The microvascular hypothesis underlying neurologic manifestations of long COVID-19 and possible therapeutic strategies
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With the ongoing distribution of the coronavirus disease (COVID) vaccines, the pandemic of our age is ending, leaving the world to deal with its well-documented aftereffects. Long COVID comprises a variety of symptoms, of which the neurological component prevails. The most permeating theory on the genesis of these symptoms builds upon the development of microvascular dysfunction similar to that seen in numerous vascular diseases such as diabetes. This can occur through the peripheral activation of angiotensin-converting enzyme 2 receptors, or through exacerbations of pro-inflammatory cytokines that can remain in circulation even after the infection diminishes. Several drugs have been identified to act on the neurovascular unit to promote repair, such as gliptins, and others. They also succeeded in improving neurologic outcome in diabetic patients. The repurposing of such drugs for treatment of long COVID-19 can possibly shorten the time to recovery of long COVID-19 syndrome. Cardiovasc Endocrinol Metab 10: 193–203 Copyright © 2021 The Author(s). Published by Wolters Kluwer Health, Inc.

Keywords: long COVID-19, microvascular dysfunction, neurologic manifestations, neurovascular regenerative drugs

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Background
The COVID-19 pandemic caused by the SARS-CoV-2 virus, which started in Wuhan China [1,2], has to date affected 182 million people and caused 3.93 million deaths worldwide [3]. Early on in the disease vulnerable groups, such as the obese, diabetic and elderly, were at high risk of severe disease, the need for hospitalizations, or even death [4]. Preexisting cardiovascular disease was one of the earliest identified risk factors for a poor COVID outcome. Soon after, the underlying vascular inflammation, endothelial injury, and IL-6 mediated cytokine effects were identified [5–8].

A year into the pandemic, postinfection sequelae and chronicity of COVID-19 is a major problem [9]. Long COVID syndrome (symptoms beyond 3 weeks) is a multi-system syndrome that requires the rehabilitation of patients on physical, cognitive, psychological, social, and vocational levels [10]. The symptoms of long COVID include fatigue, loss of taste and smell, headache, confusion, ‘brain fog’, autonomic neuropathy, muscle weakness, pain, physical disability, dyspnea, chest pain, myocarditis, and postorthostatic tachycardia syndrome [11]. These lingering symptoms may further complicate at risk groups especially diabetics, as it may impact disease management. The pathophysiology of long COVID syndrome is theorized as a combination of vasculitis and cytokine effects [5,12]. Additionally, this chronic postinfection inflammation is suggested to have accelerated neurodegenerative processes, and therefore neurorehabilitation is needed [13–15].

It is hypothesized that a connection exists between the neurological manifestations of COVID-19 and blood-brain barrier (BBB) dysfunction which is a result of preexisting vascular pathologies (diabetes, aging, and hypertension) that facilitate infiltration of the virus and pro-inflammatory cytokines into the central nervous system (CNS) resulting in neuroinflammation and neurological symptoms [16,17].

This evidence suggests the role of targeted therapeutic anti-microangiopathic strategies for the treatment of long COVID neurological symptoms [17]. These would include Glitpions, which are part of a class of oral hypoglycemic that function as dipeptidyl peptidase-4 inhibitors [18], peroxisome proliferator-activated receptors (PPARs) [19], and natural remedies such as Ginkgo Biloba [20]. Low-cost early supportive interventions in the form of manual treatments to improve central lymphatic drainage have also been suggested.

It is hypothesized that most of Long COVID-19 manifestations, which are mainly neurologic in nature, are caused by underlying microangiopathic mechanisms. In this review, we explore the potential role of regenerative...
microangiopathic therapies to alleviate the burden of long COVID symptoms and promote the rehabilitation of patients’ at the physical, cognitive, social, and vocational levels.

**Long COVID-19, a wide spectrum of neurologic manifestations**

**Microvascular hypothesis for persistent anosmia and dysgeusia**

**Acute anosmia in COVID-19 and underlying theories**

Anosmia is one of the various neurological manifestations described in a considerable number of case reports. It is not new that critically ill patients frequently experience physical, cognitive, and psychological limitations over a long interval after hospital discharge. Long-term follow-up on patients revealed that 10% experienced persistent problems including anosmia, hyposmia, parosmia, and phantosmia in addition to dysgeusia and reduced chemesthesis [21].

