classes are normally provided in patient groups, although they might be available online. These web-based alternatives may also help alleviate feelings of isolation, which is another unintended result of the current pandemic. Children recommend to leave visiting their PD-affected parents if possible, and grandkids should be at a distance. Perhaps social interactions as a result of home-based nursing care have decreased [30]. Digital alternatives are critical for reducing feelings of isolation and providing peace and happiness to PD patients confined within their homes.

2.1. Parkinson's disease vulnerability and Covid-19

Jon Stoessl et al. write in a recent editorial focused on movement disorders around the world during COVID-19 that there is no clinical evidence with movement disorders at higher risk of coronavirus infection than others of the same age and comorbidity [44]. Fasano et al. undertook a single-centre case-control study assessing clinical predictors of COVID-19 infection and outcome in a reasonably unselected and big homogeneous cohort of PD patients from one of Milan's largest tertiary facilities to answer rising issues on this topic. They found 105 PD patients, 32 confirmed COVID-19 cases, and 73 suspected COVID-19 cases [45]. COVID-19 risk, morbidity, and mortality in patients with mild to moderate PD do not differ from the normal population, according to their findings.

The existing COVID-19 epidemic presents a chance to test the theory that virus invasion might cause dementia. SARS-CoV-1, a pathogenic homolog of SARS-CoV-2, invades the brain via ACE2 and may be neurotropic as well. SARS-CoV-2 too accesses cells through the ACE2R [46], which is present in the CNS, along with the nigrostriatal region, and here the virus may cause or exacerbate degeneration of the neurons [47–49]. SARS-CoV-2 could enter the CNS via the bloodstream & the olfactory/vagus nerves. Virus invasion could lead to cytotoxic protein aggregation, especially α-synuclein. The data in animal studies suggesting virus invasion can

cause CNS α-synucleinopathies supports this notion [50]. The different neuronal groups are prone to deterioration in different ways, and the dopaminergic neurons are particularly sensitive due to their inherent features. High cellular metabolic requirements from extremely arborised axons & defective proteostasis due to larger axons can encourage α-synuclein accumulation to lead to a targeted threat to noncellular self-governing factors that influence α-synuclein placings, like environmental neurotoxins and neuroinflammation. Increased neuronal production of α-synuclein following viral infection of West Nile suggests that it might work as a natural antiviral component inside neurons [51]. SARS-CoV-1 and West Nile virus are quite similar since both are encapsulated, positive-sense RNA, single-stranded viruses with similar viral entrance and multiplication strategies. As a result, SARS-CoV-2 infection may cause identical α-synuclein overexpression.

A marginal inflammatory reaction, as seen in COVID-19, could worsen the implications of this diseased phase. In a peripheral H5N1 influenza rat model, researchers discovered chronic microglial stimulation in the CNS and aberrant phosphorylation of α-synuclein, as well as dopaminergic neuronal loss in the nigrostriatal region [52]. Antiviral α-synuclein buildup after the contamination by SARS-CoV-2 could exacerbate previous cell-autonomous threat, resulting in α-synuclein transmission & extensive degradation of the neurons. Prospective longitudinal research in COVID-19 sufferers may be able to strengthen this theory. SARS-CoV-2 infection may similarly impair α-synuclein elimination. H1N1 influenza virus can inhibit protein elimination, making contaminated host cells unwilling to counteract α-synuclein buildup [53]. Proteins from SARS-CoV-2 can bind to human protein transportation molecules. ORF8, one of these proteins, is associated with endoplasmic reticulum control. Unless SARS-CoV-2 may disrupt proteostasis by attaching to ORF8 and causing abnormal endoplasmic reticulum protein transportation, α-synuclein could clump together uncontrollably [54]. Finally, the SARS-CoV-2 neuroinvasion's bioenergetic stress may be insurmountable for some neurons. Nigrostriatal dopaminergic neurons have high cellular energy demands to support heightened basal oxidative mitochondrial phosphorylation, high axon terminal density, and extensive axonal arborisation. Given this high metabolic energy demand, the cellular stress caused by COVID-19 infection could push these sensitive neurons over the edge of neurodegeneration if extracellular energy reserves are not present.

