Autoimmunity Reviews 20 (2021) 102899

Contents lists available at ScienceDirect

Autoimmunity Reviews

journal homepage: www.elsevier.com/locate/autrev

Review

# Similarities between COVID-19 and systemic sclerosis early vasculopathy: A "viral" challenge for future research in scleroderma

Marco Matucci-Cerinic [a,b,*], Michael Hughes [c], Gloria Taliani [d], Bashar Kahaleh [e]

[a] Department of Experimental and Clinical Medicine, University of Florence & Division of Rheumatology AOUC, Florence, Italy
[b] Unit of Immunology, Rheumatology, Allergy and Rare Diseases (UnIRAR), IRCCS San Raffaele Hospital, Milan, Italy
[c] Department of Rheumatology, Royal Hallamshire Hospital, Sheffield Teaching Hospitals NHS Foundation Trust, Sheffield, UK
[d] Infectious Diseases Unit, Department of Translational and Precision Medicine, Sapienza University of Rome, Rome, Italy
[e] Division of Rheumatology, Allergy and Immunology, University of Toledo Medical Center, Toledo, OH, USA.

ARTICLE INFO

*Keywords:*
SarsCov2
COVID-19
Systemic sclerosis
Autoimmunity
Endothelial damage

ABSTRACT

*Objective:* To review similarities between COVID-19 and systemic sclerosis (SSc) early vasculopathy to provide novel insights into both diseases.
*Methods:* A narrative review of the literature supplemented with expert opinion.
*Results:* There is clear evidence that the endothelium is at the centre stage in SSc and COVID-19, with endothelial cell activation/injury and dysfunction creating the crucial evolving step in the pathogenesis of both diseases. The angiotensin system has also been implicated in the early stages of both COVID-19 and SSc. Autoptic studies provide novel insights into the effects of SARS-CoV-2 on the endothelium. Normal endothelium and endothelial dysfunction in COVID-19 and SSc are discussed. It is debated whether SARS-CoV-2 infection triggers autoimmunity with production of autoantibodies which is of mechanistic interest because other viral illnesses are potentially involved in endothelial dysfunction and in SSc pathogenesis.
*Conclusion:* COVID-19 is due to a direct assault of SARS-CoV-2 on the vascular system as an acute infection, whereas SSc remains a chronic/sub-acute autoimmune disease of largely unknown etiology Further study and exploration of the SARS-CoV-2 pathogenic mechanisms might provide further useful milestones in the understanding of the early SSc pathogenesis.

## 1. The SarsCov2 pandemic and the main pathogenetic mechanisms

The SARS-CoV-2 pandemic has swarmed worldwide and the COVID-19 has taken a significant death toll in all continents. In fact, the virus has a highly unrestrained replication capacity which is met with unbalanced immune response, a weak production of type I interferons (IFN-Is) and a brisk release of proinflammatory cytokines [1]. Apoptosis, autophagy and pyroptosis are upregulated [2], significant lymphopenia occurs, and NK and T cells become functionally deficient. In the meanwhile, there is an increase of angiotensin II (ANG II) levels with induction of interleukin-6 (IL-6) and other pro-inflammatory cytokines (IL-2, IL-7, IL-10, G-CSF, MCP-1, MIP-1A and TNF-alpha) that mediate lung injury in COVID-19 disease [3,4]. Moreover, activation of the coagulation cascade, which correlates with disease severity, is associated with high levels of D-dimers [5]. The Sars-Cov-2 invasion leads to the downregulation of angiotensin convertase enzyme-2 (ACE-2) and the intracellular accumulation of angiotensin II which promotes premature endothelial cells senescence along with dysfunctional coagulation and immunity [3]. Binding of SARS-CoV-2 to ACE-2 through the ectodomain of the trimeric spike protein is followed by endocytosis and translocation of the virus/ACE-2 complex with down regulation of ACE surface expression [6]. The specific link of the SarsCov2 for the ACE-2 receptor has opened a new area of investigation because this interaction leads to a functional inhibition of the enzyme with deleterious effects due to the loss of the protective role of ACE-2 in acute lung injury [7]. Therefore, ACE-2 downregulation may exacerbate lung inflammation, vascular damage, coagulation and altered immunity mediated by increased levels of ANGII [3] (Fig. 1). Accordingly, ANGII blockers might help, containing either the clotting process and/or the immune dysregulation [7,8] (Fig. 1), possibly changing the prognosis of severe COVID-19 patients.

* Corresponding author at: Div Rheumatology, University of Florence, via delle Oblate 4, 50139 Firenze, Italy.
*E-mail address:* marco.matuccicerinic@unifi.it (M. Matucci-Cerinic).

https://doi.org/10.1016/j.autrev.2021.102899
Received 18 May 2021; Accepted 26 May 2021
Available online 15 July 2021

Moreover, the role of complement activation during lung inflammation due to SARS-CoV-2 infection has been recently raised in the literature [9]. Complement plays an important role in the innate immune response to viruses and in the development of proinflammatory responses. Therefore, the virus may not only induce microangiopathy and activate homeostasis but also activate complement [10], in particular, the C3 signaling which is positioned upstream in the innate immunity cascade [11]. Recently, it has been reported that in lung tissue from patients with severe SARS-Cov-2 pneumonia C3a generation and C3-fragment deposition are associated with increased serum levels of C5a. [12]. The N protein of SARS-CoV-2 binds to MASP-2, the key serine protease in the lectin pathway of complement activation, resulting in aberrant complement activation, thus contributing to aggravate inflammatory lung injury [12].

Eventually, the tight relationship between the SARS-CoV-2 and the endothelium has led to the suggestion that COVID19 is a vascular disease [11,12,13]. Recent histopathological studies have pointed out that both pulmonary type 2 alveolar epithelial cells and endothelial cells (ECs) equally contribute to the evolution of lung pathology and have a determinant role in vascular dysfunction, inflammation, and thrombosis that occur in SARS- Cov-2 infection [14]. In addition, autopsies demonstrated acute capillaritis in the lung with massive infiltration of neutrophils that extravasate into the alveolar space [15] and cause neutrophil extracellular traps (NETs) [16] which attach to the capillary endothelium, aggregate the platelets and induce coagulation. The damage to the alveolar–capillary barrier leads to vascular leakage, edema and finally ARDS [16] with pulmonary microembolism, detected in most of patients in spite of anticoagulation therapy [17]. Inflammasome activation and pyroptosis are under reported events that are central to COVID-19 pathogenesis. Pyroptosis, or caspase 1-dependent cell death, is inherently inflammatory form of cell death process [18]. Cell death occurs as the result of membranous pore formation and cytoplasmic swelling, and leakage of cytosolic contents. Pyroptotic cells may also display DNA fragmentation and nuclear condensation. Pyroptosis requires cleavage and activation of the pore-forming effector protein gasdermin D by inflammatory caspases. Physical rupture of the cell causes release of the pro-inflammatory cytokines IL-1β and IL-18, alarmins and endogenous danger-associated molecular patterns, signifying the inflammatory potential of pyroptosis. Activation of pyroptosis pathway in the pulmonary samples from COVID-19 patient has been reported [18,19], and also considered as a possible target for specific therapy [20].

