Chapter

# Autoimmunity, Vascular Dysfunction and Metabolic Alterations: A Trifecta of Impacts in Postacute COVID-19 Vaccination Syndrome (PACVS)

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**Abstract**

The pathology of postacute COVID-19 vaccination syndrome (PACVS) involves interacting disease mechanisms. This work aims to elucidate the effects of three pathological mechanisms in PACVS and long COVID-19: altered energy metabolism, autoimmunity, and vascular alterations, the latter category further broken down into thrombotic alterations and endothelial dysfunction. All three provide possibilities for disease monitoring and treatment. For each pathological mechanism, we establish an association by examining relevant clinical phenotypes occurring after COVID-19 vaccination, relate the pathological mechanism to observations in patients with PACVS and long COVID-19, and suggest treatment implications where available. This review provides a framework for clinicians and researchers seeking to treat PACVS, offering therapeutic avenues to address this novel condition.

**Keywords:** postacute COVID-19 vaccination syndrome (PACVS), long COVID-19, spike protein, autoimmunity, coagulopathies, endothelial dysfunction, mitochondria, G-protein-coupled receptors (GPCRs)

## 1. Introduction

Researchers are still attempting to describe the disorder known as postaAcute COVID-19 vaccination syndrome (PACVS), which has commonly been compared to (and is often confused with) long COVID or postacute COVID-19 syndrome (PACS). This disorder presents similarly to myalgic encephalomyelitis or chronic fatigue syndrome (ME/CFS), and patients experience fatigue with unrefreshing rest, exercise intolerance, and brain fog.

So far, therapeutic options remain limited, owing in part to a lack of recognition by the medical community [1, 2]. Patients often have trouble finding physicians to treat their symptoms, let alone attributing them to vaccination. Some work has been done on the characterization of immune effects in PACVS, though major undertakings remain unpublished. Several research groups have provided new perspectives on the etiology of PACVS (and PACS). This review focuses on three important causes: thrombotic and vascular disorders, autoimmunity, and metabolic alterations, as well as their interplay. This review aims to provide a therapeutic framework to explain the etiology and guide the development of novel therapeutics. While these are not the only contributing factors, as factors such as metabolite and neurotransmitter disturbances can also have a profound effect, this review aims to provide a parsimonious framework for PACVS etiology.

PACVS can be a multifactorial disease; depending on the contributing factors, it is important to adjust the treatment strategy accordingly.

## 2. Metabolic dysfunction

### 2.1 Clinical presentation

#### *2.1.1 Clinical phenotype*

For most COVID-19 vaccine recipients, no metabolic alterations were observed following administration. Indeed, infection may contribute to metabolic deterioration and new-onset diabetes [3], and vaccination may be protective against diabetes [4–6].

COVID-19 vaccination may induce a transient increase in blood sugar in patients with preexisting type 1 diabetes [7]. Additionally, there have been rare instances of new-onset or exacerbated diabetes after COVID-19 vaccination [8].

#### *2.1.2 Contribution in PACVS*

Metabolic dysfunction is among the most frequently reported biological abnormalities in both PACS and PACVS, and there is convergent evidence that the central causal factor in symptoms is mitochondrial energetic failure. Multiomics analysis of long COVID-19 demonstrates that there are extensive changes in tricarboxylic-acid (TCA) cycle intermediates, redox metabolites, and amino-acid metabolism, with the implication that oxidative phosphorylation is disrupted at an early stage of the disease process [9–11]. Investigations using cardiopulmonary exercise testing (CPET) show that PACS patients achieve their anaerobic threshold at much lower workloads than healthy controls, even with retained cardiac and ventilatory capacity, which suggests that it is mitochondrial energy production that causes the reduction in exertional tolerance, and not cardiopulmonary limitation [12, 13]. Reduced mitochondrial density, a decline in the capacity of oxidative phosphorylation, and an increase in acyl-carnitine levels in PACS/PACVS cohorts are typical features of mitochondrial stress and defective β-oxidation [14, 15]. Taken together, the above findings clarify why even moderate activity in such a patient results in a rapid build-up of lactate, extreme fatigue, and aggravation of postexertional symptoms.

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### 2.2 Mechanisms

There is growing evidence that the SARS-CoV-2 spike protein is a primary mechanistic agent in the development of this bioenergetic collapse. Structural biology investigations reveal that the spike protein contains a conserved free fatty acid (FFA) binding pocket that can sequester linoleic acid, modulate lipid metabolism, disrupt cellular homeostasis, and shift energy use away from mitochondrial fatty acid oxidation [16, 17]. Cell-based experiments further elucidate the mechanism: exposure to spike proteins induces mitochondrial fragmentation, mitophagy inhibition, disruption of redox homeostasis, and reactive oxygen species (ROS) production in cardiomyocytes, endothelial cells, and microglia [18, 19]. The same pathways are also seen to be active in PACVS, where persistent spike protein has been reported months to years following vaccination [20], and metabolomic changes are observed, including increases in acyl-carnitines, serine and taurine deficits, and inhibition of β-oxidation, which strongly resembles structural changes in postinfectious PACS [21–23]. Collectively, the results indicate that a common pathway of mitochondrial damage mediated by spike proteins connects postinfection and postvaccination metabolic phenotypes.