Some of the suggested theories and hypotheses were the inflammatory theory, the conductive or obstructive theory, the local olfactory epithelial disruption theory, the retrograde propagation theory, and the microvascular theory, which is to be mentioned in detail later in our study.

Conductive or obstructive anosmia was reported by Cain et al. [22] in the pre-COVID era to contribute to 14–30% of patients with anosmia due to mucosal congestion and edema of the nasal epithelium. Disruption of olfactory epithelium following local infection is another proposed mechanism that was thought to contribute to anosmia with some viruses such as HCoV-229E.

Retrograde propagation to higher-order neurons in the olfactory pathway with the human herpesvirus, which is to be mentioned later in our study.

**Inflammation theory** Virally infected olfactory sensory neurons show upregulation of nitric oxide and major histocompatibility complex. Further studies demonstrated olfactory bulb expression of cytokines of the innate immunity such as IL-1, IL-12, and tumor necrosis factor. These cytokines decrease the viral titers in the olfactory bulb and are in direct correlation with the rapid recruitment of CD4+, CD8+, and natural killer cells [23].

**Increasing evidence of persistent anosmia**

Several series are increasingly reporting the persistence of anosmia as one of the main features of long COVID-19. Sampaio Rocha-Filho and Voss described a COVID-19 positive 40-year-old lady with a history of migraines, presenting with diarrhea, nonproductive cough, myalgia and fatigue, sudden onset of anosmia, facial pain in the bilateral malar region, and bilateral frontotemporal pulsating continuous and severe headache. The headache, together with the anosmia persisted despite the resolution of other symptoms [24]. Other reports of persistent anosmia in COVID-19 were reported in Table 1 [24–33].

**Postviral anosmia, is it exclusive to COVID-19?**

Postviral olfactory dysfunction (PVOD) was not only reported in COVID-19, but in other viruses too, such as influenza A, herpesviruses, poliovirus, paramyxoviruses, vesicular stomatitis, rabies, parainfluenza, adenoviruses, Japanese encephalitis, West Nile, chikungunya, La Crosse, mouse hepatitis, and bunyaviruses [34]. However, Welge-Lüssen et al. [35] reported common cold and influenza to be the most commonly associated with PVOD, with a higher incidence in women and a prevalence ranging from 11% to 40%.

Suzuki et al. conducted a study on 24 patients, 10 of which showed rhinoviruses in their nasal secretions by electrophoresis, and four were confirmed by nucleotide sequences. Out of those four, one had anosmia while another had dysosmia. Although the acoustic rhinometry of the four cases showed an improvement, no improvement in olfactory testing was detected after 4, 8, 11, and 24 weeks [36].

Hwang depicted a case of a 27-year-old female with SARS, complaining of anosmia of acute onset, which persisted for more than 2 years. Peripheral neuropathy was reported during the convalescent stage, but persistent anosmia was not reported before. Hence, olfactory neuropathy is the suggested etiology, being a special type of neuropathy caused by coronavirus [37].

Persistent anosmia for more than 6 months following HCoV-229E infection has been also reported in 2007 by Suzuki et al. [36].

**Microvascular theory**

Despite the previous pieces of evidence on the involvement of direct viral invasion in inducing postviral anosmia, microvascular injury of olfactory neurons and bulbs remains the strongest proposed mechanism, as evidenced by MRI brain scans of 13 autopsies, 10 of which showed abnormalities. Specimens studied by Lee et al. showed punctate hyperintensities, interpreted as foci of microvascular injury and fibrinogen leakage. Punctate hypointensities were also detected reflecting microhemorrhages.

Furthermore, 19 matched brain samples were also studied in the National Institute of Neurological Disorders and Stroke. In addition to the aforementioned findings, 13 showed perivascular infiltrates, six were found to have acute ischemic hypoxic neurons and five showed activated microglia next to neurons, suggestive of neuronophagia [38].

The microvascular pathogenesis is also emphasized by Aragão et al. [34] who stated that olfactory bulbs showing abnormal enhancement in MRI brain scans of five adult patients are probably the result of micro bleeding.