## 2. The effects of SARS-CoV-2 on the endothelium- evidence from autoptic studies

Autoptic studies have revealed that SARS-CoV-2 infection induces a wide-ranging number of serious effects on the endothelium including (but not limited to) severe endothelial injury and inflammation (endotheliitis), capillary inflammation, widespread thrombosis with microangiopathy, and neoangiogenesis. In fact, widespread thrombosis of lung structures is now well recognised in SARS-CoV-2 [21]. In the lungs obtained during autopsy of SARS-CoV-19 patients, compared to influenza A (H1N1) lungs and age-matched, uninfected lungs, distinctive vascular features were found [22]. These consisted of 'severe endothelial injury associated with the presence of intracellular virus and disrupted cell membranes' [22]. In addition, pulmonary vessels revealed the presence of widespread thrombosis with microangiopathy [22]. Of note, alveolar microthrombi were 9 times as prevalent compared to patients with influenza H1N1 [22].

Platelet-rich microthrombi consistent with coagulopathy are now well recognised in SARS-CoV-2 infection [23]. In a systematic review of pathological findings in SARS-CoV-2, almost two thirds of cases ($n = 76/129$, 59%) displayed a vascular pattern of lung injury, with features of vasculopathy which included microthrombi and proteinaceous and fibrinous exudates [24]. Furthermore, gross examination of the lungs from 92 patients revealed the presence of macroscopic pulmonary emboli in 9 cases (10%) [23]. Ongoing thrombosis has also been reported in the small to medium-sized pulmonary vessels [25]. In an autopsy study of the first consecutive 80 patients with SARS-CoV-19, 8 deaths were from pneumonia *with* fulminant pulmonary artery embolism, while peripheral pulmonary artery embolisms was found in another 9 cases [26]. Furthermore, deep vein thrombosis was detected in nearly half (40%) of cases [26]. Similarly, in another prospective cohort study, autopsies performed in 12 patients revealed the presence of deep vein thrombosis in 58% of patients, in whom venous thromboembolism was not suspected prior to death [27].

It is interesting to remark that abnormal neoangiogenesis has been observed in SARS-CoV-2 infection [21]: the amount of new blood vessel growth (which was mainly through intussusceptive angiogenesis) was 2.7 times as high as the lungs from patients with influenza H1N1 infection. Furthermore, the capillary structure was grossly abnormal with deformed and elongated capillaries, and evidence of ultrastructural endothelial damage [22].

Although the lung is considered a key site of SARS-CoV-2, pathological findings have been reported in other organs and tissues [24].

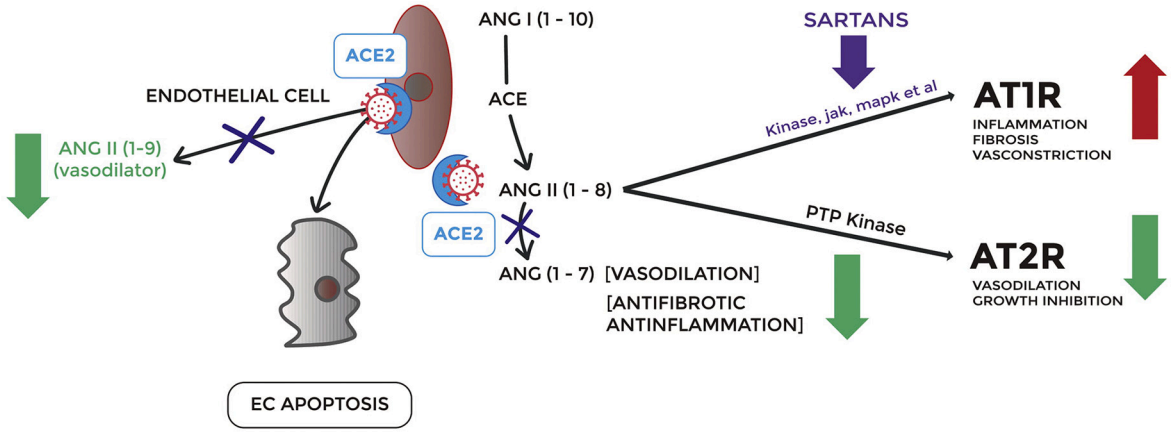


**Fig. 1.** SarsCov2 depletes ACE2 and devastates EC cells containing ACE2. Therefore, it promotes AT1R mediated inflammation, fibrosis and coagulation. Membrane-bound ACE2 is depleted as a result of this entry mechanism. The consequence is that the protective renin-angiotensin system (RAS), of which ACE2 is a fundamental component, is jeopardized due to lack of production of the angiotensin- [1–7] and angiotensin- [1–9], and consequently decreased stimulation of Mas (receptor Mas) and angiotensin AT2-receptors (AT2R), while angiotensin AT1-receptors (AT1R) are overstimulated due to less degradation of Ang II by ACE2. The role of Sartans is to prevent Angiotensin II from binding to AT1R on muscle cells regulating blood vessel contraction and reducing inflammation and evolution to fibrosis.

Viral presence has been also documented within the myocardium, but it is currently unclear whether this is associated with inflammatory cardiac disease (e.g. myocarditis) [28,29]. Variable renal vascular pathology has been also reported including (but not limited to) fibrin and hyaline thrombi, thrombotic angiopathy, and lymphocytic endotheliitis [24,30,31]. Gastrointestinal epithelial damage, prominent endotheliitis, and ischaemic enterocolitis have been reported [24,32–34]. Variable splenic involvement has been documented including necrosis, infarction, congestion, haemorrhage and atrophy [24,27,34]. Cutaneous manifestations with perivascular lymphocytic or neutrophilic infiltrates, have been described in SARS-CoV-19 infection [24,35–37].

