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**
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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 multisystem 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 Gliptins, 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

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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 2 types of recovery: the normal rapid recovery in two-thirds of patients and the slow or partial recovery that was associated with trigeminal nerve affection Every 1–3 COVID positive patients suffered from persistent olfactory dysfunction
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 8.2 relative ratio after a maximum of 60 days follow up
UK	[27]	Watson *et al.*	9000 users of the AbScent Covid-19 Smell and Taste Loss moderated Facebook support group	10% suffered from persistent anosmia, hyposmia, parosmia and phantosmia, dysgeusia, and reduced chemesthesis
Multinational	[28]	Menni *et al.*	200	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
France	[29]	De Melo *et al.*	89	29 (22.7%) reported persistent anosmia and ageusia after 60 days of onset of symptoms.
Italy	[30]	Vaira *et al.*	150	8 patients (5.8%) had moderate to severe olfactory dysfunction 6 patients (4.3%) had a significant taste disorder 4 patients had isolated smell impairments 2 patients had isolated taste disorders after 60 days of observation
USA	[31]	Yan *et al.*	316	Complete recovery in 46 Persistent olfactory dysfunction in 23
Greece	[32]	Tsivgoulis *et al.*	8	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
UK	[33]	Hopkins *et al.*	382	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].

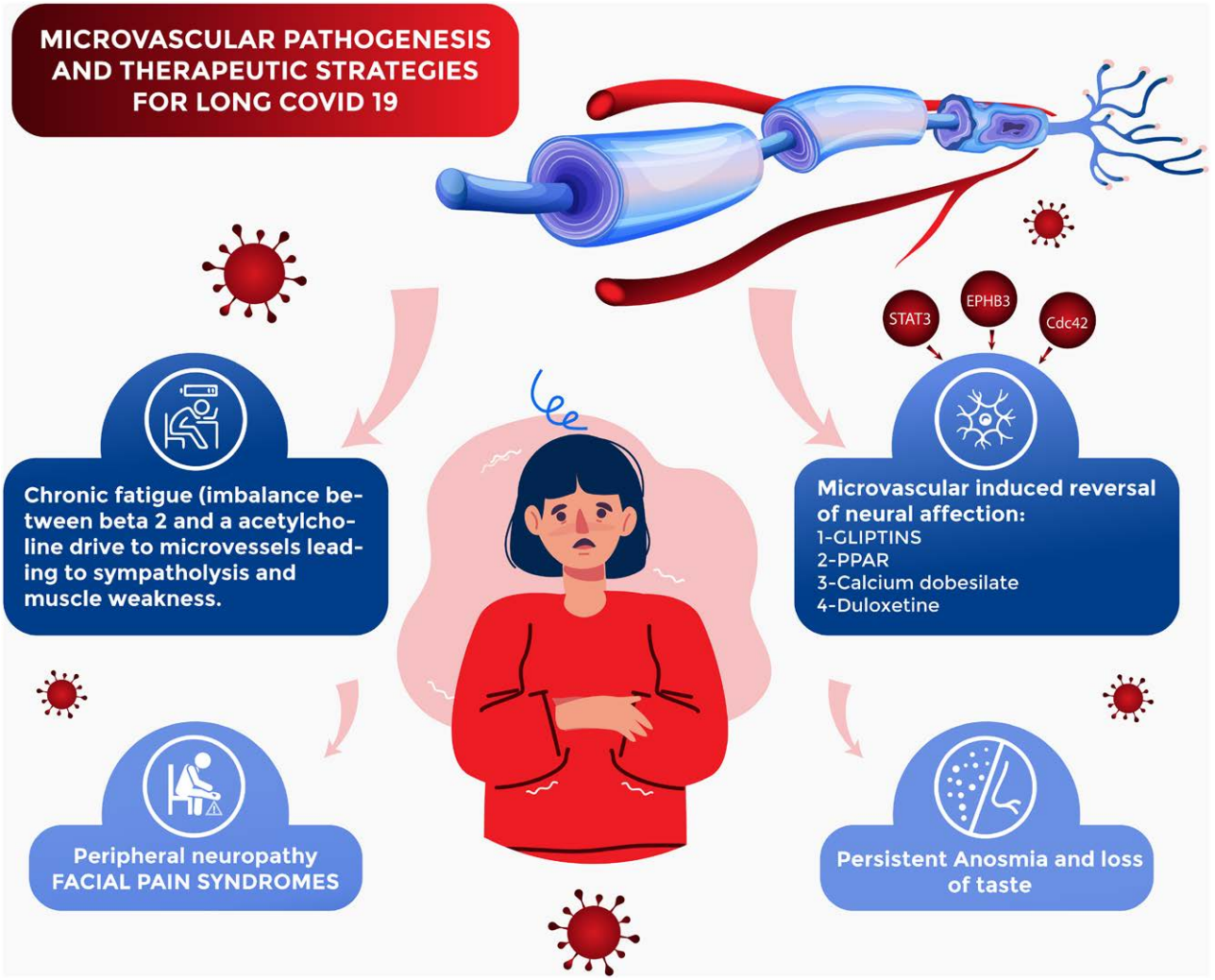
Interestingly, a microvascular basis was also found in the pathogenesis of MS, as reported by Ge *et al.* [45]. With the help of 7T ultra-high-field MRI, they were able to delineate a very intimate relation between MS lesions and the anatomical distribution of veins, as the lesions showed a strict perivascular 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].