The long-lasting effects of COVID-19 were proven to be due to vascular abnormalities, namely hypercoagulability and cytokine-mediated injury ending in
Table 1. Summary of reports of anosmia/parosmia of long COVID-19

| Country | Reference number in text | Name of first author | Number of cases | Results |
|---------|--------------------------|----------------------|-----------------|---------|
| Greece  | [25]                     | Konstantinidis et al.| 79              | 29 patients (36.7%) suffered from loss of smell and taste functions. Some patients had slow recovery. The article suggests that CNS affection via the olfactory bulb is the underlying cause of persistent anosmia as evidenced by MRI olfactory bulb changes in previous literature. |
| Brazil  | [24]                     | Rocha-Filho et al.   | A COVID-19 positive case with persistent headache and anosmia. | The article suggests that CNS affection via the olfactory bulb is the underlying cause of persistent anosmia as evidenced by MRI olfactory bulb changes in previous literature. |
| Mexico  | [26]                     | Galván-Tejada et al. | 219             | Persistent anosmia by 5.8% after a median of 60 days follow up. 10% suffered from persistent anosmia, hyposmia, parosmia and phantosmia, dysgeusia, and reduced chemesthesis. |
| UK      | [33]                     | Hopkins et al.       | 382             | Multinational in 24% rate of persistence of olfactory or gustatory symptoms more than 7 months after the onset of symptoms, with 23.3% and 11.5% of patients with persistent symptoms reporting complete anosmia or ageusia. Complete recovery in 46% of patients. Persistent olfactory dysfunction in 23% of cases. OB atrophy in 88% of cases. Bilateral OB height in cases was significantly lower compared to controls. These findings are consistent with persistent loss of smell in these cases. 17.3% developed persistent anosmia. |
| France  | [29]                     | De Melo et al.       | 89              | Complete recovery in 15% of patients. Persistent olfactory dysfunction in 23% of cases. OB atrophy in 88% of cases. Bilateral OB height in cases was significantly lower compared to controls. These findings are consistent with persistent loss of smell in these cases. 17.3% developed persistent anosmia. |
| Italy   | [30]                     | Vaira et al.         | 150             | Complete recovery in 15% of patients. Persistent olfactory dysfunction in 23% of cases. OB atrophy in 88% of cases. Bilateral OB height in cases was significantly lower compared to controls. These findings are consistent with persistent loss of smell in these cases. 17.3% developed persistent anosmia. |
| USA     | [31]                     | Yan et al.           | 316             | Complete recovery in 46% of patients. Persistent olfactory dysfunction in 23% of cases. OB atrophy in 88% of cases. Bilateral OB height in cases was significantly lower compared to controls. These findings are consistent with persistent loss of smell in these cases. 17.3% developed persistent anosmia. |
| Greece  | [32]                     | Tsigouris et al.     | 8               | Complete recovery in 46% of patients. Persistent olfactory dysfunction in 23% of cases. OB atrophy in 88% of cases. Bilateral OB height in cases was significantly lower compared to controls. These findings are consistent with persistent loss of smell in these cases. 17.3% developed persistent anosmia. |

CNS, central nervous system; COVID-19, coronavirus disease; OB: olfactory bulb.

vascular endothelial damage, microvascular thrombosis, and ischemia, as suggested by Gavriatopoulou et al., Lang et al., Jaunmuktane et al., MacLean et al., and AbdelMassih et al. [5,17,39–41].

Moreover, the reported cases of olfactory and gustatory dysfunction associated with other vascular diseases such as diabetes, Churg–Strauss syndrome, and giant cell arteritis (GCA) as well as multiple sclerosis back up the microvascular injury theory.

A systematic review and meta-analysis conducted by Kim et al. concluded an overall odds that people with diabetes are 1.58 times more likely to have olfactory dysfunction than non-diabetics. They also stated that the majority of included studies concluded that peripheral neuropathy lies in close association with olfactory disorders in people with diabetes; both could be attributed to microvascular injury of neurons [42].

Chan et al. [43] also confirmed that people with diabetes requiring more aggressive oral and insulin treatment tend to have more severe anosmia or hyposmia compared to those who reported no use of drug treatment.

