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REVIEW ARTICLE

Decrypting the cellular and molecular intricacies associated with COVID-19-induced chronic pain

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Abstract

Pain is one of the clinical manifestations that can vary from mild to severe symptoms in COVID-19 patients. Pain symptoms can be initiated by direct viral damage to the tissue or by indirect tissue injury followed by nociceptor sensitization. The most common types of pain that are reported to occur in COVID-19 patients are headache, myalgia, and chest pain. With more and more cases coming in the hospitals, many new and unique symptoms of pain are being reported. Testicular and abdominal pain are rare cases of pain that are also being reported and are associated with COVID-19. The SARS-CoV-2 virus has a high affinity for angiotensin-converting enzyme-2 receptor (ACE-2) which acts as an entry point for the virus. ACE-2/Ang II/AT 1 receptor also participates directly in the transmission of pain signals from the dorsal horn of the spinal cord. It induces a series of complicated responses in the human body. Among which the cytokinetic storm and hypercoagulation are the most prominent pathways that mediate the sensitization of sensory neurons facilitating pain. The elevated immune response is also responsible for the activation of inflammatory lipid mediators such as COX-1 and COX-2 enzymes for the synthesis of prostaglandins (PGs). PG molecules especially PGE2 and PGD2 are involved in the pain transmission and are found to be elevated in COVID-19 patients. Though arachidonic acid pathway is one of the lesser discussed topics in COVID-19 pathophysiology, still it can be useful for explaining the unique and rarer symptoms of pain seen in COVID-19 patients. Understanding different pain pathways is very crucial for the management of pain and can help healthcare systems to end the current pandemic situation. We herein review the role of various molecules involved in the pain pathology of COVID-19.

Keywords *C*OVID-19 · Pain · ACE-2 · Cytokinetic storm · IL-6 · PGE2 · Headache

Introduction

The COVID-19 pandemic has been affecting millions of lives around the globe. COVID-19 is a viral respiratory disease caused by SARS-CoV-2. Its symptoms mainly include shortness of breath, dry cough, fever, fatigue and dizziness (Mizrahi et al. 2020). These highly contagious pneumonia-like symptoms first started appearing in Wuhan city, China in December 2019. In less than three months it has engulfed the whole world like a storm. It has been one and a half years of tackling this pandemic situation. The beta coronavirus SARS-CoV-2 is a large enveloped positive-strand RNA genome with a unique spike protein gene. SARS-CoV-2 shares some similar characteristics with SARS-CoV but with some fluctuations in the number of amino acids present in its proteins (Ali and Vijayan 2020). Similar to SARS-CoV, SARS-CoV-2 has also been reported to have a high affinity for the angiotensin-converting enzyme-2 receptor (ACE-2). ACE-2 receptors act as an entry point for SARS-CoV-2 (Luan et al. 2020). It induces a series of complicated responses in the human body. Among which the cytokinetic storm and hypercoagulation are the heavily studied pathways. Apart from the damage caused by hypoxemia that is low blood oxygen, the exaggerated immune response further leads to more inflammation and multiple organ damage in the body.

Several factors are responsible for the pathogenesis of COVID-19. SARS-CoV-2 has a high affinity for ACE-2 receptors. The spike protein of SARS-CoV-2 binds to ACE-2 receptors after being cleaved by protease furin. Since the ACE-2 receptor is expressed at various parts of our body, the virus gets many

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sites for its invasion (Shang et al. 2020). Thus, its consequences can be seen at different systems as respiratory, gastrointestinal, renal, and neurological problems. With more and more cases coming in the hospitals, many new and unique symptoms are being reported but the most common complaint that patients have is pain. Chest pain, myalgia and headache are the most frequently reported types of pain in COVID-19 patients (Kim et al. 2020; Şahin et al. 2021). The ACE-2 receptor is investigated to be the prime initiator of the pain mechanism in the COVID-19 patients as ACE-2 receptor and serine protease TMPRSS2 both are previously shown to be involved in the musculoskeletal system (Dong et al. 2020). Hence, indicating its role in pain manifestation. Also, neuro-invasion of the SARS-CoV-2 virus has been stated in many studies, prompting its involvement in causing headache which is reportedly experienced by most of the COVID-19 patients (Li et al. 2020b; McFarland et al. 2021). Though the presence of pain was common among the patients, the range of severity varied. The patients already suffering from any kind of chronic pain reported experiencing an increase in pain during infection. Whereas in rare cases, some patients developed chronic pain after COVID-19 infection. Pain management is very important for the treatment of any disease as it helps to improve patient's adherence to the therapy. Proper understanding of pain manifestation and its transmission in COVID-19 can help better the current treatment methods in this pandemic situation.