Another metabolic imbalance between PACS and PACVS involves impaired fatty acid oxidation and a pathological shift to glycolysis, which elevates lactate production at the lowest workloads. A number of independent clinical studies indicate that patients with long COVID show significantly lower fat-oxidation rates, disrupted CPT-1 activity, and disturbed substrate switching during exercise, resulting in anaerobic metabolism developing rapidly [24–29]. PACVS plasma metabolomics invariably display disrupted fatty-acid oxidation, increased carnitine-fatty-acid conjugates, and severe mitochondrial ROS generation. Hypoperfusion and microvascular dysfunction, which are well described in both PACS and PACVS, seem to worsen the situation by introducing localized tissue hypoxia, which further exacerbates the impact of glycolytic compensation and leads to muscle pain and postexertional symptoms [30, 31]. Such a combination of defective β-oxidation, mitochondrial structural pathology, redox imbalance, and prematurely advanced glycolytic dependence offers a complete mechanistic account of the chronic fatigue, cognitive retardation, breathlessness, and exercise intolerance that characterize both PACS and PACVS.

### 2.3 Therapeutic interventions

The proposed therapeutic approaches to both PACS and PACVS now place greater emphasis on correcting the three closely interconnected metabolic dysfunctions: abnormal lactate threshold, dysregulated CO2 (capnia), and impaired fatty acid oxidation. Studies show that PAC(V)S patients experience a rapid increase in blood lactate levels during minimal physical activity, which has also been established in multiple CPET cohorts of long COVID patients [24, 32]. Structured low-intensity aerobic conditioning, extracellular buffering salts such as sodium bicarbonate and sodium citrate [33, 34], and nutritional interventions such as branched-chain amino acids (BCAAs), beetroot-derived nitrates, and nitrite-rich preparations have demonstrated significant changes in lactate threshold and skeletal muscle oxygenation that can modify the behavior of lactate therapeutically [35, 36]. All of these interventions improve mitochondrial efficiency, delay the transition to

anaerobic metabolism, and may reduce postexertional symptom increases in PAC(V)S.

The second therapeutic axis is the restoration of carbon dioxide homeostasis. $CO_2$ physiology is often disregarded, but long COVID patients exhibit chronic hypocapnia, ventilatory overshoot, and an exaggerated chemoreflex response due to hypersensitivity of the carotid body [37, 38]. While hypercapnic training acutely raises the partial pressure of $CO_2$ ($PaCO_2$) [39], long-term adaptations are less well understood. In the short term, hypercapnic training can increase oxygen delivery [40], potentially improving aerobic metabolism in patients with PAC(V)S. Breathing techniques that slow the rate of ventilation, including resonant-frequency breathing, diaphragmatic breathing, breath-hold protocols, and simulated-altitude exposure, can normalize CO2 levels and enhance oxygen delivery. Although no clinical trials have been conducted in PAC(V)S yet, similar studies performed in ME/CFS and dysautonomia suggest that capnia-guided training contributes to better autonomic control and alleviates dyspnea [41–45]. Another theoretical approach is P2X3 antagonists, such as gefapixant, which have the potential to inhibit chemoreceptor hypersensitivity but are still under investigation [46].

Restoring β-oxidation is the third therapeutic area. Compensatory fat oxidation rates in PACS patients are considerably lower during exercise, with corresponding increases in glucose oxidation rates [24, 47]. While initially proposed as an intervention aimed at reducing levels of spike protein [48, 49], fasting can increase beta-oxidation levels during the fast [50, 51], as well as after the completion of the fast [52]. For long COVID, individuals undergoing fasts showed symptom improvements [53, 54], illustrating fasting as a potential therapeutic option [55].

Low-intensity endurance training, carbohydrate periodization, and incremental fat adaptation [47, 48] have been shown to induce CPT-1 upregulation, increase intramyocellular lipid stores, enhance mitochondrial enzyme activity, and improve substrate adaptability. Coenzyme Q10 (CoQ10) supplementation has also demonstrated efficacy in randomized controlled trials in ME/CFS and mitochondrial diseases, including improvements in fatigue, lactate metabolism, and electron-transport coupling [56–58]. The botanical compound baicalin and the pharmacologic agent metformin have been shown to restore palmitate oxidation, reverse fibrotic signaling, and normalize TGF-β-induced metabolic inhibition in cellular models [59]. Collectively, these results suggest that manipulating lactate, CO2, and β-oxidation constitutes a logical, mechanistically based therapeutic strategy for managing the underlying metabolic derangements of PACS and PACVS.

## 3. Autoimmunity

### 3.1 Clinical presentation

The purpose of vaccination is to elicit an immune response to a foreign antigen, which may reduce the likelihood of infection and/or the severity of infection compared to the unvaccinated state. Given the immunogenicity of vaccination, it is important that the immune response targets the antigen of the infectious agent that the vaccine is designed to address.