Fig. 1



Microvascular pathogenesis and therapeutic strategies of long COVID-19. COVID-19, coronavirus disease 2019; PPAR, peroxisome proliferator-activated receptors.

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 etiological 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].

Gliptins 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 neuropathies. Sharma *et al.* showed that on adding Gliptins 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 gliptins 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 palmitoylethanolamide, 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, Aliskiren, 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 Taladfil markedly increases local blood flow in the sciatic nerve tissue thus ameliorates peripheral neuropathy [89]. Zhang *et al.* proved that tadalafil increases brain cGMP selectively but not cAMP and improves neurogenesis in rats during stroke recovery. In comparison with saline-treated rats, tadalafil significantly improved neurological functional recovery and increases cerebral vascular density. In addition, rats treated with Tadalafil showed more ipsilateral proliferation of SVZ cells than saline-treated rats [90].

Finally, yet importantly, duloxetine is increasingly prescribed for diabetic neurpathic 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 ($\alpha 2$ 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
Gliptins	Anti-inflammatory decreasing adhesion molecules Decrease smooth muscle proliferation Increases NO production	Anti-diabetic agent
PPARα and γ	Attenuates production of endothelin 1 through inhibition of protein kinase C Attenuates VEGF Decreases the yield of circulating pro-coagulants such as thrombin Anti-inflammatory improve endothelial function through endothelial cell proliferation and anti-thrombotic	α: anti-dyslipidemic agent γ: anti-diabetic agent
Calcium dobesilate	Decreases activity of endothelin 1 Decreases VEGF Has a special protective role on neurovascular unit by decreasing glial apoptosis and improving perfusion of glial cells	Off-label use, largely experimental drug
Aliskiren	Improve endothelial repair capacity through stimulation of: 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	New anti-hypertensive drug (direct renin inhibitor)
Duloxetine	Unclear mechanisms: however it acts mainly by decreasing VEGF in the neurovascular unit leading to improvement of glial and endothelial rejuvenation	Anti-depressant

NO, nitric oxide; NOS, nitric oxide synthase; PPAR, peroxisome proliferator-activated receptors; VEGF, vascular endothelial growth factor.

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.