Taken together, autoptic studies have provided novel insights into

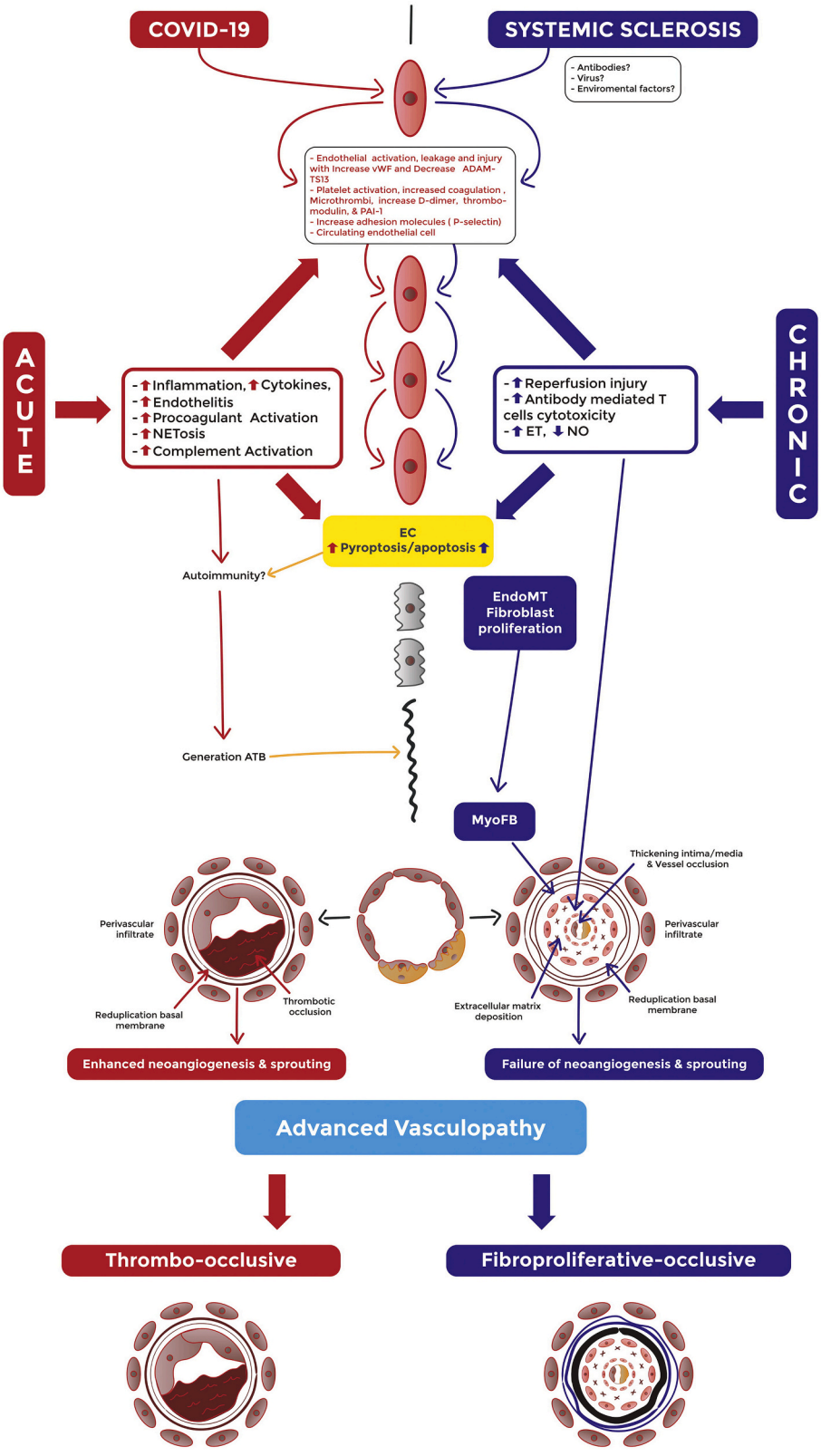


**Fig. 2.** Successive endothelial cells alteration in COVID-19 and in systemic sclerosis (SSc). Although the pace of vascular changes is strikingly different (acute in COVID-19 and chronic in SSc), the two tracks share common pathologic alterations that trigger similar pathways and molecules with similar pathologic consequence. In the early stages, both pathways share functional EC changes including increase in vascular permeability, adhesion molecule expression, platelet activation, coagulation, microthrombosis, fibrinolysis and increased D-dimer and PAI-1 levels. Yet, each pathway has unique characteristics as noted in the prominence of vascular fibrotic changes and diminished angiogenesis in SSc and enhanced angiogenesis and macrothrombosis in COVID-19. The initial trigger in SSc is not known but viral, environmental (silica), and antibodies all can lead to functional and ultrastructural changes resulting in EC apoptosis, In COVID-19, direct EC invasion by SARS-CoV-2 and inflammasome activation triggering neutrophils adhesion, and the formation of neutrophil extracellular traps that damage endothelial further culminating in EC pyroptosis. It is assumed that autoimmune reaction and the generation of autoantibodies follows pyroptosis, while both are very prominent early in SSc. The resulting vascular disorder is more fibrotic in SSc and more thrombotic in COVID. Nonetheless, the impact on surrounding tissues is the same with prominent tissue ischemia and organ underperfusion.

SARS-CoV-2 effects on EC and revealed key insights into disease pathogenesis.

## 3. Endothelial dysfunction, *early* similarities between COVID-19 and SSc

### 3.1. The Normal endothelium

The normal vascular endothelium is a single cell layer that actively participate and mediate remarkably crucial and diverse functions. It regulates tissue inflammation by limiting EC interactions with immune and inflammatory cells, and it also inhibits thrombosis and coagulation by preventing EC interactions with the platelets and by expressing coagulation inhibitors and blood clot-lysing enzymes with anti-coagulation properties. The EC also regulate vascular permeability, vascular tone and surrounding cell metabolism and nutrition. In the disease, EC dysfunction correlates with a pathologic shift in their functional profile from an anticoagulant, anti-inflammatory and vaso-relaxant cell type to a procoagulant, vasospastic and proinflammatory phenotype. Today, it is well known that EC dysfunction is consistently linked with defective endothelial nitric oxide (NO) production which is related to repressed EC nitric oxide synthase (eNOS) gene expression [38]. Thus, NO generated constitutively by EC controls vascular tone, regulates blood pressure and acts as an antithrombotic and cytoprotective agent. Moreover, it inhibits adhesion molecule expression, platelet adhesion and aggregation and smooth muscle cell proliferation [39]. Clearly, NO released at basal levels protects the vascular endothelium against oxidation injury, a major component in the pathophysiology of vasculopathy of any etiology. Consequently, the reduced steady state of NO release would limit its ability as a free radical scavenger and a potent chemical barrier protecting the vascular endothelium from oxidation injury [40].

### 3.2. Endothelial dysfunction in SSc

The hallmarks of endothelial dysfunction in SSc are early EC apoptosis, vascular leakage and deficient NO release (Fig. 2) [41]. The latter leads to dysregulated vascular tone and increased endothelial adhesiveness and thickening of the vascular wall. Failure of endothelium-dependent vasodilatation in response to substance P and other mediators has been shown in the acral circulation, the kidneys and the lungs, suggesting failure of NO production at the endothelial level. A vicious cycle of oxidation injury, loss of EC adaptation and consequent functional alteration may enhance and/or follow deficiency in the basal protective effect of NO against oxidation injury, endothelial activation, and increased expression of a host of adhesion molecules including endothelial leucocyte adhesion molecule 1 (ELAM-1), intercellular adhesion molecule 1 (ICAM-1), vascular adhesion molecule 1 (VCAM-1), and e-selectin and p-selectin [42]. In the disease course, vascular leakage is an early event responsible for one of the first disease signs like " puffy fingers" [43]. In SSc, platelets are activated granular release as is demonstrated by increased spontaneous platelet aggregation and aggregation induced by ADP and collagen and by increased platelet adhesion to collagen. Microvascular thrombosis and enhanced fibrin deposition are frequently encountered in SSc [44]. Shorter fibrinogen half-life and enhanced fibrinolytic system activity results in high levels of fibrin breakdown products (D-dimers) [45]. Moreover, it is interesting to note here that injured SSc-EC display a remarkable and difficult to understand reduction of ACE expression [46], as it happens in some vasculitides [47], suggesting a potential role in pathogenesis of vasculopathy. It is also clear that EC injury in SSc leads to a disruption of the physiological chain linked to ACE with a significant production of peptides that are involved in the dysregulation of vascular tone control [48] (see Fig. 1). These events in SSc are also linked to the increase of circulating kallikrein, and are associated with the early clinical signs of microvascular dysfunction and injury [49].

### 3.3. Endothelial dysfunction in COVID-19

It is clear now that SARS-CoV-2 infection affects the vasculature in the lung, heart, GI tract, kidney, and brain, resulting in a widespread EC dysfunction and severe injury. Widespread vascular thrombosis with microangiopathy and occlusion of alveolar capillaries have been described [50]. Vascular leakage in COVID-19 is the first manifestation of EC dysfunction. It is seen early and thought to be mediated by direct viral invasion "endotheliitis" and consequently resulting in EC apoptosis (Fig. 2). Therefore, there is a widespread vascular involvement and its effects on the cardiovascular system are clearly shown [51].