Autoimmunity is a longstanding concern in vaccination. Several prominent vaccines are associated with increased rates of autoimmune disorders in recipients.

These include the swine flu vaccine developed and deployed in 1976, which was later recalled due to 532 cases of Guillain-Barré syndrome (GBS) being observed following influenza vaccination between October 1976 and January 1977 in the USA [60]. GBS is a demyelination disorder caused by autoantibodies and T-cells attacking myelin [61].

Other cases of autoimmunity resulting from vaccination include immune thrombocytopenic purpura (ITP) after measles, mumps, and rubella (MMR) vaccination [62], arthritis after rubella vaccination [63–65], and vaccine-induced immune thrombotic thrombocytopenia after COVID-19 vaccination [66].
A systematic review with meta-analysis evaluated the literature on the association between vaccinations and the risk of systemic lupus erythematosus (SLE) and rheumatoid arthritis (RA), that is, chronic autoimmune diseases that are treatable but rarely curable [67]. The relative risk (RR) of developing RA and SLE in vaccinated versus unvaccinated individuals was calculated using 12 studies on vaccination and SLE risk and 13 studies on vaccination and RA risk. The pooled results suggested that vaccinations significantly increase the risk of SLE (RR = 1.50, 95% CI 1.05–2.12, P = 0.02) and RA (RR = 1.32, 95% CI 1.09–1.60, P = 0.004). This finding pertains to a heterogeneous set of different vaccinations, and the available evidence is insufficient to determine which vaccine type is more strongly implicated.

Several autoimmune manifestations are observed after COVID-19 vaccination [68], including autoimmune hepatitis [69–97], rheumatoid conditions [98–100], colitis [101], neurologic disorders [102–104], ITP [105], and diabetes mellitus [106].

### 3.2 Contribution to PACVS

Beyond those with acute autoimmune adverse reactions to COVID-19 vaccines, there is another population characterized by chronic, nonresolving health issues postvaccination [107]. In this population, autoimmunity may also be driving symptoms. The most common symptoms were asthenia, memory or concentration problems, headache, tachycardia and hypertension, widespread burning sensations, fainting or dizziness, and visual disturbances. The symptoms were severe, persistent, or recurrent over months or years.

One survey of PACVS patients tested for autoantibodies and found autoantibodies for several G-protein-coupled receptors in affected vaccinated individuals [107]. The most common autoantibodies were MAS1 (positive in 94% of patients), ACE2 (65%), CHRM4 (59%), ADRA1 (53%), and ADRB2 (53%). Anti-GPCR autoantibodies also have prognostic value in COVID-19, where they are associated with disease severity [108].

Among patients with anti-ACE2 positivity, the percentage of symptomatic cases was higher, and the difference between antibody-positive and antibody-negative cases was particularly evident for hypertension, headache, gastritis, skin bruising, edema or rash, thrombosis, and visual impairment. Considering the correlation between anti-S and anti-ACE2 autoantibodies, a hypothesis suggesting that the latter would be formed through an antiidiotype immunologic mechanism has been presented [107].

PACVS patients have measured autoantibodies, and the identity of autoantibodies shows some association with the symptom profile. Observational data indicate that several types of autoantibodies may emerge following vaccination.

The class of autoimmune disorders is a well-documented acute reactogenicity to COVID-19 vaccines [103], as well as comprising an etiology of chronic postvaccine complications [107]. It should also be noted that COVID-19 infection can drive autoimmune disorders, and COVID-19 vaccination may be protective.

One of the most critical aspects of PACVS is the presence of autoantibodies directed against various receptors in the autonomic and cardiovascular systems. Autoantibodies target adrenergic and cholinergic GPCR receptors, ACE2, MAS1, AT1R, ETAR, CXCR3, Stab1, FGFR3, and PF4 [109–113]. Testing for these antibodies, or at least anti-ACE2, could become routine for this type of disease.

In addition to the idiotypic network theory, autoimmunity in PACS and PACVS has also been explained by the mechanism of molecular mimicry between the spike protein and human proteins, which become the target of antibodies and T lymphocytes [114–118]. Among the human proteins involved in the peptide sharing, many are implicated in cellular signaling pathways that regulate crucial processes such as proliferation, differentiation, apoptosis, and immune response [119]. These authors have underscored the cross-reactivity with adenosine receptor A2b (AA2BR), adiponectin, C163A protein (a membrane-bound receptor selectively expressed in macrophages), CREB1 (a key transcription factor that inhibits NF-κB activation), and IL-10. Several homologies were also found with proteins of the pericardium [120], proteins related to oogenesis and uterine receptivity [121], thrombopoietin (which may induce thrombocytopenia), and tropomyosin (linked to cardiac disease) [122]. A molecular mimicry between the spike protein and angiotensin 2 [123] could explain the formation of autoantibodies that react with ACE2 causing blood pressure dysregulation, a very frequent symptom in PACVS.