Prevalence of pain symptoms in COVID-19 patients

COVID-19 pathophysiology is mostly driven by inflammatory processes in the body resulting in lung and musculoskeletal tissue damage (Wiersinga et al. 2020). Therefore, resulting in pain. In the current pandemic situation, many COVID-19 patients were reported to have pain mainly in the chest, head, back and upper and lower limbs area. According to a survey conducted on hospitalized and then recovered COVID-19 patients, it was found that the patients experienced a higher magnitude of pain during infection when compared with pre infectious and post-infectious stages. Patients with chronic pain conditions before COVID-19 infection also stated to have an increase in their pain symptoms during this viral infection. The earliest pain symptom to appear in most of the patients were found to be at neck and head region. These pain symptoms were found to be manifested even before the respiratory symptoms (Bolay et al. 2020; Kim et al. 2020; Şahin et al. 2021). The Head and peripheral limb areas are investigated to be one of the first areas to experience pain in COVID-19 cases. Pain in the chest, head, back and limbs area were found prominent during the symptomatic stage of COVID-19 infection (Şahin et al. 2021).

In another study, 95% of the patients admitted with COVID-19 were reported to experience active pain. Out of the total, 30.1% of patients had a headache, 23.3% had chest pain, 24.7% had back pain, 17.8% had myalgia, 17.8% had arthralgia and the remaining 12.3% of patients were found to have fibromyalgia or diffuse pain (Şahin et al. 2021). During this course of study, the authors suspected that the prevalence of pain specifically headache might be related to the severity of the COVID-19. It was found that patients who complained of headache as their main symptom were less likely to require ICU admission and were less likely to expire (Trigo et al. 2020). The mortality rate and the severity of the disease in patients who did not experience pain were found to be higher. In patients with a severe condition, the nociceptors are suspected to be weakened by continuous pain perception block the pain signaling. In the previous outbreak of SARS and MERS, the associated coronaviruses were also reported to cause a headache as one of the primary symptoms of the disease. Headache in the earlier phase of the disease is primarily considered to be caused due to systemic viral infection, and it appeared to be as the earliest symptom in most of the COVID-19 patients (Bolay et al. 2020). Whereas, at the later stage of the disease that is the cytokinetic storm phase, the severe headache experienced is mainly due to viral neuro-invasion and hypoxia in the brain.

While headache is the most studied and focused topic in COVID-19 related pain, some cases of abdominal and testicular pain were also observed (Bolay et al. 2020; Kim et al. 2020; Su et al. 2020). About 10% of COVID-19 patients were reported to have gastrointestinal symptoms as well. These patients were described to have a constant sharp pain that originated from their groin region and then migrated to the abdomen, chest and back. In many other studies, abdominal pain was found to be present in about 30% of the COVID-19 patients, but testicular and groin pain was recently reported as the first symptoms in some cases (Kim et al. 2020; Saeed et al. 2020). Table 1 shows the clinical characteristics of different types pain associated with COVID-19. The actual mechanism of COVID-19 and its associated pain is still not fully known but it is clear from the data that the manifestation of pain in patients involves an interplay of various molecules.

Deciphering the mechanism of pain associated with COVID-19

Role of ACE receptor in manifestation and transmission of pain in COVID-19

Angiotensin-converting enzyme-2 (ACE-2) receptors are expressed in various parts of the body such as lungs, kidneys, heart, small intestine, gall bladder,