In the literature, a bulk of data indicate that viruses can infect EC, triggering different cascades and pathways. Among these mechanisms, the programmed cell death of pulmonary endothelial cells apoptosis seems one of the most significant events important for the viral life cycle. As an example, the coronavirus known as infectious bronchitis virus was able to induce an apoptotic process in the advanced phase of the disease [52], whereas the human influenza virus and the Zika viruses may induce apoptosis of human microvascular EC, thus fostering a peculiar capillary permeability [53–55]. In pulmonary EC, ACE2 induced apoptosis uses AT2 receptor 9. In COVID19, likely the SARSCoV-2 entering into the cell may trigger apoptosis of microvascular EC exposing ACE2 receptors [31]. One of the most important mechanisms is linked to impaired ACE2 activity, leading to activation of the kallikrein–bradykinin pathway, contributing to vascular permeability in addition to the effects of inflammatory cells and cytokines already fostering vascular leaking [56].

The ACE2 receptor is a type-I transmembrane receptor with a catalytic extracellular domain, a single transmembrane domain and a cytoplasmic carboxyl domain. The ACE2 has a metalloprotease enzymatic activity regulating the effects of ANGII, generated by ACE by its fragmentation in two smaller peptides (Ang 1–9 and Ang 1–7. See Fig. 1). These peptides play, with the renin-angiotensin system, a critical role in the control of vascular tone and cardiovascular activity (Fig. 1) [57]. The ACE2 is expressed in EC and epithelial cells and is known to serve as a functional receptor for SARS-CoV mediating its entry in the cells (Fig. 1) [58,59]. This mechanism seems to be very relevant in triggering EC damage (Fig. 2), the hyperactivation of the immune response, and the consequent cytokine storm [60] culminating in the development of the acute respiratory distress syndrome (ARDS). The activation of coagulation pathways ensues because of EC barrier damage, which results in a thrombogenic surface, enhanced platelet binding and aggregation and the release of tissue factor [61]. Thrombosis will trigger the fibrinolytic system to dissolve fibrin-rich blood clots, resulting in high levels of fibrin breakdown products (D-dimers) [62]. In fact, markers of endothelial and platelet activation are significantly elevated in patients, including vWF antigen, soluble P-selectin and soluble thrombomodulin [62]. The proposed endothelial centered hypothesis for the pathogenesis of COVID [63,64] is also supported by the evidence that COVID-19 patients demonstrate microvascular abnormalities at nailfold capillaroscopy with acute and post-acute microvascular damage evident at capillaroscopy [65]. Moreover, the evidence that SARS-CoV-2 is present in dermal EC in the skin lesions of children with chilblains, is a further confirmation that an EC dysfunction and damage may be induced by direct EC infection [66].

## 4. Other viral illnesses potentially involved in endothelial dysfunction and in SSc pathogenesis

Today we are aware that the link between viral infections, inflammation and the activation/injury of the EC is a reality. It has been shown that the human herpes virus 8 may infect EC and foster vessel permeability and leaking, while the Dengue virus has a specific tropism for dendritic cells, monocyte and macrophages leading to an increased production of secretion and consequently the activation of EC and vessel leaking [67,68].

Human cytomegalovirus (hCMV), a beta herpesvirus which establishes a lifelong infection, may be present in EC, that serve as natural hosts in vivo. The infection with hCMV can induce an anti-migratory and anti-angiogenic EC phenotype, viral gene transcription dependent downregulation of the expression of angiogenesis-associated genes, including angiopoietin-2, TEK receptor and vascular endothelial growth factor receptors [69]. Also, CMV- EC infection enhances platelet binding to EC and in parallel increases the expression of vWF, ICAM-1, VCAM-1, *E*-selectin, and P-selectin [70]. Also in Dengue, Hematopoietic Necrosis Virus and Hematopoietic Necrosis Virus infection, EC dysfunction has been also described [71–73]. There is an indirect evidence that infectious agents may trigger SSc, and CMV is the virus which is postulated to play a role in SSc pathogenesis. Apparently, CMV may infect EC and monocytes/macrophages leading to dysregulation of the immune system, upregulating the expression of fibrogenic cytokines [74,75]. Moreover, CMV antibodies in SSc sera are associated with SSc specific autoantibodies [76]. Rat and mouse models show that CMV infection leads to formation of intimal lesions [77,78]. An immune suppressed mouse model of mCMV-induced neointima development shares many characteristics with SSc, including EC apoptosis, myofibroblast development, and increase TGF-β and PDGF expressions [79]. Blood samples from SSc patients were found to have anti-HCMV immune responses (IgM, IgG antibodies, and T cells reactive to peptide pools spanning most immunogenic HCMV proteins). Statistically significant increase of HCMV-specific CD8+ T cell responses in SSc patients vs. healthy subjects was also observed [80].

Parvovirus B19 has also been implicated is the pathogenesis of SSc, as it is much more commonly found as an active infection in SSc patients (4%) than in the general population (0.6%) [81]. Parvovirus B19 was detected in bone marrow biopsies from a high percentage of SSc patients (57%), who did not have an active B19 infection [82]. Further studies have found a correlation between B19 expression levels and severity of EC dysfunction in SSc [83]. This suggests a potential role for the virus in SSc pathogenesis.

Scleroderma-specific autoantibodies may arise through molecular mimicry, driven by the interaction of specific viral antigens with the corresponding HLA. A recent study demonstrated that immunodominant peptides of self-antigens have homology viral protein sequences from Mimiviridae and Phycodnaviridae families. This led to suggest that scleroderma-specific autoantibodies may arise through molecular mimicry, driven by the interaction of specific viral antigens with corresponding HLA [84].

Epstein Barr Virus is a herpesvirus which has a specific tropism for lymphocytes and which infect a large part of the population. In SSc patients, a persisting infection of skin fibroblasts and EC has been detected by the expression of the EBV noncoding small RNAs (EBERs) and the increased expression of immediate-early lytic and latency mRNAs and proteins [85]. Also the activation of an aberrant EBV may prompt the expression of selected IFN-regulatory factors (IRFs) and IFN-stimulated genes (ISGs), transforming growth factor-b1 (TGFb1), and other FB activation markers like smooth muscle actin and Endothelin-1 [86]. This may thus explain how these genes may be involved in fostering the SSc-FB profibrotic phenotype. Therefore, EBV reactivation might trigger some mechanisms involved in the pathogenetic fibrotic events in SSc.

It is well known that SSc is a complex autoimmune disease characterized by vascular damage, and tissue fibrosis [87]. Fibroblasts, and in particular myofibroblasts, have a fundamental role in the genesis of fibrosis in SSc [88,89]. Several decades ago, the hypothesis that viruses could trigger SSc and autoimmune diseases have been suggested and some viruses like CMV and EBV have been identified as potentially involved in SSc pathogenesis (see above). The question is now, after the evidence of the disruptive effect of SARS-CoV-2 on EC leading to early modifications similar to those found in SSc, whether viruses trigger the onset of SSc pathogenetic pathways, either in the diffuse or limited subset.

It is without doubt that the SARS-CoV-2 infection has raised a great interest in considering that COVID-19 can teach us about common and similar pathways leading to acute EC injury. It is clear that COVID-19 is an *acute illness*, while SSc, even in its more aggressive subset, is a *sub-acute/chronic disease*. Both diseases manifest significant lung inflammation with comparable HRCT imaging, and after sharing some early pathogenetical steps the two disorders take different pathways in their progression even if the final outcome (lung fibrosis) is very similar in both. However, both diseases share early pathogenetic steps that include targeting the vascular endothelium with subsequent vessel leakage, thrombosis and cellular apoptosis, using the host immune/inflammatory system to mediate tissue injury vasculopathy, ILD and lung fibrosis.