Churg–Strauss syndrome is another example. Tallab and Doty denoted the olfactory and gustatory chemosensory dysfunction as the first symptoms in a patient who was later confirmed to be diagnosed with CSS. The patient experienced an improvement in smell and taste functions after immunosuppressive therapy. Small vessel vasculitis of the olfactory epithelium was one of the suggested possibilities in understanding the underlying cause of chemosensory dysfunction in this patient [44]. Interestingly, a microvascular basis was also found in the pathogenesis of MS, as reported by Ge et al. [45]. With the help of 7T ultra-high-field MRI, they were able to delineate a very intimate relation between MS lesions and the anatomical distribution of veins, as the lesions showed a strict perivascular distribution following the form, orientation, and course of vessels.

Moreover, changes in the venous wall signaling as well as an increase in the size of some lesions and decrease in others were detected during follow-up imaging, suggesting a dynamic vascular inflammatory activity [46].

Additionally, Ciurleo et al. reported two cases of MS associated with parosmia. The first patient developed parosmia 1 year before clinical evaluation associated with 8 kg weight loss due to abstinence from eating to avoid the perception of bad smell from food. Other causes of parosmia were excluded and an MRI was done and depicted brain lesions compatible with MS diagnosis.

The second case developed parosmia 5 years after a clinically stable course of MS. An MRI was done and new lesions in the orbitofrontal cortex were found, so the patient started corticosteroid therapy for 7 days, after which the parosmia improved [47].
Another case report of a patient with GCA presenting with anosmia also goes in line with our hypothesis. Zacharias et al. attributed the loss of scent and alteration in taste in a lady diagnosed with GCA to vasculitis of the internal carotid artery, which compromised the blood supply to the peripheral olfactory structures and olfactory bulb. Symptoms showed a slight improvement with the subsidence of vasculitis, however, there was some degree of persistent dysosmia, probably due to the lingering effects of ischemia of the olfactory pathway [48].

**Headache and facial pain syndromes**

As mentioned earlier, COVID-19 is associated with an array of neurological afflictions, among which headaches and facial pain appear to be a particularly prevalent source of its accompanied diminished quality of life. Numerous accounts describe this phenomenon, which is established in about 13.1% of COVID patients [49] and has shown a particular predilection to occur with anosmia and ageusia [34,50,51]. Notably, Planchuelo-Gómez et al. [52] who reported the incidence of progressive persistent headache with migraine features in COVID patients, affirmed their association with elevated biomarkers of endothelial dysfunction, such as procalcitonin test and C-reactive protein (CRP), thus implicating the role of microvascular injury in the pathogenesis of headaches in COVID patients.

Furthermore, headaches seem to be one of the most common persistent COVID sequelae, which strikes the supposition of post-COVID long-standing symptoms. This especially applies to those experiencing more severe than mild COVID symptoms as expressed by Liu et al. [53] with 8.96% of patients with mild symptoms...
experiencing persistent headaches, compared to 22.5% of severe COVID patients. Moreover, a study conducted by Kamal et al. [54], including 287 COVID-19 survivors, showed that 90.2% of the cases had some unresolved symptoms after recovery, mainly in the form of fatigue and continuous headache (72.8% and 28.9%, respectively). Additionally, a prospective study by Caronna et al. [55] showed that while 74 out of 130 patients experienced headaches during the disease, 28 out of those 74 patients had a persistent headache after 6 weeks of follow up.

Persistent neurological alterations in post-COVID cases demonstrate a rising manner, ranging from a continuous headache to severe migraine, triggering the peripheral activation of the trigeminovascular system either indirectly through its inflammatory cytokine storm or through the direct role of SARS-CoV-2 itself [55]. Furthermore, headaches in COVID-19 are characterized by their influence on cranial nerves, though often manifesting as anosmia and ageusia, can also simulate migraines by provoking the trigeminovascular system through the activation of angiotensin-converting enzyme 2 (ACE2) receptors [55]. Migraines involve the enhancement of the local release of afferent products, causing local vascular pulsations along with higher sensitivity of peripheral terminals to mechanical stimulation [51]. The latter pathogenesis can justify the presence of trigeminal neuralgia in cases with persistent headaches post-COVID infection, as the progression of the headache can mimic the pathophysiology of migraines.