Table 1 Clinical characteristics of pain associated with COVID-19

S.no	Type of pain	Percentage pain prevalence	Onset of pain	Pain characteristics	Blood parameters	Possible mechanisms	References
1.	Headache	30.1%	Early phase of COVID-19	Bilateral, pulsating, pressing, stabbing	Elevated C-reactive protein (CRP) Significantly low level of IL-6 and Lactate Dehydrogenase (LDH)	Neuroinvasion, stress, inflammatory processes	(Caronna et al. 2020; Rocha-Filho and Magalhães 2020; Uygun et al. 2020)
2.	Chest pain	23.3%	Later or severe stages of COVID-19	Increased pain intensity with increased severity	Elevated CRP and D-dimer Decreased lymphocyte ratio and lymphocyte count	Inflammation of lung tissue, fibrosis, pulmonary embolism	(Francone et al. 2020; Li et al. 2020a)
3.	Myalgia	17.8%	Before the emergence of respiratory tract symptoms	Persistent, widespread	Elevated CRP, ferritin, and LDH levels Elevated creatine kinase (CK) level	Fibromyalgia, Myositis	(Murat et al. 2021)
4.	Arthralgia	17.8%	Variable onset mostly during or after COVID-19 infection	Proximal muscle weakness, joint pain, Guillain-Barré syndrome (GBS) may appear as post-viral consequence	Elevated CK level, IL-6 ferritin and d-dimer	Cytokinetic storm, PG and COX-2 mediated inflammatory mechanisms	(Ono et al. 2020; Shah et al. 2020; Bedoui et al. 2021)
5.	Abdominal pain	30%	Early phase of COVID-19	Abdominal tenderness, sharp pain in periumbilical region	Lymphopenia, Elevated d-dimer and CRP	Cytokinetic storm, thromboembolism	(Kim et al. 2020; Mahan et al. 2020)
6.	Testicular or groin pain	10%	Before the emergence of respiratory tract symptoms	Radiating pain from groin to testicular and abdominal region	Level of inflammatory markers were found normal before the onset of respiratory tract symptoms	PG and COX-2 mediated inflammatory mechanisms	(Kim et al. 2020; Desai et al. 2021)

etc. It is a membrane protein present on the surface of cells and it is a very important constituent of the renin–angiotensin–aldosterone (RAA) system. The main function of ACE-2 is to cleave the larger protein angiotensin I into smaller protein angiotensin II, which causes the vasodilator effect. Along with angiotensin I, ACE-2 also cuts other molecules such as bradykinin, dynorphin A and neurotensin. In the case of COVID-19, ACE-2 has emerged as the vital entry site for SARS-CoV-2. This virus shows a high affinity for ACE-2 receptors, where its spike protein is mainly responsible for binding with ACE-2 receptors leading to membrane diffusion with the release of viral RNA into the cell. With the help some proteases (furin, TMPRSS2) the spike protein of SARS-CoV-2 binds to ACE-2 receptor in order to facilitate its entry into the cell (Dong et al. 2020). ACE-2 expression is not limited to the epithelial cells of the respiratory tract. These receptors are found in various parts of our body thus providing an easy entrance to the virus at different locations of the body. Gastrointestinal tract, heart, kidney and central nervous system, all have shown to have ACE-2 expression on their cells, making them vulnerable to SARS-CoV-2 invasion. Although solid evidences for the presence of ACE-2 expression in human musculoskeletal system is not yet found but several pre-clinical studies using single cell RNA sequencing and transcriptome on mouse skeletal muscle cells have indicated ACE-2 expression specially on its limbs (Schaum et al. 2018; Giordani et al. 2019). Since, muscular pain, and injury are clinical observations in COVID-19 patients, it is plausible that skeletal muscle cell might be susceptible to SARS-CoV-2 through ACE-2 expressions. Also, studies have proven the presence of viral RNA of SARS-CoV-2 in cells other than lung cells. For example, in a study conducted in China, the fecal samples collected from COVID-19 patients was showed positive for viral RNA even after nasal samples were declared to be negative (Xiao et al. 2020), indicating SRAS-CoV-2 invasion in gastrointestinal tract. Also, abdominal pain and other gastrointestinal complication are often reported in infected patients, suggesting the involvement of ACE-2 receptor expression causing viral invasion and subsequent tissue damage (Saeed et al. 2020). Similarly, the cerebrospinal fluid samples of the COVID-19 patients have also been found to show the presence of SARS-CoV-2 virus (Huang et al. 2020). Since, ACE-2 expression is identified in the neuron of spinal dorsal horn, it is can be the most critical site for manifestation of pain signal. Studies have shown that in the spinal dorsal horn, the ACE/Ang II/AT1 receptor pathway is responsible for facilitating pain transmission along with direct or indirect tissue damage induced by SARS-CoV-2 infection. The ACE-2 containing neurons and microglia in the spinal cord is suspected to be invaded by the virus causing decrease in ACE-2^{+} cells with angiotensin II accumulation and angiotensin (1–7) reduction. This imbalance in ACE/ACE2 ultimately induces pain from the spinal dorsal horn (Su et al. 2020). Moreover, ACE-2 containing other cells in various parts of the body may be affected in the similar manner. This is the possible cause of myalgia and widespread pain in COVID-19 patients is the expression of ACE2 gene in human skeletal muscle and other organs of the body, causing direct damage to muscle tissue. On the other hand, the p38 mitogen activated protein kinase inhibition by phosphorylation in the ACE/Ang (1–7)/Mas receptor pathway may mitigate the pain signals (Su et al. 2020).