In SSc, lung inflammation is characterized by lymphocyte infiltration in pulmonary septa, along with capillary leaking, extravasation of neutrophils into the alveolar space, EC activation and injury leading eventually to vessel lumen obliteration. Contemporarily, a specific activation of EC leading to endothelial to mesenchymal transition into myofibrolasts [90] may take place accelerating the progression to interstitial fibrosis [91]. The lung parenchymal distortion (honey combing) is a final result of the disease progression which is rarely reversible. On the other hand, COVID19 is characterized by an acute scenario with massive neutrophil infiltration in pulmonary capillaries, capillaritis and capillary leaking with extravasation of neutrophils into the alveolar space [15,92].

## 5. Conclusions

It is abundantly clear now that the endothelium is at the centre stage in SSc and in COVID- 19, with EC activation/injury and dysfunction creating the crucial evolving step in both pathogeneses (Fig. 2). Moreover, the immune activation and the ACE2 involvement are common key features of the early phase of both diseases, favouring the dysfunction and the presence of a “fragile” and damaged endothelium. It is interesting to note that both diseases meet at the crossroad of the enzymatic machinery of ACE devoted to the production of ANGII peptides. This evidence corroborates the hypothesis that the Angiotensin system should be an early target of the treatment to control, either in COVID19 and in SSc, the progression from alveolar inflammation to endothelial damage (Figs. 1 and 2) [12,93].

Yet, and despite the many similarities, COVID19 is due to a direct assault of SARS-CoV-2 on the vascular system as an acute infection, while SSc remains a chronic/sub-acute autoimmune disease of unknown etiology. Nonetheless, the question of a viral etiology for SSc is an important issue which was raised in the past and is now intensified after the current description of COVID-19 pathology. Is it possible that there is a viral infection in the asymptomatic very early phase of SSc? Can a dormant and concealed virus get activated at disease onset or does the elusive virus have to be present at disease onset? In the future, these questions and others need to be taken into account when we will search for a viral etiology of SSc.

It is now debated whether SarsCov2 is triggering autoimmunity with production of autoantibodies [94–99]. In patients that survived COVID19, the appearance of specific antibodies like MDA5 and SSA may raise the suspicion that the virus may have a role in inducing autoimmunity, thus indicating a link between the viral infection and the onset of autoimmunity [99,100].

It has been suggested that molecular mimicry between Sars-Cov2 and human proteins may support the large part of pathogenetic events in the disease evolution [98,99].

However, the further study and exploration of the SarsCov2 pathogenic mechanisms might provide further useful milestones in the understanding of the early SSc pathogenesis, either at alveolar and vascular level. A viral etiology for SSc has long been suggested and it is still a major challenge for the next future. Nonetheless, the COVID19 may have made this challenge less daunting. In SSc, it will be a “viral” challenge to understand whether an acute infectious disease may

eventually trigger a chronic indolent but progressive autoimmune systemic disease.

## References


[1] Chu H, Chan JF, Wang Y, Yuen TT, Chai Y, Hou Y, et al. Comparative replication and immune activation profiles of SARS-CoV-2 and SARS-CoV in human lungs: an ex vivo study with implications for the pathogenesis of COVID-19. Clin Infect Dis 2020. https://doi.org/10.1093/cid/ciaa410 [Online ahead of print].

[2] Xiong Y, Liu Y, Cao L, Wang D, Guo M, Jiang A, et al. Transcriptomic characteristics of bronchoalveolar lavage fluid and peripheral blood mononuclear cells in COVID-19 patients. Emerg Microbes Infect 2020;9:761–70.

[3] Sfera A, Osorio C, Jafri N, Diaz EL, Campo Maldonado JE. Intoxication with endogenous angiotensin II: a COVID-19 hypothesis. Front Immunol 2020 Jun 19; 11:1472. https://doi.org/10.3389/fimmu.2020.01472 [eCollection 2020].

[4] Mihara M, Hashizume M, Yoshida H, Suzuki M, Shiina M. IL-6/IL-6 receptor system and its role in physiological and pathological conditions. Clin Sci 2012; 122:143–59.

[5] Huang C, Wang Y, Li X, Ren L, Zhao J, Hu Y, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. Lancet 2020;395: 497–506.

[6] Hoffmann M, Kleine-Weber H, Schroeder S, Krüger N, Herrler T, Erichsen S, et al. SARS-CoV-2 cell entry depends on ACE2 and TMPRSS2 and is blocked by a clinically proven protease inhibitor. Cell 2020;181:271–80.

[7] Imai Y, Kuba K, Rao S, Huan Y, Guo F, Guan B, et al. Angiotensin-converting enzyme 2 protects from severe acute lung failure. Nature 2005;436:112–6.

[8] Kaur U, Acharya K, Mondal R, Singh A, Saso L, Chakrabarti S, et al. Should ACE2 be given a chance in COVID-19 therapeutics: a semi-systematic review of strategies enhancing ACE2. Eur J Pharmacol 2020;887:173545.

[9] Chauhan AJ, Wiffen LJ, Brown TP. COVID-19: a collision of complement, coagulation and inflammatory pathways. J Thromb Haemost 2020;18(9):2110–7. https://doi.org/10.1111/jth.14981 [Epub 2020 Aug 27].

[10] Gao T, Hu M, Zhang X, Li H, Zhu L, Liu H, et al. Highly pathogenic coronavirus N protein aggravates lung injury by MASP-2-mediated complement over-activation. 2020. https://doi.org/10.1101/2020.03.29.20041962.

[11] Song WC, FitzGerald GA. COVID-19, microangiopathy, hemostatic activation, and complement. J Clin Invest 2020;130(8):3950–3.

[12] Pons S, Fodil S, Azoulay E, Zafrani L. The vascular endothelium: the cornerstone of organ dysfunction in severe SARS-CoV-2 infection. Crit Care 2020;24(1):353.

[13] 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: 1417–8.

[14] Fox SE, Akmatbekov A, Harbert JL, Gi L, Brown JQ, Vander Heide RS. Pulmonary and cardiac pathology in COVID-19: the first autopsy series from new orleans. MedRxiv [Preprint] 2020:50575. https://doi.org/10.1101/2020.04.06.200.

[15] Zuo Y, Yalavarthi S, Shi H, Gockman K, Zuo M, Madison JA, et al. Neutrophil extracellular traps in COVID-19. JCI Insight 2020;5:138999.

[16] Sørensen OE, Borregaard N. Neutrophil extracellular traps—the dark side of neutrophils. J Clin Invest 2016;126:1612–20. https://doi.org/10.1172/jci84538.

[17] Man SM, Karki R, Kanneganti TD. Molecular mechanisms and functions of pyroptosis, inflammatory caspases and inflammasomes in infectious diseases. Immunol Rev 2017;277(1):61–75. https://doi.org/10.1111/imr.12534.

[18] Yap JKY, Moriyama M, Iwasaki A. Inflammasomes and pyroptosis as therapeutic targets for COVID-19. J Immunol 2020;205(2):307–12. https://doi.org/10.4049/jimmunol.2000513. Epub 2020 Jun 3. PMID: 32493814; PMCID: PMC7343621.