Autoimmunity could also be promoted by an interaction of the spike with specific HLA alleles. According to Karami et al. [124], the RRARSVAS peptide of the spike protein binds to various HLAs, including HLA-B*08:01 and HLA-B*07:02, which are typically associated with neurological autoimmune diseases. The DEDDSEPV peptide is reported to bind to the HLA-B*40:01 allele, linked to various conditions, notably increasing the risk for ankylosing spondylitis. Others have observed a significant association of HLA-A*03:01 and HLA-A*29:02 with systemic side effects of SARS-CoV-2 vaccines, while HLA-B*08:01 appeared to be protective [125]. It is therefore very likely that vaccines based on the spike protein induce antibodies and cross-reactive T lymphocytes also by molecular mimicry, possibly amplified by epitope spreading [126], when the immune response to one specific part (epitope) of a protein expands to target other epitopes on the same protein or different proteins, causing the immune attack to broaden and become more damaging by revealing hidden self-antigens after tissue damage.

### 3.3 Treatment of autoimmune manifestations in PACVS

Glutathione modulates the immune response, reducing the levels of inflammatory cytokines (such as IL-6 and IL-8) and protecting tissues from the collateral damage of inflammation [127]. Glutathione acts as a direct "shield," preventing oxidative damage that contributes to interstitial pneumonia and microthrombosis. It appears that a cellular environment rich in glutathione (a balanced redox state) can hinder viral replication, making the intracellular environment less hospitable to the pathogen [128]. The crucial implications of glutathione dysregulation and the beneficial effects of GSH supplementation have

been pointed out in both the long-COVID syndrome and PACVS, which share several biochemical mechanisms [129–131]. Aiming to correct oxidative stress and restore redox homeostasis is also consistent with more recent evidence that patients vaccinated against SARS-CoV-2 showed widespread transcriptional dysregulation with mitochondrial dysfunction and oxidative stress [132].

Hesperidin and quercetin are two flavonoids important for restoring the immune system to physiological conditions, reducing inflammation, and combating oxidative stress associated with inflammation [133–136]. Molecular docking studies have shown that these substances exhibit high affinity for the viral spike protein and the ACE2 receptor on host cells [137, 138]. By binding to these structures, they physically hinder spike protein attachment and its inflammatory and thrombotic consequences [139]. The use of quercetin supplementation in COVID-19 is also supported by clinical studies and meta-analyses [140, 141]. Furthermore, hesperidin and quercetin are known to have neuroprotective [137] and broad-spectrum antiviral activities that can counteract viral reactivation, particularly those of the herpesvirus family [142–144], which are very frequent in this type of patient. This does not exclude the possibility that antiviral drugs are necessary for short-to medium-term periods when intense herpes viral reactivation is underway. The use of antioxidant vitamins and polyphenols in PACVS has also been suggested by others [145].

The rationale for using Ang 1–7 is that patients with COVID-19 and PACVS have a significant dysregulation of the ACE2/Ang 1–7/MAS1 axis [107, 139, 146] and the severity of several inflammation-related diseases has been associated with autoantibodies to Ang 1–7 receptors and against ACE2 [147]. Among other things, it should be noted that in patients with heart failure, an Ang 1–7/Ang II ratio is an independent and incremental predictor of positive outcomes, increased survival rates, and reduced length of hospitalization [148]. Experimental studies suggest that an Ang-1–7 oral formulation improves physical performance in athletes [149], and animal studies support the use of oral supplementation of Ang 1–7 as an antithrombotic, antiinflammatory, and neuroprotective agent in different models [150–154]. These results provide important preclinical evidence supporting strategies to promote the beneficial Ang 1–7/MAS1 axis. In our experience, Ang 1–7 reactivates the Threg antibody response, modulates inflammation, and reduces the procoagulant and inflammatory tendencies of vessels. The efficacy of a neuroimmune therapy including Ang 1–7 and endocannabinoids in cancer, autoimmune, and neurodegenerative diseases has been reported in an observational study by an Italian group, including one of the authors (GDF) [155].

In selected and particularly severe cases, therapeutic plasmapheresis may be recommended to remove inflammatory mediators and autoantibodies [156, 157]. A study program on the effects of immunoglobulin infusion has also recently been launched, which, in a certain percentage of cases, appears to produce positive and lasting effects [158].

## 4. Clotting pathology

### 4.1 Clinical presentation

Thrombosis with thrombocytopenia, or vaccine-induced immune thrombocytopenia and thrombosis (VITT), is a rare but severe reaction seen mainly with adenoviral vector

(AV) vaccines [1]. The strongest association has been reported with the ChAdOx1 nCoV-19 vaccine. In the Pavord et al. cohort, 170 of 294 patients met VITT criteria, typically presenting 14 days after vaccination, with a mean age of 48. Mortality reached 73% in those with severe thrombocytopenia and intracranial hemorrhage [66]. Consistent with this, VITT is characterized by sudden thrombocytopenia, extremely high D-dimer, low fibrinogen, and thrombosis in unusual sites such as cerebral venous sinuses or splanchnic veins [66, 159]. Although late detection contributed to the initial high mortality [159], outcomes improved significantly with PF4-ELISA testing, early IVIG, and nonheparin anticoagulation [66, 159].