Besides the direct attack to the ACE-2 containing cells, an indirect approach for tissue damage and subsequent pain, may also be considered by activation of innate immune response. When SARS-CoV-2 virus enters the cell, a series of molecular processes is activated inside the cell. Among which is the synthesis of type I interferons via activation of regulatory factors IRF3/7 in the cell nucleus. The viral non-structural protein nsp13 and nsp6 are found responsible for regulating synthesis and phosphorylation of the regulatory factor IRF3 in the cytoplasm. IRF3 is plays a critical role in regulation of innate immune response against viral infection by regulating transcription of interferon stimulating genes (ISG) and both IFNα/b but is more prominent for IFNβ gene by inducing formation of dsRNA activated factor-1 by association with CREB binding protein. This process has also been reported to cause activation of distinct gene expressions in macrophages which may significantly lead to cell apoptosis. For the regulatory factor IRF 7, it is activated via TLR/MyD88 pathway by binding to ssRNA of SARS-CoV-2 (Acharya et al. 2020; Lopez et al. 2020). IRF7 is well-documented for activating transcription of virus inducible cellular gene such as interferon-α genes. SARS-CoV-2 encode five major open reading frames (ORFs), among which ORF 1a/b are involved in replication process whereas ORF6 is mainly reported to inhibit the formation of inflammatory type I interferons in case of high viral load. Due to high viral load the regulatory system for the production type I interferons gets hampered (Acharya et al. 2020). The synthesized molecules of IFNα and IFNβ leave the cell and further contributes in augmenting pain throughout the body via systemic circulation by promoting not only cytokine production but also recruiting other immune cells.

Cytokinetic storm as a key mediator for persistent pain with COVID-19 infection

The host's immune system plays an important role in fighting against viral infection. Macrophages, dendritic cells, mast cells and epithelial cells are the vital components of innate immunity which are responsible for identifying foreign substances and regulating immune responses accordingly until