References

1 Yang J, Zheng Y, Gou X, Pu K, Chen Z, Guo Q, *et al*. Prevalence of comorbidities and its effects in patients infected with SARS-CoV-2: a systematic review and meta-analysis. *Int J Infect Dis* 2020; **94**:91–95.
2 Liu YC, Kuo RL, Shih SR. COVID-19: The first documented coronavirus pandemic in history. *Biomed J* 2020; **43**:328–333.
3 Dong E, Du H, Gardner L. An interactive web-based dashboard to track COVID-19 in real time. *Lancet Infect Dis* 2020; **20**:533–534.
4 Apicella M, Campopiano MC, Mantuano M, Mazoni L, Coppelli A, Del Prato S. COVID-19 in people with diabetes: understanding the reasons for worse outcomes. *Lancet Diabetes Endocrinol* 2020; **8**:782–792.
5 AbdelMassih AF, Kamel A, Mishriky F, Ismail H-A, El Qadi L, Malak L, *et al*. Is it infection or rather vascular inflammation ? Game-changer insights and recommendations from patterns of multi-organ involvement and affected subgroups in COVID-19. *Cardiovasc Endocrinol Metab* 2020; **9**:110–120.
6 Ali A, Vijayan R. Dynamics of the ACE2-SARS-CoV-2/SARS-CoV spike protein interface reveal unique mechanisms. *Sci Rep* 2020; **10**:14214.
7 Shovlin CL, Vizcaychipi MP. Vascular inflammation and endothelial injury in SARS-CoV-2 infection: the overlooked regulatory cascades implicated by the ACE2 gene cluster. *QJM* 2020. [Epub ahead of print]
8 Hikmet F, Méar L, Edvinsson Å, Micke P, Uhlén M, Lindskog C. The protein expression profile of ACE2 in human tissues. *Mol Syst Biol* 2020; **16**:e9610.
9 Halpin S, O'Connor R, Sivan M. Long COVID and chronic COVID syndromes. *J Med Virol* 2021; **93**:1242–1243.
10 Paice JA, Dahlin C, Wholihan D, Mazanec P, Long CO, Thaxton C, Greer K. Palliative care for people with COVID-19-related symptoms. *J Hosp Palliat Nurs* 2020; **22**:421–427.
11 Morley JE. COVID-19 – the long road to recovery. *J Nutr Health Aging* 2020; **24**:917–919.
12 Becker RC. Anticipating the long-term cardiovascular effects of COVID-19. *J Thromb Thrombolysis* 2020; **50**:512–524.
13 Bektas A, Schurman SH, Franceschi C, Ferrucci L. A public health perspective of aging: do hyper-inflammatory syndromes such as COVID-19, SARS, ARDS, cytokine storm syndrome, and post-ICU syndrome accelerate short- and long-term inflammaging? *Immun Ageing* 2020; **17**:23.
14 Baig AM. Deleterious outcomes in Long-Hauler COVID-19: the effects of SARS-CoV-2 on the CNS in chronic COVID syndrome. *ACS Chem Neurosci* 2020; **11**:4017–4020.
15 Bossù P, Toppi E, Sterbini V, Spalletta G. Implication of aging related chronic neuroinflammation on COVID-19 pandemic. *J Pers Med* 2020; **10**:E102.
16 Neurology TL. The neurological impact of COVID-19. *Lancet Neurol* 2020; **19**:471.
17 MacLean MA, Kamintsky L, Leck ED, Friedman A. The potential role of microvascular pathology in the neurological manifestations of coronavirus infection. *Fluids Barriers CNS* 2020; **17**:55.
18 Avogaro A, Fadini GP. The effects of dipeptidyl peptidase-4 inhibition on microvascular diabetes complications. *Diabetes Care* 2014; **37**:2884–2894.
19 Kytikova OY, Perelman JM, Novgorodtseva TP, Denisenko YK, Kolosov VP, Antonyuk MV, Gvozdenko TA. Peroxisome proliferator-activated receptors as a therapeutic target in asthma. *PPAR Res* 2020; **2020**:8906968.
20 Huang SY, Jeng C, Kao SC, Yu JJ, Liu DZ. Improved haemorrheological properties by Ginkgo Biloba extract (Egb 761) in type 2 diabetes mellitus complicated with retinopathy. *Clin Nutr* 2004; **23**:615–621.
21 Smith B, Kelly C, Deary V. Altered smell and taste: anosmia, parosmia and the impact of long Covid-19. medRxiv Preprint. 2020;2020.11.26.20239152.