2.2. Possibility of a post-viral Parkinson's disease

Some research has already suggested a connection between COVID-19 and neurological diseases, including PD [55]. These conclusions are based on a number of findings: coronaviruses' potential to penetrate the CNS via the sinuses, resulting in neurodegeneration, as demonstrated in animal experiments [56]; a typical prodromal characteristic of PD is hyposmia and has been widely described in COVID-19 subjects lacking nasal obstruction [57]; in COVID-19, lesions of the basal ganglia may arise as a result of a thromboembolic encephalopathy [58]; the existence of antibodies against various coronaviruses which gives rise to the flu in the PD subjects compared to fit volunteers shows that virus invasion may play a role in the aetiology of the disease [18]; there have been reports that ACE2 is present in numerous systems in the body, however as mentioned above, more neuropathological research is needed. Because this protein activates interferons, it will be necessary to look at people who have CNS encephalitis or inflammation [47]; recent findings of fainting without any aberrant rhythms on cardio equipment investigation show a function of neurally-mediated fainting versus orthostasis, emphasised the role of these studies for PD subjects frequently experiencing autonomous dysfunction [59]; A case study record of a subject that had myoclonus and an acute although apparently recoverable hypokinetic stiff condition, and DaTscan revealing hyposmia and decreased dopaminergic loading in the putamen [60]; the angiotensin system, that has been linked with COVID-19 development, could have a role in the neural inflammation and degeneration pathways seen in PD [61]; proteins from SARS-CoV-2 may engage to specific proteins implicated in biochemical processes that cause protein homeostasis to fail [54], resulting in the accumulation of misfolded proteins (Fig. 2); the production of cytokines may stimulate local immune cells within CNS & allow them to infiltrate causing brain cell injury. Activated T and microglial cells can kill astrocytes, neurons, & vascular-type cells [62,63]. This can happen via the cell selection that identifies important antigens from the infections, via the common excitation of cytotoxic cells that identify certain antigens, such as α-synuclein derived autoantigens that have a link to PD, dementia (Lewy Body), atrophy & sclerosis. Elevated concentrations of TNF and IL-1-ß are linked to a higher risk of PD, whereas anti-TNF biosimilars and NSAIDs lower the risk [64]. COVID-19 is now being studied with anti-TNF biosimilars.

A lot of laboratory studies have explicitly addressed this problem in light of the potential observation data noted above, which implies a link between the virus invasion and PD. Jang et al. investigated whether a neurotropic Type H5N1 influenza A virus may cause parkinsonism in mice [22]. They discovered how this influenza virus strain attacked neurons immediately, with a preference for pathways involved in PD. Following recovery from the virus invasion, the mice developed ataxia, bradykinesia, convulsion, dopaminergic neuronal loss, primary neuron inflammation, microgliosis, and an increased expression of α-synuclein [65].

3. Anosmia and olfactory system impairment associated with Covid-19 and Parkinson's disease

The olfactory epithelium is hypersensitive to changes in the external environment and vulnerable to chemical sensation loss and irritation [66]. In the analysis of odour data, the olfactory bulb acts as a bridge between the nasal epithelium and the brain. Olfaction depends on the management of neurogenesis mediated by neural stem cells in the olfactory bulb and the epithelium. While neuroinflammation suppresses neurogenesis in the olfactory bulb and epithelium, olfactory deficits caused by neuroinflammation provide a pathological connection between PD and COVID-19 [67]. SARS-CoV-2 infection via the olfactory tube links to a decrease in the number of neural stem cells known as globose & horizontal basal cells responsible for regenerating olfactory epithelium receptors.