adaptive immunity starts functioning (Zhou et al. 2020b). When the SARS-CoV-2 virus enters and multiplies in the cell, it releases virions in the systemic circulation, triggering immune responses. In COVID-19 cases, it generally results in the production of excessive pro-inflammatory cytokines causing inflammation in that subsequent area (Diao et al. 2020; Liu et al. 2020; Zhou et al. 2020a, b). This only worsens the patient's condition. Acute respiratory distress syndrome and septic shock are the ultimate consequence of uncontrolled inflammation in COVID-19 patients (Cascella et al. 2020). The antigen-presenting cells that is macrophages and dendritic cells recognize viral RNA and initiate T-cell activity. $CD4^+$ and $CD14^+$ $CD16^+$ T cells are activated where $CD4^+$ T lymphocyte becomes Th 1 cells producing TNF α/β, IL 2, granulocyte–macrophage colony-stimulating factor (GM-CSF), etc., and $CD14^+$ $CD16^+$ monocytes produce high levels of pro-inflammatory cytokines IL 6 and TNF α (Zhou et al. 2020a). The increased activity of immune cells and production of proinflammatory cytokines cause increased infiltration and inflammation at various parts of the body including the peripheral and the central nervous system. The inflammatory cytokines and chemokines are generally released in the systemic circulation from which they are transported to different parts of the body. Some studies have also reported localized production of proinflammatory cytokines due to viral invasion of SARS-CoV-2 in COVID-19 patients. IL-6 mediates proliferation of monocytes and differentiation of T helper cells. The function of $CD8^+$ cytotoxic T cells, macrophages and dendritic cells can be suppressed by high IL-6 levels (Gubernatorova et al. 2020; Han et al. 2020). Many studies have specifically associated elevated levels of IL-6 with severe tissue injury as it dampens the activity of the immune system letting SARS-CoV-2 escape the immune surveillance (Han et al. 2020). Shreds of evidence have shown high macrophages infiltration in lungs, CNS, kidneys, joints and musculoskeletal systems (Baig et al. 2020; Huang et al. 2020; Li et al. 2020b; Ahmadian et al. 2021; Nasr et al. 2021). Along with pro-inflammatory cytokines, infiltration of the increased number of immune cells such as monocytes and neutrophils in peripheral blood and alveolar tissue is found to be contributing to lung pathology in COVID-19 (Wen et al. 2020; Zhou et al. 2020a). Also in some studies, bronchoalveolar lavage fluid (BALF) also showed increased expressions of pro-inflammatory cytokines mostly IL-1β and TNF-α, with interferon-stimulating gene (ISG) expression being the maximum (Zhou et al. 2020b). High levels of TNF-α induce apoptosis of endothelial and epithelial cells of the respiratory tract (Pelaia et al. 2020). Interferons (IFNs) that are antiviral agents were also found to be released by dendritic cells via pattern recognition receptors and were present in infected patients. The cytokinetic storm has also been reported to cause chest pain due to lung tissue damage by causing edema from infiltration and inflammation in the perivascular space (Zhang et al. 2020). Inflammation in the synovial joint is also reported in many COVID-19 patients along with the localized release of inflammatory cytokines and macrophage infiltration (Ono et al. 2020; Jovani et al. 2021). Muscle fiber atrophy along with immune cell infiltration has also been found to be widespread in COVID-19 patients (Li et al. 2020b). Inflammation in muscle tissue with myalgia and injury are the prime evidence of cytokinetic storm in the later phases of the disease. This often leads to persistent pain in infected patients until their complete recovery. In COVID-19 patients, the increased levels of cytokines, chemokines (CCL 2, CCL 3, DUSP1, IRF1, L1B) and macrophage inflammatory protein (MIP) in the systemic circulation activates mononuclear macrophages which results in systemic inflammation damaging multiple organs at the same time (Liu et al. 2020; Long et al. 2020; Zhou et al. 2020a). The peripheral mononuclear cells and elevated levels of cytokines such as TNF, IL-6 and IL-1β capable of interacting with sensory neurons also enter the dorsal root ganglion, interfering with the nociceptor signaling and initiates neurogenic inflammation. This has been proven in a study where the expression of these pro-inflammatory mediators was found to be significantly upregulated in COVID-19 patients (McFarland et al. 2021). Moreover in a recent clinical survey the high level of inflammatory cytokine IL-1β and low level of anti-inflammatory cytokine IL-10 in systemic circulation were found to be associated with high pain score in SARS-CoV-2 patients (Bussmann et al. 2022). The proliferation of immune cells and increased production pro-inflammatory cytokines around the sensory neurons and dorsal root ganglion in response to SARS-CoV-2 invasion leads to nociceptor sensitization. The activation and expansion of resident macrophages of dorsal root ganglion happen as the result of cytokine infiltration and neurogenic inflammation. This drives pain signals throughout the body causing initiation and persistence of pain.

Prostaglandins a silent facilitator of pain in COVID-19

The arachidonic pathway is one of the common pathways responsible for inducing pain in patients as a result of injury, inflammation or infection. Prostaglandins, specifically are found to be involved in the initiation of pain as an anti-viral immune response in different viral diseases such as chikungunya and influenza (Full and Gack 2014; Sander et al. 2017; Bedoui et al. 2021). Prostaglandins (PGs) are physiologically active lipid compounds that are synthesized at the site of injury and are crucial mediators of central and peripheral sensitization. They are derived from the arachidonic acid pathway by the action of isoenzymes cyclooxygenase-1 (COX-1) and cyclooxygenase-2 (COX-2). COX-1 maintains the natural levels of prostaglandins present in the body whereas

COX-2 is responsible for producing prostaglandins in case of external stimulation such as inflammation. These PG molecules are responsible for controlling different mechanisms aiding to the healing process. Among the prostaglandin family, PGE2 and PGD2 are pronociceptive molecules that is they are popularly known for mediating inflammatory pain and are also found to be elevated in COVID-19 patients. PGE2 is involved in the nociception pathway and plays an important role in triggering hyperalgesia by enhancing neuronal excitability. PGE2 helps in the transmission of nociceptor mediators in the dorsal horn neurons by activating its G-protein receptors EP1 and EP2. Recent studies have found that PGE also contributes to visceral as well as neuropathic pain. Prostaglandin PGD2 facilitates pain transmission by lowering the potential pain threshold in sensory neurons.