The mechanism by which SARS-CoV-2 causes headaches and facial pain syndromes remains undetermined. However, several mechanisms have been proposed which ultimately lead to the vascular affection of the brain and peripheral nerves [56]. This includes the cytokine storm syndrome, wherein SARS-CoV-2 provokes a pro-inflammatory reaction, resulting in the overproduction of cytokines as a result of the dysregulated immune response and eliciting a prolonged inflammatory state even after the infection subsides [57]. Another suggested mechanism is Endotheliitis and endothelial damage [17,56,58,59]. ACE2 receptors, which are expressed by endothelial cells [60], are targeted by SARS-CoV-2 causing inflammation and affecting blood vessels of the body, which includes the microcirculation and the BBB, causing ischemia and subsequent central and peripheral neurological manifestations.

These claims are further fortified by the significant correlation found between diabetic patients, a prominent cause of endothelial dysfunction, and headaches with migraine characteristics in COVID patients. According to the American Diabetes Association, type 2 diabetes is associated with generalized microvascular dysfunction as well as peripheral neuritis throughout the body. Several studies demonstrated that the presence of polyneuropathy in patients with diabetes is linked to the deterioration of microvascular endothelium-dependent and -independent vasodilation in the skin [61].

Microvascular dysfunction plays a prominent role in the genesis of diabetic complications. This is best studied in the skin, being one of the most accessible organs, via numerous noninvasive, mostly Laser-Doppler-based, procedures. Microvascular functional alterations occur even in the prediabetic state and are more complex in overt diabetes, being aggravated by the development of peripheral and/or autonomic diabetic neuropathy [62].

Arap and colleagues reported in their case series a high prevalence of facial pain syndromes, particularly, in diabetes compared to the general population. Facial pain syndromes in diabetes seem to be exacerbated by the poorly controlled glycemic state [63].

Another important evidence of the implication of microvascular dysfunction in the genesis of facial pain syndromes including migraine is the intimate association between migraine and vascular events in affected patients [64].

Furthermore, patients with a history of headaches, as opposed to those without, were more seemingly to present with retinopathy, as depicted by a sub-study of the Atherosclerosis Risk in Communities Study. In addition, the involvement of subclinical microvascular dysfunction in the pathogenesis of migraine is well evidenced by the higher prevalence of WMHs in migraineurs [64].

In view of the above, and the microvascular sequelae of COVID-19 might suggest that facial pain syndromes and headaches experienced in long COVID-19 haulers are resulting from a state of delayed microvascular healing after COVID-19.

**Peripheral neuropathies**

The spectrum of COVID-19 complications expands to include neurological sequelae. Central and peripheral nervous system involvement have been reported. In addition to the acute neurological complications as acute cerebrovascular diseases and convulsions, many COVID19 patients suffered long-term sequelae such as headache, fogginess, decreased concentration, and peripheral neuropathy [65]. Although taste and olfactory and visual disorders have been frequently reported with COVID-19 infection, there is an increasing concern about underestimated neuropathic pain as a long-term complication [66].

As per the International Association for the Study of Pain, neuropathic pain is defined as ‘pain caused by a lesion or disease of the somatosensory nervous system. It may be a result of several etiologic disorders of the peripheral and CNS, which can be metabolic, neurodegenerative, autoimmune, vascular, traumatic, neoplastic, or infectious [67]. There have not been many reports regarding the symptoms of neuropathic pain among COVID-19 patients.
A recently published study specified five main clinical presentations of neuropathic pain in COVID-19 patients: a prickling sensation, a sensation of electric shock, burns, paresthesia hyperalgesia [65]. Neuropathic pain was found in 2.3% of hospitalized COVID-19 patients in one observational case series [49]. A report by Novak [68] described a post-COVID-19 case presenting with distal burning neuropathic sensations 2 weeks after clinical recovery also reported by Aksan et al. [69]. In the post-COVID-19 follow-up of 69 patients, as mentioned in Needham et al. [70] 16% had marked focal neurological deficits related to superimposed neuropathies. A common laboratory finding in those patients was elevated CRP, IL6, and CRP.

Despite the wide spectrum of causes of peripheral neuropathies, either diabetic non-diabetic; it is increasingly recognized currently that both oxidative stress, as well as angiogenesis, were the most pronounced etiologies of perfusion-dependent peripheral neuropathy. The role of endothelium-dependent and endothelium-independent microvasodilation and their correlation with neural microcirculatory control was examined in type 1 and type 2 diabetic patients by Kilo et al., in 2000. They used iontophoresis acetylcholine and nitroprusside studied in a dose-response technique to generate C-fiber mediated vasodilation. As expected, endothelium-dependent vasodilation of the cutaneous microcirculation was less in diabetic subjects [71].