Furthermore, SARS-CoV-2 linked neuroinflammation throughout the olfactory bulb might be linked to neurogenesis degradation at the stage of abnormalities in neural stem cell proliferation and the differentiation of dopaminergic neurons in the vicinity of the glomerular layer, identical to the pathophysiology seen in PD. Anosmia may be due to the inability to replace deteriorating olfactory receptors in the epithelium and dopaminergic neuronal cells in the bulb in PD and COVID-19 subjects [68]. COVID-19 management should consider the supply of pro neurogenic medications and therapies towards dopamine changes to protect and overcome this hurdle. In addition, more research is needed to understand neurogenesis as well as the pathways that overlap with other neurological illnesses in the COVID-19 subjects' brains [69]. Upper respiratory tract illness is thought to be linked with olfactory bulb impairment in general. However, independent of the beginning of respiratory dysfunctioning, anosmia caused by olfactory bulb disease has been described in most COVID-19 occurrences. As a result, the WHO has identified anosmia as a separate primary

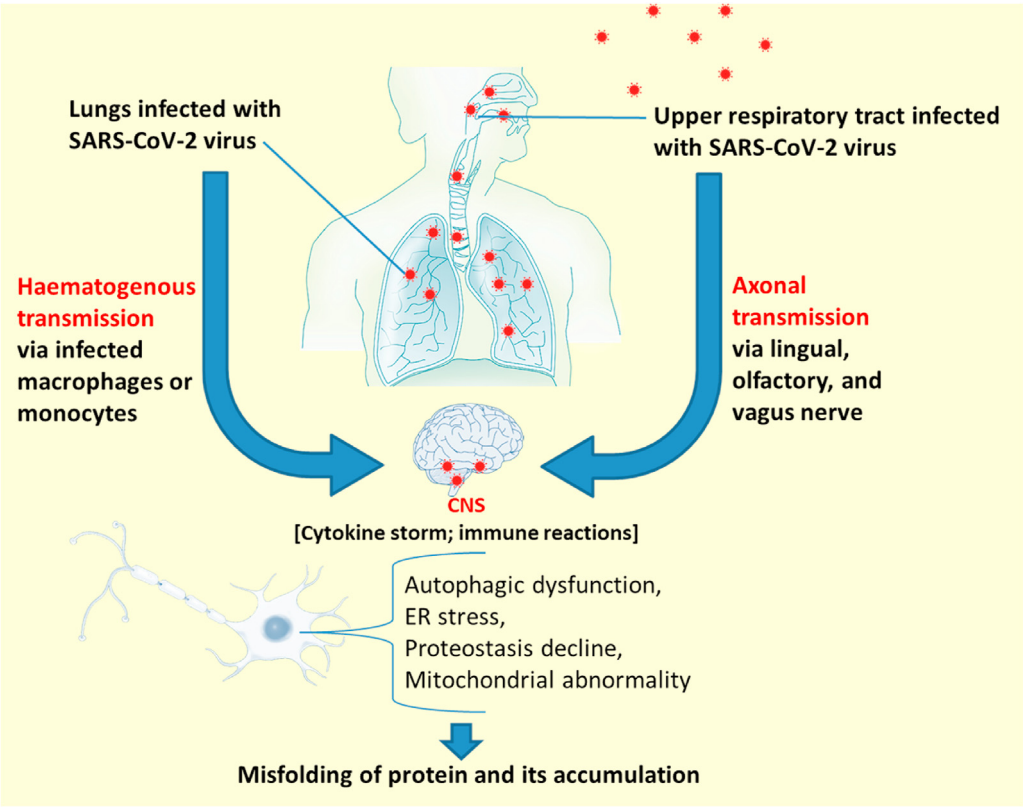

Fig. 2. SARS-CoV-2 entry routes into CNS and the consequences.