In many studies, the respiratory system associated viral infections like chikungunya and influenza, the level of PGE-2 was found to be increased in the lungs. In a clinical study with SARS-CoV-2 infected patients, increased levels of lipid mediators along with pro-inflammatory cytokines were found (Smeitink et al. 2020). Lungs, liver and brain has 2-arachidonoylglycerol as the major source of arachidonic acid which can be metabolized into PGs by COX-1 and CoX-2 enzymes. While the gastrointestinal tract has cytosolic phospholipase A2 for the production of arachnoid acid. COX-2 only gets activated during inflammatory conditions. Upregulation of TNFα cytokine has been reported to stimulate the production of prostaglandins by the endothelial cells (Smeitink et al. 2020). IL-1β is also found to upregulate transcription of COX-2 enzyme facilitating the production of PGE-2. Since, in COVID-19, the cytokinetic storm is very prominent it can be a possible pathway for facilitating pain. COX-2, as well as COX-1 enzymes, catalyze the conversion of arachidonic acid to PGH2 by phospholipase A_2. Also, the microsomal PGE synthase-1 (mPGES-1) expression is found to be up-regulated by 1α-X-box-binding protein in the presence of cell debris due to infection (Fig. 1). The primary function of mPGES-1 is to promote the synthesis of prostaglandins PGE2 from PGH2 and thromboxane B2, which is found to be significantly increased in COVID-19 patients (Kawabata 2011; Kazancioglu et al. 2021). In the peripheral nociceptors, PGE2 leads to activation of protein kinase A and protein kinase C through EP2 receptor which causes sensitization of voltage-gated sodium ion channels and purinergic P2X3 receptors along with upregulation of secondary messenger cAMP resulting in inflammatory hyperalgesia (Kawabata 2011). The elevated expression of secondary messenger cAMP also increases which contributes to inflammation neurotoxicity exacerbating pain signals. PGE2 also binds with EP1 receptor protein activating phospholipase C (PLC), phosphatidylinositol 4,5-bisphosphate (PIP2) and inositol triphosphate (IP3) pathway which results in the mobilization and sensitization of calcium ions. The increased concentration of intracellular calcium ions further enhances neuronal excitability (Fig. 1). Other innate immune cells such as, resident microglia of the spinal cord after recognizing viral infection produce PGD2 which further decreases the pain threshold by increasing the expression of TRP channels on the DRG neurons. This increased excitability of sensory neurons can possibly lead to neurogenic inflammation. So, prostaglandins can be one of the less discussed mediators of pain in COVID-19. The prostaglandin pathway can also explain the occurrence of testicular pain in COVID-19 (Kim et al. 2020) patients as the lipids present in human testes consist of polyunsaturated fatty acids including arachidonic acid and COX-2 is abundantly expressed in the Leydig cells of human testes. Post-viral arthralgia is another consequence of COVID-19 which can be found to be mediated by PG and COX-2 mediated inflammatory mechanisms (Ono et al. 2020; Bedoui et al. 2021). Increased activity of COX-2 along with upregulated PGE2 production in found prominent in the joint tissues. In many studies, prostaglandins have been actively associated with pain development in post-viral arthralgia conditions as a result of CHIKV infection (Bedoui et al. 2021). Similarly, joint pain and inflammation have been observed in COVID-19 patients in the later phase of the disease (Mourão 2020). The cytokinetic storm and COX-2 mediation are the plausible factors that can develop severe arthralgia in infected patients. Since post-viral arthralgia is rather a rare consequence of SARS-CoV-2 infection, further investigation is required.

Generally, NSAIDs are used for the treatment of inflammation and pain by inhibiting the activity of COX-1 and/or COX-2 enzymes. Ibuprofen, which is a popular NSAID, works by downregulating IL-6 in patients (Abu Esba et al. 2021). NSAIDs are being used in COVID-19 line of treatment but it has some limitations (Pergolizzi et al. 2020; Giollo et al. 2021). Indigestion, stomach ulcers and increased risk of renal and cardiovascular problems are some of the side effects of NSAIDs. A recent study has stated that the inhibition of mPGES-1 can be a potential target for anti-inflammatory effects as well as for pain management in COVID-19 patients.