22 Cain WS, Gent JF, Goodspeed RB, Leonard G. Evaluation of olfactory dysfunction in the Connecticut Chemosensory Clinical Research Center. *Laryngoscope* 1988; **98**:83–88.
23 Han AY, Mukdad L, Long JL, Lopez IA. Anosmia in COVID-19: mechanisms and significance. *Chem Senses* 2020; **45**:423–428.
24 Sampaio Rocha-Filho PA, Voss L. Persistent headache and persistent anosmia associated with COVID-19. *Headache* 2020; **60**:1797–1799.
25 Konstantinidis I, Delides A, Tsakiropoulou E, Maragoudakis P, Sapounas S, Tsiodras S. Short-term follow-up of self-isolated COVID-19 patients with smell and taste dysfunction in Greece: two phenotypes of recovery. *ORL J Otorhinolaryngol Relat Spec* 2020; **82**:295–303.
26 Galván-Tejada CE, Herrera-García CF, Godina-González S, Villagrana-Bañuelos KE, Amaro JDDL, Herrera-García K, *et al*. Persistence of covid-19 symptoms after recovery in mexican population. *Int J Environ Res Public Health* 2020; **17**:1–12.
27 Burges Watson DL, Campbell M, Hopkins C, Smith B, Kelly C, Deary V. Altered smell and taste: anosmia, parosmia and the impact of long Covid-19. medRxiv Preprint. 2020:1–19.
28 Menni C, Valdes AM, Freidin MB, Sudre CH, Nguyen LH, Drew DA, *et al*. Real-time tracking of self-reported symptoms to predict potential COVID-19. *Nat Med* 2020; **26**:1037–1040.
29 de Melo GD, Lazarini F, Levallois S, Hautefort C, Michel V, Larrous F, *et al*. COVID-19-associated olfactory dysfunction reveals SARS-CoV-2 neuroinvasion and persistence in the olfactory system. bioRxiv Preprint. 2020.
30 Vaira LA, Deiana G, Fois AG, Pirina P, Madeddu G, De Vito A, *et al*. Objective evaluation of anosmia and ageusia in COVID-19 patients: single-center experience on 72 cases. *Head Neck* 2020; **42**:1252–1258.
31 Yan CH, Prajapati DP, Ritter ML, DeConde AS. Persistent smell loss following undetectable SARS-CoV-2. *Otolaryngol Head Neck Surg* 2020; **163**:923–925.
32 Tsivgoulis G, Fragkou PC, Lachanis S, Palaiodimou L, Lambadiari V, Papathanasiou M, *et al*. Olfactory bulb and mucosa abnormalities in persistent COVID-19-induced anosmia: a magnetic resonance imaging study. *Eur J Neurol* 2021; **28**:e6–e8.
33 Hopkins C, Surda P, Whitehead E, Kumar BN. Early recovery following new onset anosmia during the COVID-19 pandemic - an observational cohort study. *J Otolaryngol Head Neck Surg* 2020; **49**:26.
34 Aragão MFVV, Leal MC, Cartaxo Filho OQ, Fonseca TM, Valença MM. Anosmia in COVID-19 associated with injury to the olfactory bulbs evident on MRI. *AJNR Am J Neuroradiol* 2020; **41**:1703–1706.
35 Welge-Lüssen A, Wolfensberger M. Olfactory disorders following upper respiratory tract infections. *Adv Otorhinolaryngol* 2006; **63**:125–132.
36 Suzuki M, Saito K, Min WP, Vladau C, Toida K, Itoh H, Murakami S. Identification of viruses in patients with postviral olfactory dysfunction. *Laryngoscope* 2007; **117**:272–277.
37 Hwang CS. Olfactory neuropathy in severe acute respiratory syndrome: report of A case. *Acta Neurol Taiwan* 2006; **15**:26–28.
38 Lee MH, Perl DP, Nair G, Li W, Maric D, Murray H, *et al*. Microvascular injury in the brains of patients with Covid-19. *N Engl J Med* 2021; **384**:481–483.