Beyond VITT, milder postvaccine thrombotic events such as DVT, PE, MI, and ischemic stroke generally occur in individuals with preexisting cardiovascular risk factors [160]. In a vascular context, an endothelial-function RCT found that the second BNT162b2 dose produced a surge in inflammatory markers and a transient 1.5% reduction in flow-mediated dilation, which normalized within 48 hours [161].

Across vaccine types, thrombotic risk varies substantially. Adenoviral-vector vaccines show the strongest association with VITT/TTS, with incidence estimates around 1 per 64,000–125,000 (ChAdOx1) and 1 per 200,000–310,000 (Ad26.COV2.S) [162]. Women appear over-represented in early VITT case series because of early vaccination rather than being related to sex [162]. In contrast, mRNA vaccines (BNT162b2, mRNA-1273) and inactivated vaccines (CoronaVac, BBIBP-CorV) have not shown increased rates of VTE, CVST, or thrombocytopenia above background levels [160]. Scully et al. further reinforced this by reporting 23 VITT cases occurring 6–24 days after ChAdOx1 [13].

As evidence accumulated, a clearer pattern began to emerge: thromboembolic events after vaccination can span a range of severities, shaped by age, sex, comorbidities, and platform differences [163]. This is reflected in US VAERS data, where thrombosis with thrombocytopenia syndrome (TTS) after AV vaccines occurred at ~3.83 cases per million doses [164], while mRNA-associated rates remained much lower [165]. Additional reports describe rare complications such as AKI, renal artery thrombosis with AV vaccines, and a delayed pulmonary hemorrhage 555 days after Pfizer vaccination [166].

Across 20 pooled studies, most postvaccination thromboembolic events occurred around day 10, mostly in younger individuals (mean age ~48), with women overrepresented and venous events, especially CST, far more common than arterial ones. CST mortality approached 30%, and over 90% of cases followed ChAdOx1 vaccination [167]. Mortality among CST cases approached 30%, and a large proportion of reported thromboembolic events (over 90%) occurred after the administration of the AstraZeneca (ChAdOx1) vaccine [167]. WHO VigiBase data similarly highlighted stroke as a major vascular signal [168].

Platelet activation is a feature present during and after COVID-19 infection [169–171], as well as long COVID [172–175] and postvaccination disorders [176–178]. Cohort studies of COVID-19 survivors show that platelets remain hyperreactive months after discharge, with enhanced degranulation, spreading on fibrinogen, and heightened responses to subthreshold thrombin stimulation, indicating a persistently primed platelet phenotype [169–171]. These findings suggest that platelet hyperreactivity is not confined to the acute phase but extends into the postacute period, providing a biological bridge between acute COVID-19, long COVID, and postvaccination clotting phenotypes.

### 4.2 Mechanism

Rather than producing sudden, large-vessel thrombosis, as seen in VITT, a rare adverse event, PACVS reflects a chronic, low-grade procoagulant state that mirrors patterns observed in Long COVID, ME/CFS microclots, and endothelial autoantibody-driven dysfunction. This persistent clotting seems to stem from immune dysregulation, autoantibodies targeting endothelial GPCRs, microvascular inflammation, and platelet-activation abnormalities [179].

In survivors of moderate–severe COVID-19, platelets display sustained surface expression of activation markers such as P-selectin, CD63, and activated GPIIb/IIIa, with increased secretion of granule products and heightened thrombin sensitivity, indicating a chronically primed, hyperreactive state [169–171]. Complementary work in Long COVID describes ongoing low-grade inflammation and persisting platelet activation in patients [172–175]. In both settings, low-grade inflammation and immune-driven, antibody-mediated platelet activation appear central. Postvaccination platelet activation fits into the same pattern: COVID-19 vaccines can transiently increase inflammation and platelet activation, and in rare cases, such as VITT, anti-PF4 or antispike immune complexes activate platelets via FcγRIIa, mirroring the immune-mediated pathways implicated after infection and in Long COVID [176–178].

Because all COVID-19 vaccines express the spike protein, its effects on coagulation remain relevant. The spike protein has been associated with hypercoagulability [180], including microclots observed in pulmonary tissue. Pretorius and Kell [3] expanded on this with the "microclotting hypothesis," showing through proteomic analysis that individuals with postinfection or postvaccination syndromes exhibit elevated levels of serum amyloid A1/A2, attractin, and coagulation factors X and XI, along with downregulated immune-regulatory proteins [181]. These findings indicate sustained immune activation and changes in coagulation pathways. In fact, across COVID-19, PACS, and PACVS – autoantibodies, endothelial dysfunction, amyloid fibrin microclots, platelet hyperactivation, and persistence of viral mRNA or proteins – arise consistently [182]. Ryu et al. further demonstrated that fibrinogen-related clotting abnormalities correlate with post-COVID cognitive impairment and may serve as predictive biomarkers [183], highlighting the central role of fibrin in ongoing inflammation.