The group also used two other neurophysiological techniques to assess small nerve fiber function in patients with non-diabetic peripheral neuropathy; they unleashed similar microcirculatory injuries in different types of non-diabetic neuropathies [71].

The knowledge of the microvascular dysfunction induced by COVID-19 can suggest that the main mechanism involved in the persistence of peripheral neuropathies in long COVID-19 might be due to impaired microvascular perfusion of affected nerves. While this remains largely hypothetical, it can play an important role in tailoring therapeutic strategies in light of the diabetes model.

**Dysautonomia/chronic fatigue syndrome**

Upon a long-term follow-up of 143 recovered COVID-19 cases, 53.1% of the patients have experienced fatigue, in a study by Carfì et al. [72]. Halpin et al. [73] showed similar results in a study, where two-thirds of the patients reported ongoing fatigue after 4–8 weeks of infection. Of 128 participants, more than half complained of persistent fatigue (52.3%) at a median of 10 weeks after initial COVID-19 symptoms in a study by Townsend et al. [74]. A meta-analysis of the literature from previous epidemics (SARS and Middle East respiratory syndrome) demonstrated a high incidence of confusion, depressed mood, anxiety, impaired memory, and insomnia [75].

The pathogenesis of chronic fatigue syndrome (CFS) is not clearly understood to date, however Wirth and Scheibenbogen presented a unified hypothesis for the syndrome. This hypothesis involves microvascular dysfunction as a result of auto-antibodies against B2 and acetylcholine receptors. The resultant microvascular dysfunction would result in hypoperfusion to many body systems and therefore to the problematic multi-organ manifestations of CFS. This impaired vasodilatation results in orthostatic intolerance, functional sympatholysis in skeletal muscles with subsequent easy fatigability [76].

The vascular endothelium is an active paracrine, endocrine, and autocrine organ that is crucial for the regulation of blood vessel tone and the maintenance of vascular homeostasis. Endothelial dysfunction is a main determinant of microvascular dysfunction by shifting the vascular equilibrium towards vasoconstriction with leads to the development of organ ischemia and inflammation with associated tissue edema, and a hypercoagulable state [77].

Our findings show the presence of viral elements within endothelial cells and an accumulation of inflammatory cells, with evidence of endothelial and inflammatory cell death. Several postmortem specimens suggest that SARS-CoV-2 infection facilitates endothelial inflammation in several organs (as noted with the presence of viral bodies) and stimulation of the host inflammatory response. In addition, patients with COVID-19 showed endothelial cell injury that may be through the induction of apoptosis and pyroptosis. COVID-19–endotheliitis could explain the widespread impairment of microcirculatory function in different vascular beds and their CFS sequelae in patients with long COVID-19 [5].

**Therapeutic implications**

Given the suggested microvascular pathogenesis of persistent microvascular pathogenesis of long COVID-19, drugs enhancing microvascular rejuvenation can play an important role in reversing such manifestations. Most of these drugs are derived from the ‘diabetes’ model and operate by glycemic and non-glycemic effects.

In addition to this, Wang et al. elegantly identified in their report how microvascular regeneration shares common molecular targets for nerve rejuvenation. These commonalities are not only related to the fact that rapid and adequate vascular network reconstruction is a prerequisite and guarantee for tissue regeneration and physiological function restoration. Their data revealed three key molecules (STAT3, EPHB3, and Cdc42) regulating both peripheral nerve regeneration and angiogenesis in proximal nerve stump. The possible modulation of such molecular targets can help to reverse neurologic manifestations of long COVID-19; given the potential microvascular contribution to their pathogenesis. The following medications were found to affect these three key molecules,
and below is an evidence to their potential of reversing microvascular-induced neurologic injury [78].