indication of SARS-CoV-2 [70–72]. Anosmia was also long known as PD's pre-clinical indicator. It is worth noting that, unlike other nerve cells in human brains, sensory neurons which exhibit the olfactory receptors crucial for odour are constantly renews entire life. Through the development of axon coupling within the glomerular layer, the sensory nerves of the nasal epithelium transmit excitable connections with the granular cell layer's inhibitory interneurons of the bulb in the olfaction system [73]. Notably, during adulthood, olfactory receptors within the nasal epithelium are reactive for juvenile neuron indicators like doublecortin. Matured neurogenesis leads to the formation of GABAergic interneurons (inhibitory type) in the granular cell layer of the olfactory bulb. In contrast, the inhibitory interneurons have a crucial part in the synaptic transmission of sensory nerve cells [74]. Furthermore, sensory neurons' axon processing in the glomerular layer appears to be vital in olfactory categorisation. The continuous production of dopaminergic nerve cells occurs through neural stem cells, and neural progenitors seem crucial [75]. Thus, in the physiological environment, the control of olfactory neurogenesis gives a pathway towards smell sensation. It is worth noting that dopamine deficiency in the matured brain seems to affect the mitotic cells number in the forebrain of people with PD and experimental animals. In autopsy brain samples of PD non-dementia sufferers, a weak connection was found among the duration of illness and the amount of Musashi-positive neural stem cells within the subventricular region [76]. Furthermore, it is confirmed that the autopsy brain having Lewy body has a lower amount of progenitor cells and Musashi-positive neural stem cells within the subventricular region. Furthermore, decreased neurogenesis inside the olfactory bulb has been shown in numerous parkinsonian animal models [77]. Inflammation in the neurons tends to affect neurogenesis in many neurodegenerative diseases, such as PD [78]. The adult brain's neurogenic capacity stops when dopamine production reduces. Adult neurogenesis appears to be aided by blocking neuroinflammation; consequently, the replenishing of the olfactory bulb's dopaminergic neurons compensation and odour sensation restores in PD.

4. Vitamin-D sustains Covid-19 and Parkinson's disease progression

Vitamin D receptors are widely distributed all over the body, and it is thought to have a role in various key activities and diseases. Vitamin D imbalance has a link to various diseases, like cardiovascular disease, hypertension, cognitive decline, diabetes, inflammation, immunological dysregulation, some cancers, and osteoporosis. Surprisingly, the majority of these diseases have a link with growing older [79,80]. The causality direction in these interactions is still unknown. On the other hand, many studies have demonstrated that reaching and ensuring good vitamin D levels can assist clinical outcomes and/or lower the risk of developing common diseases. Past researches on vitamin D and its effect on disease, particularly respiratory tract disorders such as influenza, has yielded inconsistent results [81]. There are few large-scale, randomised controlled trials in the contemporary environment, which is ruled by minor research with specific populations. This could explain why there is not yet an agreement on vitamin D's antiviral properties. Various features of vitamin D, findings across animals & humans in vitro & in vivo research imply that antiviral advantages are possible [82,83]. Vitamin D has a number of functions, mostly in innate immunity.

Activated vitamin D promotes human beta-defensin 2 (HBD2) peptide and cathelicidin expression in combination with toll-like receptors [84]. The bacterial cell membrane disruption occurs due

to cathelicidin (LL-37). This feature is believed to apply to viruses, especially encapsulated viruses, and could affect viral entrance. 1-OHase levels are high in lung epithelial cells; increasing cathelicidin throughout the nasal passages may protect from respiratory diseases. Some inflammatory cells may be attracted to HBD2 as a chemoattractant [85]. Vitamin D could also assist the transfer of inflammatory mediators to the infection site by increasing capillary permeability. It is also hypothesised to be involved in the management of various cell junction types. The body's first defence mechanism against infections is strong physical barriers created by endothelial cell junctions. In addition, vitamin D and the stimulation of its receptors produce unique natural killer (NK) T cells, which serve as a link to adaptive immunity [83]. Vitamin D could have antioxidant qualities and also the potential to lengthen telomeres and stabilise DNA. Vitamin D also has a link to improved immunity against vaccinations; as COVID-19 vaccines are ultimately created, this could be a key element to consider [86]. As stated earlier, previous research on vitamin D's antiviral capabilities has yielded inconsistent results. However, several studies have linked increased vitamin D levels to a decline in the onset, duration, and severity of sickness. Bacterial and viral pneumonia, dengue fever, chronic hepatitis B, influenza, and rotavirus were among the viruses considered in some of these initiatives. Vitamin D's effect on the ACE2R has been controversial. Several studies have suggested that the ACE2 receptor may be directly down-regulated by the vitamin D and its receptor, lowering the probability of COVID-19 infection [87]. Others, on the other hand, believe that vitamin D stimulates the production of ACE2. Although this may assist in minimising the subsequent consequences of COVID-19, it may also increase the chance of infection. More evidence on the link among vitamin D & ACE2R and how this may affect COVID-19 incidence and pathogenesis are required [88].