Further studies provide additional clarity as the SARS-CoV-2 spike protein, specifically the S1 subunit [184], can directly alter fibrin formation. When S1 is introduced into healthy plasma, it modifies key clotting proteins, including fibrinogen β/γ chains, complement component 3, and prothrombin [185], producing dense amyloid-like fibrin structures that resist normal fibrinolytic enzymes [186]. This impaired fibrinolysis offers a clear explanation for the persistence and resilience of microclots across postacute syndromes. Clinical studies on long COVID-19 support these mechanistic findings. Patients had markedly higher microclot burdens than healthy controls [187]. These protease-resistant microclots can also sequester circulating biomarkers [188], potentially hindering early recognition.

The downstream consequences of persistent fibrin amyloid microclots are systemic. Obstruction of the lung microvasculature limits oxygen delivery, contributing to dyspnea and exercise intolerance. Microvascular flow restriction may also drive cardiovascular and neurological complications, dysautonomia, renal impairment, elevated lactate production, and postexertional symptom worsening.

These mechanisms help explain why the effects of COVID-19 extend far beyond the respiratory tract and why some patients improve with hyperbaric oxygen therapy.

Amyloid fibrils themselves pose an additional challenge, as they can disrupt cell membranes and cause direct tissue injury. Taken together, these processes position microclot formation and impaired fibrinolysis as a coherent pathogenic framework underlying Long COVID, PACS, and PACVS.

*Mechanistically, the recurring combination of thrombocytopenia, high D-dimer, low fibrinogen, and thrombosis parallels heparin-induced thrombocytopenia and other FcγRIIa-mediated immune platelet-activation syndromes*, reinforced by widespread anti-PF4 positivity [189]. Proposed drivers include adenoviral-DNA–PF4 interactions or cross-reactivity between spike-induced antibodies and platelet factors, potentially explaining platform-specific risks [190].

Large epidemiologic datasets further confirm a transient increase in thrombotic risk after vaccination. A national SCCS of 29 million adults showed increased thrombocytopenia and a slight VTE elevation after ChAdOx1, and a small rise in arterial events after BNT162b2 [191]. Similar results appeared in Scandinavian data, which linked AZD1,222 to increased CVT and thrombocytopenia in both sexes [192]. Hong Kong analyses of >8.6 million BNT162b2 and CoronaVac doses further identified several hundred thromboembolic and hemorrhagic stroke cases within 28 days of vaccination [193]. Taken together, these findings indicate the overall pattern reflects a spectrum of vaccine-associated vascular effects shaped by platform biology, host factors, and underlying immune mechanisms.

### 4.3 Treatment

In the context of long COVID-19, triple anticoagulant therapy has been examined in an unpublished preprint [194]. The anticoagulation regimen consisted of dual antiplatelet therapy (DAPT) with clopidogrel 75 mg and aspirin 75 mg once daily, along with a direct oral anticoagulant (DOAC), apixaban 5 mg twice daily. Additionally, a proton pump inhibitor (PPI), pantoprazole 40 mg daily, was prescribed for gastric protection [194].

Triple anticoagulant therapy was associated with marked improvement or resolution of most Long COVID symptoms in the majority of 91 patients. Patients reported substantial reductions in fatigue, cognitive dysfunction, shortness of breath, pain, mood symptoms, palpitations, sleep disturbance, and digestive problems, as reflected in a median Patient Global Impression of Change score of 6, indicating a definite, worthwhile improvement in daily functioning and quality of life [194]. There are currently no studies evaluating anticoagulant therapy for PACVS patients, as opposed to PACS patients (i.e., patients with long COVID-19). The clotting hypothesis remains controversial and requires verification in both the context of long COVID [195] and PACVS [145].

Another treatment modality is the removal of clots through plasmapheresis. However, this modality does not show efficacy in treating Long COVID-19 [196, 197] and remains untested for PACVS.

## 5. Endothelial dysfunction

### 5.1 Clinical presentation

Acute endothelial dysfunction following COVID-19 vaccination has been reported and most often presents as small-vessel inflammatory and microvascular syndromes [198, 199]. The clinical manifestations include cutaneous leukocytoclastic vasculitis, urticarial vasculitis, Raynaud phenomenon, and livedo reticularis, typically occurring within days to weeks after vaccination [200–202]. Histopathologic evaluation has reported vasculitic cases that demonstrate perivascular inflammatory infiltrates, endothelial swelling, fibrinoid changes, and immune-complex deposition, supporting an immune-mediated process centered on endothelial activation rather than direct cytotoxic injury [199, 203]. While many cases improve with immunomodulatory therapy, these findings highlight that COVID-19 vaccination can, in some instances, trigger clinically significant microvascular inflammatory responses requiring medical recognition and management [204, 205].