Hypercoagulation and Hypoxemia induced injuries causing Pain in COVID-19

Complications related to hypercoagulation and hypoxemia are a major cause of morbidity and mortality in patients with COVID-19. The risk of thrombocytopathy and coagulopathy is higher in patients with obesity, diabetes

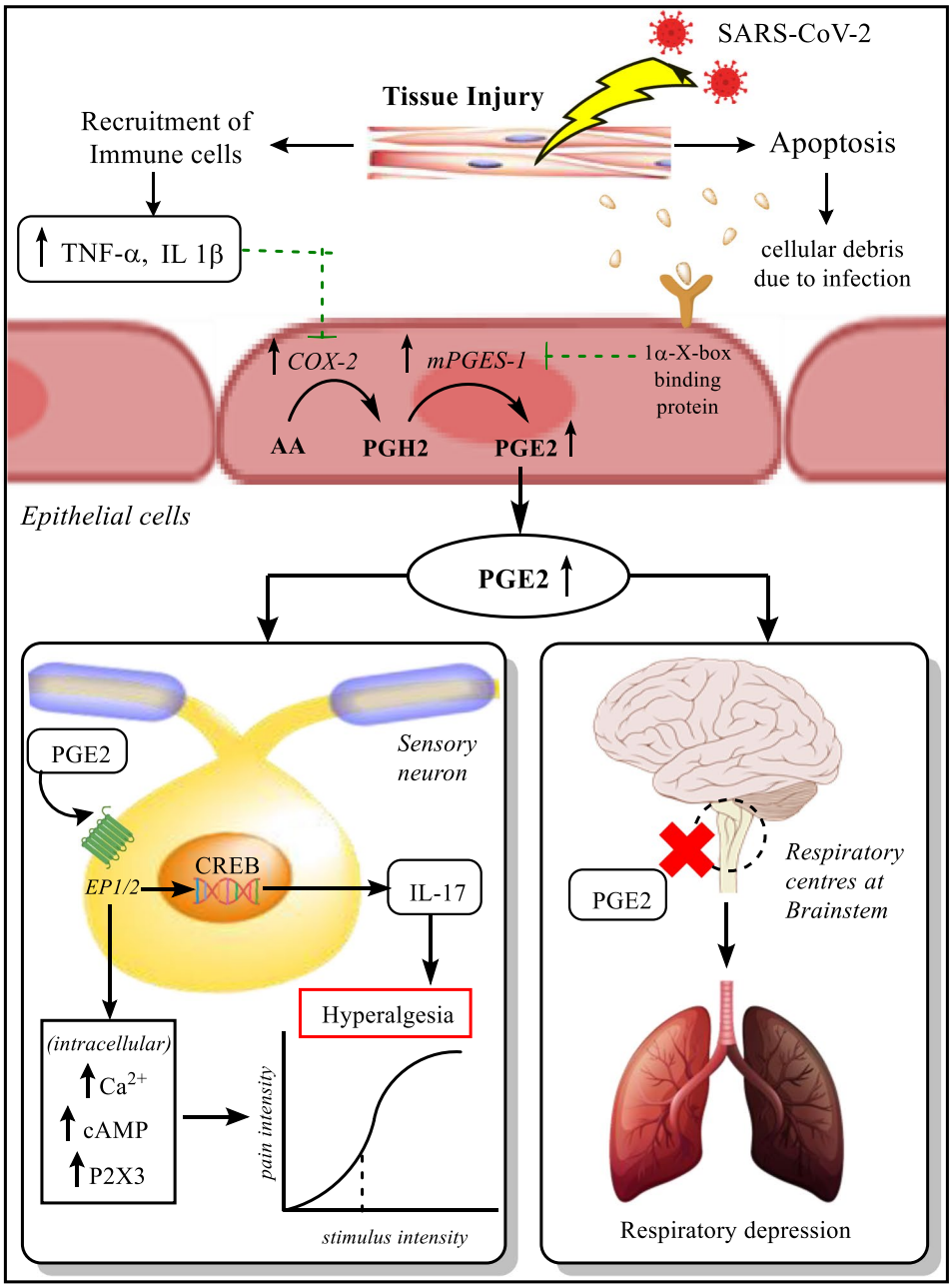

Fig. 1 SARS-CoV-2 is capable of causing direct injury to tissues leading to cellular apoptosis and, recruitment and activation of innate immune cells such as CD8+, natural killer cells, etc. producing high levels of pro-inflammatory cytokines (TNF-α, IL 1β). TNF-α is responsible for synthesis of different types of prostaglandins (PGs) whereas elevated levels of IL 1β mediates synthesis of prostaglandin E2 (PGE2) specifically. These pro-inflammatory cytokines activate cyclooxygenase-2 (COX-2) enzyme facilitating the production of PGH2 from arachidonic acid (AA). PGH2 is the percussor of PGE2. The conversion of PGE2 from PGH2 is catalysed by the microsomal PGE synthase-1 (mPGES-1) expression which is found to be up regulated by 1α-X-box binding protein upon recognition of cell debris due to infection. The upregulated PGE2 acts via EP1 and EP2 receptors present on the sensory neurons of dorsal horn of spinal cord. EP2 is a G-protein receptor which on binding with PGE2 activates protein kinase A sensitizing voltage gated sodium ion channels and purinergic P2X3 receptors through upregulated secondary messenger cAMP. On the other hand, EP1 receptors upon activation by PGE2 increases the mobilization of calcium ions inside the cell, increasing the excitability of sensory neurons of DRG. All these factors not only help in exacerbating the pain signalling through neurons but can also result in neurogenic inflammation. Upregulation of PGE2 can also worsen the symptoms in COVID-19 as it attacks the respiratory centres at the brainstem leading to a condition of respiratory depression in the patients

mellitus and hypertension. Thrombocytopenia or low platelet count is also found common in severe COVID-19 patients due to excessive engagement and exhaustion of platelets (Lippi et al. 2020). The SARS-CoV-2 virus leads to endothelial dysfunction and abrupt inflammatory responses by increasing pro-inflammatory cytokines and activating the coagulation cascade in the body. Thrombin is an enzyme responsible for the conversion of fibrinogen to fibrin is essential for the process of clot formation. Thrombin interacts with proteinase-activated receptors (PARs), PAR 1 