39 Gavriatopoulou M, Korompoki E, Fotiou D, Ntanasis-Stathopoulos I, Psaltopoulou T, Kastritis E, *et al*. Organ-specific manifestations of COVID-19 infection. *Clin Exp Med* 2020; **20**:493–506.
40 Lang M, Li MD, Buch K, Yoon BC, Applewhite BP, Leslie-Mazwi TM, *et al*. Risk of acute cerebrovascular events in patients with COVID-19 infection. *AJNR Am J Neuroradiol* 2020; **41**:E92–E93.
41 Jaunmuktane Z, Mahadeva U, Green A, Sekhawat V, Barrett NA, Childs L, *et al*. Microvascular injury and hypoxic damage: emerging neuropathological signatures in COVID-19. *Acta Neuropathol* 2020; **140**:397–400.
42 Kim SJ, Windon MJ, Lin SY. The association between diabetes and olfactory impairment in adults: a systematic review and meta-analysis. *Laryngoscope Investig Otolaryngol* 2019; **4**:465–475.
43 Chan JYK, García-Esquinas E, Ko OH, Tong MCF, Lin SY. The association between diabetes and olfactory function in adults. *Chem Senses* 2017; **43**:59–64.
44 Tallab HF, Doty RL. Anosmia and hypogeusia in Churg-Strauss syndrome. *BMJ Case Rep* 2014; **2014**:bcr2014203959.
45 Ge H, Wang X, Yuan X, Xiao G, Wang C, Deng T, et al. The epidemiology and clinical information about COVID-19. *Eur J Clin Microbiol Infect Dis* 2020; **39**:1011–1019.
46 Obradovic J. 7T MRI: new vision of microvascular abnormalities in multiple sclerosis yulin. *Bone* 2005; **23**:1–7.
47 Ciurleo R, De Salvo S, Bonanno L, Marino S, Bramanti P, Caminiti F. Parosmia and neurological disorders: a neglected association. *Front Neurol* 2020; **11**:543275.
48 Zacharias H, Magliano M, Sandhu K, Weatherall M. A case of anosmia. *Rheumatol Adv Pract* 2018; **2** (Suppl 1):rky033.010.
49 Mao L, Jin H, Wang M, Hu Y, Chen S, He Q, *et al*. Neurologic manifestations of hospitalized patients with coronavirus disease 2019 in Wuhan, China. *JAMA Neurol* 2020; **77**:683–690.
50 Zhang Q, Shan KS, Abdollahi S, Nace T. Anosmia and ageusia as the only indicators of coronavirus disease 2019 (COVID-19). *Cureus* 2020; **2019**:1–6.
51 Munhoz RP, Pedroso JL, Nascimento FA, Almeida SM, Barsottini OGP, Cardoso FEC, Teive HAG. Neurological complications in patients with SARS-CoV-2 infection: a systematic review. *Arq Neuropsiquiatr* 2020; **78**:290–300.
52 Planchuelo-Gómez Á, Trigo J, de Luis-García R, Guerrero ÁL, Porta-Etessam J, García-Azorín D. Deep phenotyping of headache in hospitalized COVID-19 patients via principal component analysis. *Front Neurol* 2020; **11**:583870.
53 Liu HQ, Yuan B, An YW, Chen KJ, Hu Q, Hu XP, *et al*. Clinical characteristics and follow-up analysis of 324 discharged COVID-19 patients in Shenzhen during the recovery period. *Int J Med Sci* 2021; **18**:347–355.
54 Kamal M, Abo Omirah M, Hussein A, Saeed H. Assessment and characterisation of post-COVID-19 manifestations. *Int J Clin Pract* 2021; **75**:e13746.
55 Caronna E, Ballvé A, Llauradó A, Gallardo VJ, Ariton DM, Lallana S, *et al*. Headache: a striking prodromal and persistent symptom, predictive of COVID-19 clinical evolution. *Cephalalgia* 2020; **40**:1410–1421.