Outside of cutaneous involvement, acute endothelial dysfunction following COVID-19 vaccination has been reported in other vascular beds. Reports describe IgA vasculitis with renal involvement, presenting as hematuria, proteinuria, or nephrotic syndrome after immunization, with kidney biopsies confirming immune-complex vasculitis and glomerular injury [206–208]. In addition, isolated cases of medium-vessel vasculitis associated with mRNA vaccination have been documented, including patients with systemic symptoms and histologic evidence of vascular inflammation affecting the muscular arteries [209–211]. Other reports have documented large-vessel vasculitis, ANCA-associated vasculitis, and isolated central nervous system vasculitis following COVID-19 vaccination [212–218]. Collectively, these reports indicate that COVID-19 vaccination may be followed by clinically significant vasculitic syndromes beyond the skin.

Importantly, the endothelial manifestations reported after COVID-19 vaccination overlap mechanistically with those observed during acute SARS-CoV-2 infection, although they occur less frequently and with substantially lower clinical impact. COVID-19 infection is characterized by widespread endothelial activation and endotheliitis affecting pulmonary, renal, cardiac, and systemic vascular beds, driven by inflammatory cytokines, immune cell-endothelial interactions, and endothelial anticoagulant dysregulation. Histopathologic studies have demonstrated endothelial inflammation and injury across multiple organs. In contrast, clinical studies have documented impaired endothelial function and elevated endothelial activation markers that correlate with disease severity and adverse outcomes [219–221]. While the incidence of endothelial complications following COVID-19 vaccination remains lower than that observed with acute COVID-19 or post-COVID-19 endothelial dysfunction, the documented occurrence of immune-mediated vasculitic and microvascular syndromes underscores the importance of clinical awareness and postvaccination surveillance, as these endothelial manifestations may lead to significant morbidity.

### 5.2 Mechanism

The mechanism underlying endothelial dysfunction following COVID-19 vaccination is not fully clear; however, it is primarily attributable to the immune response rather than direct endothelial toxicity. Current evidence suggests that vaccine-induced spike protein expression triggers transient innate immune activation, characterized by cytokine release and complement system activation, which can affect endothelial homeostasis. Endothelial cells may become activated by exposure to circulating inflammatory mediators, immune complexes, and complement fragments, leading to increased vascular permeability, adhesion molecule expression, and proinflammatory signaling [222]. These effects may be amplified by the immunogenicity of mRNA-lipid nanoparticle platforms, which function as endogenous adjuvants that activate innate immune pathways, including interferon signaling and toll-like receptor signaling. In some individuals, systemic dissemination or persistence of vaccine-derived spike protein may prolong inflammatory signaling, while spike-ACE2 interactions and molecular mimicry contribute to immune dysregulation and endothelial activation [223]. In susceptible individuals, these immune responses may culminate in localized endothelitis or small-vessel vasculitis.

### 5.3 Treatment

Therapeutic strategies for endothelial function in PACVS are currently based on pathophysiological and observational data, as well as clinical experience. Proposed approaches emphasize immune modulation, redox balance restoration, and vascular homeostasis, including the use of antioxidants such as glutathione to counteract oxidative stress and inflammatory endothelial injury [129, 130] as well as flavonoids (hesperidin and quercetin) with antiinflammatory and potential antithrombotic properties [134, 135]. In patients with evidence of renin-angiotensin system dysregulation and vascular inflammation, angiotensin [1–7] has been proposed to restore the protective ACE2/Ang(1-7)/MAS 1 axis, exerting endothelial protective, antiinflammatory, and antithrombotic effects [134, 224]. Additional therapies, such as vitamin D and enzymatic agents with antithrombotic activity (nattokinase, bromelain), have been used in selected cases [225–227].

## 6. Conclusion

The pathological mechanisms of metabolic dysfunction, coagulation, and autoimmunity are important drivers of PACVS and long COVID pathology. Therapeutics targeting these axes may be effective in treating PACVS.

PACVS and long COVID involve a characteristic pattern of metabolic failure, low lactate threshold, disrupted CO2 regulation, and impaired fatty acid oxidation, which may be amenable to mechanistically targeted interventions such as low-intensity aerobic conditioning, buffering strategies, breathing/hypercapnic protocols, and fat adaptation training. Adjunctive use of agents such as CoQ10, BCAAs, nitrate/nitrite supplements, and drugs such as metformin or baicalin may support mitochondrial function and beta-oxidation, though these strategies remain investigational.

For autoimmunity, a coherent model is emerging in which a subset of PACVS behaves as a chronic autoimmune disorder driven by GPCR- and RAS-directed autoantibodies [107]. Within this framework, therapies that restore redox homeostasis and rebalance the ACE2–Ang 1-7–MAS1 axis may be beneficial, including flavonoids, which demonstrate therapeutic benefits in COVID-19 infection [140, 141], and Ang 1-–7, which can improve athletic performance in athletes [149]. Plasmapheresis and intravenous immunoglobulin may be helpful in severe, refractory cases, as they may attenuate autoimmune activity and improve outcomes; however, results remain preliminary.

Current evidence suggests that thrombotic and microvascular pathology in PACVS and long COVID may justify antithrombotic strategies in selected patients [194], but the data remain preliminary and do not yet support the routine use of aggressive regimens. For plasmapheresis to remove blood clots, data are more limited, and current studies on plasmapheresis for long COVID do not demonstrate benefit [196, 197].