[19] Nagashima S, Mendes MC, Camargo Martins AP, Borges NH, Godoy TM, AFRDS Miggiolaro. Endothelial dysfunction and thrombosis in patients with COVID-19. Arterioscler Thromb Vasc Biol 2020;40(10):2404–7.

[20] Klok FA, Kruip MJHA, Van der Meer NJM, Arbous MS, DAMPJ Gommers, Kant KM, et al. Confirmation of the high cumulative incidence of thrombotic complications in critically ill ICU patients with COVID-19: an updated analysis. Thromb Res 2020;191:148–50. https://doi.org/10.1016/j.thromres.2020.04.041.

[21] Ackermann M, Verleden SE, Kuehnel M, Haverich A, Welte T, Laenger F, et al. Pulmonary vascular Endothelialitis, thrombosis, and angiogenesis in COVID-19. N Engl J Med 2020 Jul;383(2):120–8.

[22] Carsana L, Sonzogni A, Nasr A, Rossi RS, Pellegrinelli A, Zerbi P, et al. Pulmonary post-mortem findings in a series of COVID-19 cases from northern Italy: a two-centre descriptive study. Lancet Infect Dis [Internet] 2020 Aug 8. https://doi.org/10.1016/S1473-3099(20)30434-5. Available from.

[23] Polak SB, Van Gool IC, Cohen D, von der Thüsen JH, van Paassen J. A systematic review of pathological findings in COVID-19: a pathophysiological timeline and possible mechanisms of disease progression. Mod Pathol [Internet] 2020. https://doi.org/10.1038/s41379-020-0603-3. Available from.

[24] Bösmüller H, Traxler S, Bitzer M, Häberle H, Raiser W, Nann D, et al. The evolution of pulmonary pathology in fatal COVID-19 disease: an autopsy study with clinical correlation. Virchows Arch [Internet] 2020 Jun;30:1–9. Available from: https://pubmed.ncbi.nlm.nih.gov/32607684.

[25] Edler C, Schröder AS, Aepfelbacher M, Fitzek A, Heinemann A, Heinrich F, et al. Dying with SARS-CoV-2 infection-an autopsy study of the first consecutive 80 cases in Hamburg, Germany. Int J Legal Med [Internet] 2020;134(4):1275–84. Available from: https://pubmed.ncbi.nlm.nih.gov/32500199.

[26] Wichmann D, Sperhake J-P, Lütgehetmann M, Steurer S, Edler C, Heinemann A, et al. Autopsy findings and venous thromboembolism in patients with COVID-19. Ann Intern Med [Internet] 2020 May 6. https://doi.org/10.7326/M20-2003. Available from.

[27] Lindner D, Fitzek A, Bräuninger H, Aleshcheva G, Edler C, Meissner K, et al. Association of cardiac infection with SARS-CoV-2 in confirmed COVID-19 autopsy cases. JAMA Cardiol [Internet] 2020 Jul 27. https://doi.org/10.1001/jamacardio.2020.3551. Available from.

[28] Schaller T, Hirschbühl K, Burkhardt K, Braun G, Trepel M, Märkl B, et al. Postmortem examination of patients with COVID-19. JAMA [Internet] 2020 Jun 23;323(24):2518–20. Available from, https://doi.org/10.1001/jama.2020.8907.

[29] Su H, Yang M, Wan C, Yi L-X, Tang F, Zhu H-Y, et al. Renal histopathological analysis of 26 postmortem findings of patients with COVID-19 in China. Kidney Int [Internet] 2020 Jul 1;98(1):219–27. Available from, https://doi.org/10.1016/j.kint.2020.04.003.

[30] Varga Z, Flammer AJ, Steiger P, Haberecker M, Andermatt R, Zinkernagel AS, et al. Endothelial cell infection and endotheliitis in COVID-19. Lancet (London, England) 2020;395:1417–8.

[31] Xiao F, Tang M, Zheng X, Liu Y, Li X, Shan H. Evidence for gastrointestinal infection of SARS-CoV-2. Gastroenterol Int 2020 May;158(6):1831–3. e3. Available from: https://pubmed.ncbi.nlm.nih.gov/32142773.

[32] Pernazza A, Mancini M, Rullo E, Bassi M, De Giacomo T, Della Rocca C, et al. Early histologic findings of pulmonary SARS-CoV-2 infection detected in a surgical specimen. Virchows Arch 2020 Apr:1–6.

[33] Chen Y, Feng Z, Diao B, Wang R, Wang G, Wang C, et al. The novel severe acute respiratory syndrome Coronavirus 2 (SARS-CoV-2) directly decimates human spleens and lymph nodes. medRxiv [Internet] 2020 Jan 1. https://doi.org/10.1101/2020.03.27.20045427. 2020.03.27.20045427. Available from: http://medrxiv.org/content/early/2020/03/31/2020.03.27.20045427.abstract.

[34] Magro C, Mulvey JJ, Berlin D, Nuovo G, Salvatore S, Harp J, et al. Complement associated microvascular injury and thrombosis in the pathogenesis of severe COVID-19 infection: A report of five cases. Transl Res [Internet] 2020;6(6): 489–92. Available from: https://pubmed.ncbi.nlm.nih.gov/32299776.

[35] Gianotti R, Veraldi S, Recalcati S, Cusini M, Ghislanzoni M, Boggio F, et al. Cutaneous clinico-pathological findings in three COVID-19-positive patients observed in the metropolitan area of Milan, Italy. Acta Derm Venereol 2020 Apr; 100(8). adv00124.

[36] Kolivras A, Dehavay F, Delplace D, Feoli F, Meiers I, Milone L, et al. Coronavirus (COVID-19) infection-induced chilblains: a case report with histopathologic findings. JAAD Case Reports [Internet] 2020;6(6):489–92. Available from: https://pubmed.ncbi.nlm.nih.gov/32363225.

[37] Kahaleh BM, Fan P. Down regulation of nitric oxide synthase gene in microvascular endothelial cells from lesional scleroderma: assessment by quantitative RT-PCR and possible role for cytotoxic T cells. Arthritis Rheum 1998; 41(Suppl):1469.

[38] Matucci Cerinic M, Kahaleh MB. Beauty and the beast. The nitric oxide paradox in systemic sclerosis. Rheumatology (Oxford) 2002;41(8):843–7.

[39] Gimbrone MA, García-Cardeña G. Endothelial cell dysfunction and the pathobiology of atherosclerosis. Circ Res 2016 February 19;118(4):620–36.

[40] Tousoulis D, Kampoli AM, Tentolouris C, Papageorgiou N, Stefanadis C. The role of nitric oxide on endothelial function. Curr Vasc Pharmacol 2012;10(1):4–18.

[41] Fatini C, Gensini F, Sticchi E, Battaglini B, Angotti C, Conforti ML, et al. High prevalence of polymorphisms of angiotensin-converting enzyme (I/D) and endothelial nitric oxide synthase (Glu298Asp) in patients with systemic sclerosis. Am J Med 2002;112(7):540–4. https://doi.org/10.1016/s0002-9343(02)01069-0.

[42] Blann AD, Constans J, Carpentier P, Renard M, Satger B, Guérin V, et al. Soluble P selectin in systemic sclerosis: relationship with von Willebrand factor, autoantibodies and diffuse or localised/limited disease. Thromb Res 2003;109(4): 203–6. https://doi.org/10.1016/s0049-3848(03)00209-3.