Glitptins have been known to be used in the treatment of diabetic patients beside their anti-diabetic effect, they have proven to have anti-inflammatory and vascular relaxation [79], some studies have shown that they might improve neupathies. Sharma et al. showed that on adding Glitptins in the treatment of STZ induced diabetic rats, an improvement in muscular grip strength and pain threshold were observed. In addition to this, the cross-section in the sciatic nerve of these rats showed normal nerve growth compared with the normal control group [80]. Pantanetti et al. suggested a possible use of DDP-4 I as immunomodulatory drugs in COVID-19 pneumonia patients with type 2 diabetes mellitus (T2DM). Interestingly, as glitptins are known to cause little or no hypoglycemic effects, they could also be safely used in non-diabetic patients [81].

Another example is the dual targeting of PPAR alpha gamma agonists which have anti-inflammatory action through interaction with NF-Kb [82], the main regulator of the immune response. Moreover, they reduce inflammatory cascade through macrophage M2 polarization. PPAR gamma agonists also modify endothelial progenitor cells and colony-forming cells which are necessary for endothelial cell proliferation. Furthermore, the neuroprotective function of PPAR gamma is elicited by being stimulated by docosahexaenoic acid through mitochondrial function and reducing oxidative stress [82]. Gatti et al. [83] proved via a study performed on 610 patients with chronic pain that palmitoyl ethanolamide, a PPAR alpha agonist, has a dual therapeutic influence; anti-inflammatory and pain-relieving, regardless of the pain etiology. This effect is achieved through controlling the activation of mast cells and microglia which mediate inflammatory responses in peripheral nervous tissues and spinal cord respectively. Abnormal activation of mast cells is a cornerstone in different types of neuropathies as diabetic neuropathy, herpes zoster, chemotherapy-induced peripheral neuropathy, and others. Microglia can produce inflammatory mediators besides their main role in neuropathic pain. This microglia-mast cell axis is present because microglia respond to pro-inflammatory signals produced from other non-neuronal cells mainly of immune origin that are related to mast cells. Activation of mast cells may be associated with peripheral nociceptor sensitization thus activating spinal microglia. This axis is of great importance to target in patients with chronic neuralgia who are unresponsive to drugs that mainly target neurons only. The shared role of both PPAR alpha and gamma agonists in improving neuropathic pain has encouraged the development of a ‘dual’ agonist, namely, tesaglitazar. Alsalem et al. [84] proved that this dual stimulation can improve neuropathic pain in affected patients better than monotherapy by either alpha or gamma agonists.

PPAR alpha and gamma dual agonists can represent a new drug therapy for neuropathic pain if further studies are conducted.

In addition, calcium dobesilate has a major role in diabetes through improving nerve conduction velocity and symptoms of peripheral neuropathy as well as blocking the sorbitol channel thereby inhibiting its dysfunction. It works through different mechanisms as improving capillary permeability and collagen synthesis so that reducing intimal damage. Also inhibiting vasoactive substances, prostaglandins, and bradykinin that has an effect on increasing production of nitric oxide, therefore, improving hypoxic and ischemic state of the nerve [85]. Another role is the relaxation of microvasculature and inhibiting proliferation of vascular smooth muscle and corrects albumin/globulin ratio, which has an effect in reducing the viscosity of plasma. Additionally, it acts as an anti-oxidant due to its hydroquinone structure [86].

For diabetic neuropathy, Alikiren, a direct renin inhibitor, is a potential treatment in an experiment on mice by reducing neogenesis and retinal inflammation [87]. In addition, in patients with T2DM, it improved the skin’s microcirculation through vasodilation independent of endothelium [88].

Another drug, taladafil suppresses PDE-5, increasing cGMP levels and leading to the improvement of neurovascular function and neurological outcome in diabetic patients. Taladafil reverses the diabetic action of myelin thickness, reduction of axon diameter, and increased g ratio in the sciatic nerve. It also enhances the diabetic effect of reduced NGF and PDGF-C protein levels in diabetic sciatic nerve tissue. It significantly improves sensory and motor sciatic nerve conduction velocities and peripheral thermal sensitivity. Present studies demonstrate that Taladafil markedly increases local blood flow in the sciatic nerve tissue thus ameliorates peripheral neuropathy [89]. Zhang et al. proved that taladafil increases brain cGMP selectively but not cAMP and improves neurogenesis in rats during stroke recovery. In comparison with saline-treated rats, taladafil significantly improved neurological functional recovery and increases cerebral vascular density. In addition, rats treated with Taladafil showed more ipsilateral proliferation of SVZ cells than saline-treated rats [90].