Despite these mechanistic arguments for therapeutics, clinical validation of therapeutics is limited, with a single retracted case series in the literature [228].

## Glossary

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| **ACE2** | Angiotensin-converting enzyme 2, a surface enzyme and receptor involved in SARS-CoV-2 entry and the regulation of the renin–angiotensin system. |
| **ADRA1** | Alpha-1 adrenergic receptor, a G-protein-coupled receptor (GPCR) involved in vascular tone and autonomic regulation. |
| **ADRB2** | Beta-2 adrenergic receptor, a GPCR mediating sympathetic effects on the bronchi, vasculature, and metabolism. |
| **AKI** | Acute kidney injury, a sudden decline in kidney function. |
| **Ang 1–7** | Angiotensin 1–7, a heptapeptide of the renin–angiotensin system with vasodilatory and antiinflammatory properties acting via MAS1. |
| **AT1R** | Angiotensin II type 1 receptor, a receptor mediating many vasoconstrictive and proinflammatory effects of angiotensin II. |
| **BCAAs** | Branched-chain amino acids (leucine, isoleucine, valine) used as metabolic and nutritional interventions. |
| **CNS** | Central nervous system, comprising the brain and spinal cord. |
| **CPT-1** | Carnitine palmitoyltransferase-1, a key enzyme controlling mitochondrial long-chain fatty acid uptake and β-oxidation. |
| **CST/CVST** | Cerebral (venous) sinus thrombosis, thrombosis of the dural venous sinuses. |
| **DAPT** | Dual antiplatelet therapy, typically aspirin plus a P2Y12 inhibitor, such as clopidogrel. |
| **DOAC** | Direct oral anticoagulant, a class of oral agents targeting factor Xa or thrombin. |

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|---|---|
| **ETAR** | Endothelin A receptor, a GPCR mediating vasoconstrictive and proinflammatory signaling. |
| **FFA** | Free fatty acid, circulating nonesterified fatty acids involved in energy metabolism and signaling. |
| **FGFR3** | Fibroblast growth factor receptor 3, a receptor tyrosine kinase implicated in some small-fiber neuropathy cases. |
| **GBS** | Guillain–Barré syndrome, an acute immune-mediated demyelinating neuropathy. |
| **GPCRs** | G-protein-coupled receptors, a large family of membrane receptors targeted by autoantibodies in PACVS. |
| **IVIG** | Intravenous immunoglobulin, pooled antibodies used as an immunomodulatory therapy. |
| **ITP** | Immune thrombocytopenic purpura, an autoimmune platelet-destroying disorder. |
| **LA/linoleic acid** | A polyunsaturated omega-6 fatty acid binding to a conserved pocket on the SARS-CoV-2 spike protein. |
| **ME/CFS** | Myalgic encephalomyelitis/chronic fatigue syndrome, a chronic illness characterized by exertional intolerance and postexertional malaise. |
| **MI** | Myocardial infarction, a heart attack caused by coronary artery occlusion. |
| **PACVS** | Postacute COVID-19 vaccination syndrome, persistent multisystem symptoms following COVID-19 vaccination. |
| **PACS/PASC** | Postacute COVID-19 syndrome/postacute sequelae of COVID-19 ("long COVID"). |
| **P2X3** | P2X3 receptor, a purinergic receptor implicated in chemoreflex and cough hypersensitivity. |
| **PF4** | Platelet factor 4, a platelet chemokine that can form immune complexes targeted in HIT and VITT. |
| **RAS (system)** | Renin–angiotensin system, a hormonal system regulating blood pressure and vascular tone. |
| **RA/SLE** | Rheumatoid arthritis/systemic lupus erythematosus, systemic autoimmune diseases. |
| **ROS** | Reactive oxygen species, chemically reactive oxygen-containing molecules contributing to oxidative stress. |
| **S1 (spike S1)** | S1 subunit of the SARS-CoV-2 spike protein, implicated in endothelial and coagulation changes. |
| **TCA cycle** | Tricarboxylic acid cycle (Krebs cycle), a central mitochondrial energy-generating pathway. |
| **TGF-β** | Transforming growth factor beta, a cytokine involved in fibrosis and immune regulation. |
| **Threg (Treg)** | Regulatory T cell response, immune-regulatory arm modulating autoimmunity and inflammation. |
| **TTS/VITT** | Thrombosis with thrombocytopenia syndrome/vaccine-induced immune thrombotic thrombocytopenia, a rare postvaccine autoimmune thrombotic disorder. |
| **vWF** | von Willebrand factor, a multimeric glycoprotein involved in platelet adhesion and clot formation. |

## Conflict of Interest

PB and GDF had a consultation with Vanda Omeopatici s.r.l. (Roma, Frascati), a company that produces natural medicines and food supplements, but that company had no role in the design of the study, the collection, analysis, or interpretation of the data, the writing of the manuscript, or the decision to publish the results.

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