Vitamin D may serve a role in the development and progression of PD, in addition to its potent antiviral characteristics. Several studies have revealed that people with PD, particularly in the premature PD, have decreased 25-Hydroxy Vitamin D3 baseline levels compared to control subjects; low concentrations of 25-Hydroxy Vitamin D3 have a link to higher incidence and severity of the disease [89]. It is uncertain whether vitamin D or a deficiency contributes to the development and progression of PD. However, vitamin D receptors are present on dopaminergic nerve cells in the pars compacta region, degraded in PD. Vitamin D receptors have incredible activity for the Nrf2-KEAP (an oxidative stress pathway), which stimulates calcium pumps & channels and antioxidant synthesis [90]. Vitamin D insufficiency has a link to the breakdown of the cell signals and pathways, which have a link to idiopathic PD. Vitamin D supplementation has been suggested as a possible solution, particularly for those with low baseline levels, offering protection to dopaminergic nerve cells and receptors. This neuroprotective potential has been confirmed by recent studies. As we know, no clinical trials on vitamin D's ability to preserve the nerve cells have been completed or are currently being conducted in humans. The effects of vitamin D may be visible in all stages of PD, including both types of symptoms that are motor and non-motor [91]. Sleeman et al., for example, found that age, motor score, dopaminergic drug dose, and baseline blood 25-Hydroxy Vitamin D3 levels all predicted motor disability intensity at 36 months, with lower D3 levels linked with worsening development [92]. Falls may also be greatly prevalent in PD persons that have balance issues, postural instability, and reduced motor function. Vitamin D deficiency disrupts calcium homeostasis, increasing the chances of bone fractures. A serious fall or fracture can significantly decrease a patient's quality of life if they have Parkinson's disease. Furthermore, Peterson et al. found that better neuropsychiatric results were linked to high levels of 25-Hydroxy Vitamin D3 in the blood among Patients with PD without severe dementia [93]. This was particularly true when it came to verbal fluency and memorisation. Vitamin D may also help to reduce anxiety, according to the group. Vitamin D supplementation may lower the chances of major injury from falls, enhance bone health, recover cognitive power, and reduce stress in PD patients, resulting in higher life quality and a slow progression of the disease [94].

Advance medical planning is required in the COVID-19 pandemic scenario to accomplish patient care goals while avoiding significantly undesirable procedures, including catheterisation, ventilation, and ICU admissions [95]. During regular consultations, healthcare providers should advance medical planning with PD patients and their families and discuss treatment goals. If a PD patient acquires COVID-19 and needs to be admitted to the hospital, the advance directive must precede the patient [96]. In some nations, advanced medical planning forms may provide a free text field where practitioners can record the expressed goals of the patient and family away from the level of care terms [97].

5. Future prospects

A number of recent papers go into great detail into the COVID-19 epidemic's impact on the common public. Furthermore, it is envisaged that antibody assays for universal immunity testing in large groups will be available shortly, permitting us to estimate the spread of infection and fatality rate more correctly. As coronavirus is a deadly virus that is a key concern all over the world, much more research work is needed to know about the virus transformation from one strain to another with developed antibiotic resistance.

6. Conclusion

The COVID-19 pandemic has triggered an unparalleled global disaster for the elderly. Symptoms are varied, possibly due to pre-existing illnesses and in part due to diverse mechanisms of viral entry and the existence of T cells that are reactive to previous coronavirus infections. On the other hand, this worldwide crisis may substantially impact our patients with Parkinson's disease and other movement disorders, leading to greater adoption of telemedicine consultations and assessments. Vitamin D can help out the patients with COVID-19 and PD. Vitamin D_3 supplementation may assist in improving the motor and non-motor symptoms of PD, therefore enhancing the quality of life. Although more research is needed, daily vitamin D_3 supplementation of 2000–5000 IU/day in people with PD may help to reduce the risk and severity of COVID-19.

Declaration of competing interest

None.

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