56 Brun G, Hak JF, Coze S, Kaphan E, Carvelli J, Girard N, Stellmann JP. COVID-19-white matter and globus pallidum lesions: demyelination or small-vessel vasculitis? *Neurol Neuroimmunol Neuroinflamm* 2020; **7**:e777.
57 Mehta P, McAuley DF, Brown M, Sanchez E, Tattersall RS, Manson JJ; HLH Across Speciality Collaboration, UK. COVID-19: consider cytokine storm syndromes and immunosuppression. *Lancet* 2020; **395**:1033–1034.
58 Varga Z, Flammer AJ, Steiger P, Haberecker M, Andermatt R, Zinkernagel AS, *et al*. Endothelial cell infection and endotheliitis in COVID-19. *Lancet* 2020; **395**:1417–1418.
59 Gupta A, Madhavan MV, Sehgal K, Nair N, Mahajan S, Sehrawat TS, *et al*. Extrapulmonary manifestations of COVID-19. *Nat Med* 2020; **26**:1017–1032.
60 Ferrario CM, Jessup J, Chappell MC, Averill DB, Brosnihan KB, Tallant EA, *et al*. Effect of angiotensin-converting enzyme inhibition and angiotensin II receptor blockers on cardiac angiotensin-converting enzyme 2. *Circulation* 2005; **111**:2605–2610.
61 Emanuel AL, Nieuwenhoff MD, Klaassen ES, Verma A, Kramer MH, Strijers R, *et al*. Relationships between type 2 diabetes, neuropathy, and microvascular dysfunction: evidence from patients with cryptogenic axonal polyneuropathy. *Diabetes Care* 2017; **40**:583–590.
62 Stirban A. Microvascular dysfunction in the context of diabetic neuropathy. *Curr Diab Rep* 2014; **14**:541.
63 Arap A, Siqueira SR, Silva CB, Teixeira MJ, Siqueira JT. Trigeminal pain and quantitative sensory testing in painful peripheral diabetic neuropathy. *Arch Oral Biol* 2010; **55**:486–493.
64 Tana C, Tafuri E, Tana M, Martelletti P, Negro A, Affaitati G, *et al*. New insights into the cardiovascular risk of migraine and the role of white matter hyperintensities: is gold all that glitters? *J Headache Pain* 2013; **14**:9.
65 Widyadharma IPE, Sari NNSP, Pradnyaswari KE, Yuwana KT, Adikarya IPGD, Tertia C, *et al*. Pain as clinical manifestations of COVID-19 infection and its management in the pandemic era: a literature review. *Egypt J Neurol Psychiatr Neurosurg* 2020; **56**:121.
66 Ozdag Acarli AN, Samanci B, Ekizoglu E, Cakar A, Sirin NG, Gunduz T, *et al*. Coronavirus Disease 2019 (COVID-19) From the Point of View of Neurologists: Observation of Neurological Findings and Symptoms During the Combat Against a Pandemic. *Noro psikiyatri arsivi* 2020; 57:154–159.
67 Finnerup NB, Haroutounian S, Kamerman P, Baron R, Bennett DLH, Bouhassira D, *et al*. Neuropathic pain: an updated grading system for research and clinical practice. *Pain* 2016; **157**:1599–1606.
68 Novak P. Post COVID-19 syndrome associated with orthostatic cerebral hypoperfusion syndrome, small fiber neuropathy and benefit of immunotherapy: a case report. *Eneurologicalsci* 2020; **21**:100276.
69 Aksan F, Nelson EA, Swedish KA. A COVID-19 patient with intense burning pain. *J Neurovirol* 2020; **26**:800–801.
70 Needham E, Newcombe V, Michell A, Thornton R, Grainger A, Anwar F, *et al*. Mononeuritis multiplex: an unexpectedly frequent feature of severe COVID-19. *J Neurol* 2021; **268**:2685–2689.
71 Kilo S, Berghoff M, Hilz M, Freeman R. Neural and endothelial control of the microcirculation in diabetic peripheral neuropathy. *Neurology* 2000; **54**:1246–1252.