[43] Bruni C, Frech T, Manetti M, Rossi FW, Furst DE, De Paulis A, et al. Vascular leaking, a pivotal and early Pathogenetic event in systemic sclerosis: should the door be closed? Front Immunol 2018;9:2045.

[44] Asano Y, Sato S. Vasculopathy in scleroderma. Semin Immunopathol 2015;37(5): 489–500.

[45] Matucci-Cerinic M, Kahaleh B, Wigley FM. Review: evidence that systemic sclerosis is a vascular disease. Arthritis Rheum 2013;65(8):1953–62. https://doi.org/10.1002/art.37988.

[46] Matucci-Cerinic M, Jaffa A, Kahaleh B. Angiotensin converting enzyme: an in vivo and in vitro marker of endothelial injury. J Lab Clin Med 1992 Sep;120(3): 428–33.

[47] Lombardi A, Falcini F, Pignone A, Trapani S, Leoncini G, Kahaleh BM, et al. Angiotensin converting enzyme a new tool for the follow-up of endothelial injury in paediatric vasculitides. Br J Rheumatol 1994 Dec;33(12):1197.

[48] Pignone A, Rosso AD, Brosnihan KB, Perfetto F, Livi R, Fiori G, et al. Reduced circulating levels of angiotensin-(1–7) in systemic sclerosis: a new pathway in the dysregulation of endothelial-dependent vascular tone control. Ann Rheum Dis 2007 Oct;66(10):1305–10. https://doi.org/10.1136/ard.2006.064493.

[49] Del Rosso A, Distler O, Milia AF, Emanueli C, Ibba-Manneschi L, Guiducci S, et al. Increased circulating levels of tissue kallikrein in systemic sclerosis correlate with microvascular involvement. Ann Rheum Dis 2005;64(3):382–7.

[50] Wadman M, Couzin-Frankel J, Kaiser J, Matacic C. How does coronavirus kill? Clinicians trace a ferocious rampage through the body, from brain to toes. Science April 17 2020. https://doi.org/10.1126/science.abc3208.

[51] Guzik TJ, Mohiddin SA, Dimarco A, Patel V, Savvatis K, Marelli-Berg FM, et al. COVID-19 and the cardiovascular system: implications for risk assessment, diagnosis, and treatment options. Cardiovasc Res 2020 Aug 1;116(10):1666–87.

[52] Li FQ, Tam JP, Liu DX. Cell cycle arrest and apoptosis induced by the coronavirus infectious bronchitis virus in the absence of p53. Virology. 2007;365(2):435–45.

[53] Sumikoshi M, Hashimoto K, Kawasaki Y, et al. Human influenza virus infection and apoptosis induction in human vascular endothelial cells. J Med Virol 2008;80(6):1072–8.

[54] Anfasa F, Goeijenbier M, Widagdo W, et al. Zika virus infection induces elevation of tissue factor production and apoptosis on human umbilical vein endothelial cells. Front Microbiol 2019;10:817. https://doi.org/10.3389/fmicb.2019.00817 eCollection 2019.

[55] Armstrong SM, Wang C, Tigdi J, et al. Influenza infects lung microvascular endothelium leading to microvascular leak: role of apoptosis and claudin-5. PLoS One 2012;7(10):e47323.

[56] Teuwen L, Geldhof V, Pasut A, et al. COVID-19: the vasculature unleashed. Nat Rev Immunol 2020;20:389–91.

[57] Amraei R, Rahimi N. COVID-19, Renin-angiotensin system and endothelial dysfunction. Cells 2020;9(7):1652.

[58] Kuba K, Imai Y, Rao S, Gao H, Guo F, Guan B, et al. A crucial role of angiotensin converting enzyme 2 (ACE2) in SARS coronavirus-induced lung injury. Nat Med 2005;11(8):875–9.

[59] Li W, Moore MJ, Vasilieva N, Sui J, Wong SK, Berne MA, et al. Angiotensin-converting enzyme 2 is a functional receptor for the SARS coronavirus. Nature. 2003 Nov 27;426(6965):450–4.

[60] Fung SY, Yuen KS, Ye ZW, Chan CP, Jin DY. A tug-of-war between severe acute respiratory syndrome coronavirus 2 and host antiviral defence: lessons from other pathogenic viruses. Emerg Microbes Infect 2020 Mar 14;9(1):558–70.

[61] Becker RC. COVID-19 update: COVID-19-associated coagulopathy. J Thromb Thrombolysis 2020;50(1):54–67. https://doi.org/10.1007/s11239-020-02134-3.

[62] Griffin DO, Jensen A, Khan M, Chin J, Chin K, Saad J, et al. Pulmonary embolism and increased levels of d-dimer in patients with coronavirus disease. Emerg Infect Dis 2020;26(8):1941–3.

[63] Sardu C, Gambardella J, Morelli MB, Wang X, Marfella R, Santulli G. Hypertension, thrombosis, kidney failure, and diabetes: is COVID-19 an endothelial disease? A comprehensive evaluation of clinical and basic evidence. J Clin Med 2020;9(5):1417.

[64] Libby P, Lüscher T. COVID-19 is, in the end, an endothelial disease. Eur Heart J 2020;41(32):3038–44.

[65] Natalello G, De Luca G, Gigante L, Campochiaro C, De Lorenzis E, Verardi L, et al. Nailfold capillaroscopy findings in patients with coronavirus disease 2019: broadening the spectrum of COVID-19 microvascular involvement. Microvasc Res 2020;133:104071.

[66] Colmenero I, Santonja C, Alonso-Riaño M, Noguera-Morel L, Hernández-Martín A, Andina D, et al. SARS-CoV-2 endothelial infection causes COVID-19 chilblains: histopathological, immunohistochemical and ultrastructural study of seven paediatric cases. Br J Dermatol 2020;183(4):729–37.

[67] Malavige GN, Ogg GS. Pathogenesis of vascular leak in dengue virus infection. Immunology. 2017;151(3):261–9. https://doi.org/10.1111/imm.12748 [Epub 2017 May 2].

[68] Guo H, Kaiser WJ, Mocarski ES. Manipulation of apoptosis and necroptosis signaling by herpesviruses. Med Microbiol Immunol 2015;204(3):439–48. https://doi.org/10.1007/s00430-015-0410-5 [Epub 2015 Apr 1].

[69] Gustafsson RKL, Jeffery HC, Yaiw KC, et al. Direct infection of primary endothelial cells with human cytomegalovirus prevents angiogenesis and migration. J Gen Virol 2015;96(12):3598–612. https://doi.org/10.1099/jgv.0.000301.

[70] Rahbar A, Söderberg-Nauclér C. Human cytomegalovirus infection of endothelial cells triggers platelet adhesion and aggregation. J Virol 2005;79(4):2211–20. https://doi.org/10.1128/JVI.79.4.2211-2220.2005.

[71] Dalrymple NA, Mackow ER. Endothelial cells elicit immune-enhancing responses to dengue virus infection. J Virol 2012;86(12):6408–15. https://doi.org/10.1128/JVI.00213-12.

[72] Ludwig M, Palha N, Torhy C, Briolat V, Colucci-Guyon E, et al. Whole-body analysis of a viral infection: vascular endothelium is a primary target of infectious hematopoietic necrosis virus in Zebrafish larvae. PLoS Pathog 2011;7(2):e1001269. https://doi.org/10.1371/journal.ppat.1001269.