Finally, yet importantly, duloxetine is increasingly prescribed for diabetic neuropathic pain. Duloxetine intraperitoneal injections in rats that underwent spinal nerve ligation, an antihyperalgesic effect was exhibited through increasing the withdrawal threshold and noradrenaline levels. Intrathecal injection of Idazoxan (α2 receptor antagonist) reversed the previous action. These results show that the rise of noradrenaline in the spinal cord plays a key role in the inhibiting effects of antidepressants on neuropathic pain [91].
Table 2. Potential drugs improving endothelial-microvascular dysfunction and tested in the neurovascular unit

| Drug                      | Mechanism of improvement of microvascular dysfunction                                                                 | Other indications                  |
|---------------------------|--------------------------------------------------------------------------------------------------------------------------|-----------------------------------|
| Gilptins                 | Anti-inflammatory decreasing adhesion molecules                                                                           | Anti-diabetic agent                |
|                           | Decrease smooth muscle proliferation                                                                                     |                                   |
|                           | Increases NO production                                                                                                  |                                   |
| PPARα and γ              | Attenuates production of endothelin 1 through inhibition of protein kinase C                                               | α: anti-dyslipidemic agent          |
|                           | Attenuates VEGF                                                                                                          | γ: anti-diabetic agent             |
|                           | Decreases the yield of circulating pro-coagulants such as thrombin                                                        |                                   |
| Calcium dobesilate       | Attenuates VEGF                                                                                                          |                                    |
|                           | Decreases activity of endothelin 1                                                                                       | Off-label use, largely experimental drug |
|                           | Decreases VEGF                                                                                                          |                                   |
|                           | Has a special protective role on neurovascular unit by decreasing glial apoptosis and improving perfusion of glial cells |                                   |
| Aliskiren                | Improve endothelial repair capacity through stimulation of:                                                              | New anti-hypertensive drug (direct renin inhibitor) |
|                           | Tyrosine kinase receptor, protein kinase B, and endothelial nitric oxide synthase                                         |                                   |
|                           | Those three pathways contribute to endothelial cell repair through promoting cell migration, thus promoting reendothelialization |                                   |
| Duloxetine               | Unclear mechanisms: however it acts mainly by decreasing VEGF in the neurovascular unit leading to improvement of glial and endothelial rejuvenation | Anti-depressant                    |

All the above-mentioned medications, protect cell survival and regeneration through the three key molecules previously identified in common between axonal repair and rejuvenation of microvascular bed. Table 2 summarizes their distinct molecular targets in addition to their shared effect on STAT3/CDC42/EPHB3 pathway.

Conclusion

Long COVID syndrome (symptoms beyond 3 weeks), is a multisystem syndrome that requires the rehabilitation of patients on physical, cognitive, psychological, social, and vocational levels. Symptoms of long COVID include CFS, loss of taste and smell, headache, confusion, autonomic neuropathy, muscle weakness, and pain. It is proposed that microvascular dysfunction to be the mechanism for persistent neurological sequelae after recovery from SARS-CoV-2. The available data suggests a similar underlying pathology in viruses other than SARS-CoV-2.

In addition to other systemic vascular diseases as diabetes, exhibiting neurological dysfunction also backs up the hypothesis. The micro-angiopathy theory provides a rationale for therapeutic techniques targeting microvascular regeneration to relieve symptoms caused by vascular injury and ischemia due to chronic COVID Syndrome. Another support to this hypothesis is the shared molecular pathways of endothelial and neurologic rejuvenation, particularly STAT3, EPHB3, and Cdc42 pathways. Overall, these findings can provide a potential therapeutic option to alleviate the neurological sequelae in patients with long COVID. Clinical trials should be tailored to confirm the effect of such medications on improving long COVID syndrome.

Overall, long COVID syndrome is a prolonged complication that occurs after acute COVID infection. Its symptoms require a multidisciplinary approach with special focus on neurorehabilitation in order to minimize complications. Low-cost therapies and repurposing of readily available anti-inflammatory medications may prove vital in the management of long COVID symptoms. Figure 1 summarizes the microvascular pathogenesis of COVID-19.

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Conflicts of interest

There are no conflicts of interest.

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