72 Carfì A, Bernabei R, Landi F; Gemelli Against COVID-19 Post-Acute Care Study Group. Persistent symptoms in patients after acute COVID-19. *JAMA* 2020; **324**:603–605.

73 Halpin SJ, McIvor C, Whyatt G, Adams A, Harvey O, McLean L, *et al*. Postdischarge symptoms and rehabilitation needs in survivors of COVID-19 infection: a cross-sectional evaluation. *J Med Virol* 2021; **93**:1013–1022.

74 Townsend L, Dyer AH, Jones K, Dunne J, Mooney A, Gaffney F, *et al*. Persistent fatigue following SARS-CoV-2 infection is common and independent of severity of initial infection. *PLoS One* 2020; **15**:e0240784.

75 Rogers JP, Chesney E, Oliver D, Pollak TA, McGuire P, Fusar-Poli P, *et al*. Psychiatric and neuropsychiatric presentations associated with severe coronavirus infections: a systematic review and meta-analysis with comparison to the COVID-19 pandemic. *Lancet Psychiatry* 2020; **7**:611–627.

76 Wirth K, Scheibenbogen C. A unifying hypothesis of the pathophysiology of myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS): recognitions from the finding of autoantibodies against ß2-adrenergic receptors. *Autoimmun Rev* 2020; **19**:102527.

77 Nava E, Llorens S. The paracrine control of vascular motion. A historical perspective. *Pharmacol Res* 2016; **113**:125–145.

78 Wang H, Zhu H, Guo Q, Qian T, Zhang P, Li S, *et al*. Overlapping mechanisms of peripheral nerve regeneration and angiogenesis following sciatic nerve transection. *Front Cell Neurosci* 2017; **11**:1–13.

79 Oyama J, Higashi Y, Node K. Do incretins improve endothelial function? *Cardiovasc Diabetol* 2014; **13**:21.

80 Sharma AK, Sharma A, Kumari R, Kishore K, Sharma D, Srinivasan BP, *et al*. Sitagliptin, sitagliptin and metformin, or sitagliptin and amitriptyline attenuate streptozotocin-nicotinamide induced diabetic neuropathy in rats. *J Biomed Res* 2012; **26**:200–210.

81 Pantanetti P, Cangelosi G, Ambrosio G. Potential role of incretins in diabetes and COVID-19 infection: a hypothesis worth exploring. *Intern Emerg Med* 2020; **15**:779–782.

82 Ciavarella C, Motta I, Valente S, Pasquinelli G. Pharmacological (or synthetic) and nutritional agonists of PPAR-γ as candidates for cytokine storm modulation in COVID-19 disease. *Molecules* 2020; **25**:E2076.

83 Gatti A, Lazzari M, Gianfelice V, Di Paolo A, Sabato E, Sabato AF. Palmitoylethanolamide in the treatment of chronic pain caused by different etiopathogenesis. *Pain Med* 2012; **13**:1121–1130.

84 Alsalem M, Haddad M, Aldossary SA, Kalbouneh H, Azab B, Dweik A, *et al*. Effects of dual peroxisome proliferator-activated receptors α and γ activation in two rat models of neuropathic pain. *PPAR Res* 2019; **2019**:2630232.

85 Liu J, Li S, Sun D. Calcium dobesilate and micro-vascular diseases. *Life Sci* 2019; **221**:348–353.

86 Szabo ME, Haines D, Garay E, Chiavaroli C, Farine JC, Hannaert P, et al. Antioxidant properties of calcium dobesilate in ischemic/reperfused diabetic rat retina. *Eur J Pharmacol* 2001; **428**:277–286.

87 Wilkinson-Berka JL, Tan G, Binger KJ, Sutton L, McMaster K, Deliyanti D, *et al*. Aliskiren reduces vascular pathology in diabetic retinopathy and oxygen-induced retinopathy in the transgenic (mRen-2)27 rat. *Diabetologia* 2011; **54**:2724–2735.

88 Dushay JR, Tecilazich F, Kafanas A, Magargee ML, Auster ME, Gnardellis C, *et al*. Aliskiren improves vascular smooth muscle function in the skin microcirculation of type 2 diabetic patients with normal renal function. *J Renin Angiotensin Aldosterone Syst* 2015; **16**:344–352.

89 Wang L, Chopp M, Szalad A, Lu XR, Jia LF, Lu M, *et al*. Tadalafil promotes the recovery of peripheral neuropathy in type II diabetic mice. *PLoS One* 2016; **11**:1–13.

90 Zhang L, Zhang Z, Zhang RL, Cui Y, LaPointe MC, Silver B, Chopp M. Tadalafil, a long-acting type 5 phosphodiesterase isoenzyme inhibitor, improves neurological functional recovery in a rat model of embolic stroke. *Brain Res* 2006; **1118**:192–198.

91 Obata H. Analgesic mechanisms of antidepressants for neuropathic pain. *Int J Mol Sci* 2017; **18**:E2483.