[73] Mosepele M, Mohammed T, Mupfumi L, et al. HIV disease is associated with increased biomarkers of endothelial dysfunction despite viral suppression on long-term antiretroviral therapy in Botswana. Cardiovasc J Afr 2018;29:155–61.

[74] Pandey JP, LeRoy EC. Human cytomegalovirus and the vasculopathies of autoimmune diseases (especially scleroderma), allograft rejection, and coronary restenosis. Arthritis Rheum 1998;41(1):10–5.

[75] Vaughan JH, Shaw PX, Nguyen MD, Medsger Jr TA, Wright TM, Metcalf JS, et al. Evidence of activation of 2 herpesviruses, Epstein-Barr virus and cytomegalovirus, in systemic sclerosis and normal skins. J Rheumatol 2000;27(3):821–3.

[76] Neidhart M, Kuchen S, Distler O, Bruhlmann P, Michel BA, Gay RE, et al. Increased serum levels of antibodies against human cytomegalovirus and prevalence of autoantibodies in systemic sclerosis. Arthritis Rheum 1999;42(2):389–92.

[77] Presti RM, Pollock JL, Dal Canto AJ, O'Guin AK, Virgin Hwt. Interferon gamma regulates acute and latent murine cytomegalovirus infection and chronic disease of the great vessels. J Exp Med 1998;188(3):577–88.

[78] Zhou YF, Shou M, Harrell RF, Yu ZX, Unger EF, Epstein SE. Chronic non-vascular cytomegalovirus infection: effects on the neointimal response to experimental vascular injury. Cardiovasc Res 2000;45(4):1019–25.

[79] Hamamdzic D, Harley RA, Hazen-Martin D, LeRoy EC. MCMV induces neointima in IFN-gammaR−/− mice: intimal cell apoptosis and persistent proliferation of myofibroblasts. BMC Musculoskelet Disord 2001;2:3.

[80] Arcangeletti MC, Maccari C, Vescovini R, et al. A paradigmatic interplay between human cytomegalovirus and host immune system: possible involvement of viral antigen-driven CD8+ T cell responses in systemic sclerosis. Viruses 2018;10:508. https://doi.org/10.3390/v10090508.

[81] Ferri C, Longombardo G, Azzi A, Zakrzewska K. Parvovirus B19 and systemic sclerosis. Clin Exp Rheumatol 1999;17(2):267–8.

[82] Magro CM, Nuovo G, Ferri C, Crowson AN, Giuggioli D, Sebastiani M. Parvoviral infection of endothelial cells and stromal fibroblasts: a possible pathogenetic role in scleroderma. J Cutan Pathol 2004;31(1):43–50.

[83] Zakrzewska K, Corcioli F, Carlsen KM, et al. Human parvovirus B19 (B19V) infection in systemic sclerosis patients. Intervirology. 2009;52(5):279–82.

[84] Gourh PA, Safran SA, Alexander T. HLA and autoantibodies define scleroderma subtypes and risk in African and European Americans and suggest a role for molecular mimicry. Proc Nat Acad Sci Jan 2020;117(1):552–62. https://doi.org/10.1073/pnas.1906593116.

[85] Farina A, Cirone M, York M, Lenna S, Padilla C, Mclaughlin S, et al. Epstein-Barr virus infection induces aberrant TLR activation pathway and fibroblast-myofibroblast conversion in scleroderma. J Invest Dermatol 2014 Apr;134(4):954–64.

[86] Farina A, Cirone M, York M, Lenna S, Padilla C, Mclaughlin S, et al. Epstein-Barr virus infection induces aberrant TLR activation pathway and fibroblast-myofibroblast conversion in scleroderma. J Invest Dermatol 2014 Apr;134(4):954–64.

[87] Varga J, Trojanowska M, Kuwana N. Pathogenesis of systemic sclerosis: recent insights of molecular and cellular mechanisms and therapeutic opportunities. J Scleroderma Relat Disord 2017;2(3):137–52. https://doi.org/10.5301/jsrd.5000249.

[88] Garrett SM, Baker Frost DA, Feghali-Bostwick C. The mighty fibroblast and its utility in scleroderma research. J Scleroderma Relat Disord 2017;2(2):100–7. https://doi.org/10.5301/jsrd.5000240.

[89] Varga J, Abraham DJ. Systemic sclerosis: a prototypic multisystem fibrotic disorder. J Clin Invest 2007;117(3):557–67. https://doi.org/10.1172/JCI31139.

[90] Manetti M, Romano Rosa I, Guiducci S, Bellando-Randone S, De Paulis A, Ibba Manneschi L, et al. Endothelial-to-mesenchymal transition contributes to endothelial dysfunction and dermal fibrosis in systemic sclerosis. Ann Rheum Dis 2017;76(5):924–34. https://doi.org/10.1136/annrheumdis-2016-210229. Epub 2017 Jan 6.

[91] Nihtyanova SI, Denton CP. Pathogenesis of systemic sclerosis associated interstitial lung disease. J Scleroderma Relat Disord 2020;5:6–16.

[92] Liu F, Liu F, Wang LJ. COVID-19 and cardiovascular diseases. Mol Cell Biol 2020 Nov 23. https://doi.org/10.1093/jmcb/mjaa064. mjaa064.

[93] Liu X, Long C, Xiong Q, Chen C, Ma J, Su Y, et al. Association of angiotensin converting enzyme inhibitors and angiotensin II receptor blockers with risk of COVID-19, inflammation level, severity, and death in patients with COVID-19: a rapid systematic review and meta-analysis. Clin Cardiol 2020. https://doi.org/10.1002/clc.23421.

[94] Halpert G, Shoenfeld Y. SARS-CoV-2, the autoimmune virus. Autoimmun Rev 2020;19(12):102695. https://doi.org/10.1016/j.autrev.2020.102695 [Epub 2020 Oct 28].

[95] Najafi S, Rajaei E, Moallemian R, Nokhostin F. The potential similarities of COVID-19 and autoimmune disease pathogenesis and therapeutic options: new insights approach. Clin Rheumatol 2020;39:3223–35.

[96] Dotan A, Muller S, Kanduc D, David P, Halpert G, Shoenfeld Y. The SARS-CoV-2 as an instrumental trigger of autoimmunity. Autoimmun Rev 2021 Feb 19:102792. https://doi.org/10.1016/j.autrev.2021.102792. Online ahead of print.

[97] Liu Y, Sawalha AH, Lu Q. COVID-19 and autoimmune diseases. Curr Opin Rheumatol 2020 Dec 15. https://doi.org/10.1097/BOR.0000000000000776. Publish Ahead of Print.

[98] Ehrenfeld M, Tincani A, Andreoli L, Cattalini M, Greenbaum A, Kanduc D, et al. COVID-19 and autoimmunity. Autoimmun Rev 2020 Aug;19(8):102597. https://doi.org/10.1016/j.autrev.2020.102597 [Epub 2020 Jun 11].

[99] Adiguzel Y. Molecular mimicry between SARS-CoV-2 and human proteins. Autoimmun Rev 2021 Feb 18:102791. https://doi.org/10.1016/j.autrev.2021.102791. Online ahead of print.

[100] Angileri F, Legare S, Marino Gammazza A, Conway de Macario E, Jl Macario A, Cappello F. Molecular mimicry may explain multi-organ damage in COVID-19. Autoimmun Rev 2020 Aug;19(8):102591. https://doi.org/10.1016/j.autrev.2020.102591. Epub 2020 Jun 11.