specifically, intensifying inflammation in multiple organs (Sriram and Insel 2020). Recent investigations have revealed that anti-coagulant factors such as activated protein C and anti-thrombin III are found to be hampered in patients infected with SARS-CoV-2 (McFadyen et al. 2020; Ranucci et al. 2020; Tang et al. 2020; Wichmann et al. 2020). The rate of consumption of anticoagulant agents becomes much greater than its production, leading to the formation of microthrombus (McFadyen et al. 2020). Pulmonary embolism, atrial thromboembolism, venous thromboembolism and stroke are reported in various studies as the result of hypercoagulation. Significant increases in the levels of C-reactive proteins (CRPs), lactate dehydrogenase (LDH) and d-dimer concentration were found to be common in COVID-19 patients and were associated with severe inflammation, tissue damage and fibrinolysis (Ranucci et al. 2020; Wichmann et al. 2020). It has been observed that the severity of disease increases as the levels of CPR and d-dimer concentration increase (McFadyen et al. 2020). Also, post-mortem reports of COVID-19 patients showed tissue injury along with microthrombi in small arteries and capillaries of pulmonary tissue culture of lung, heart, liver, kidney and brain (Bei 2017; Dolhnikoff et al. 2020; Rapkiewicz et al. 2020). Many cases of thrombosis that are presented in the hospital are always accompanied with pain. Micro-thrombosis in COVID-19 patients leads to microvascular damage and inflammation (Cheung et al. 2020; Kamatani et al. 2021). Hypoxia and hypoxic tissue injury are some of the consequences of tissue damage which further worsens the disease condition as shown in Fig. 2. Decrease of oxygen levels in tissue facilitates cytokine production and inflammation exacerbating tissue injury. All these factors contribute to myalgia and overall pain experienced by infected patients. SARS-CoV-2 has been investigated for multiple organ damage where ischemic tissue injury was found to be prominent and is considered the cause of different types of pain presented by the patients such as abdominal, chest and musculoskeletal pain. Such tissue damage due to viral invasion along with hyper-immunoactivity decreases the pain threshold of COVID-19 patients during the infection period. The molecules involved in the chronic pain during COVID-19 infection was depicted in the Fig. 3 (Gefen and Ousey 2020; Serebrovska et al. 2020).

Neurological complications leading to the maintenance of pain in COVID patients

Elevated proinflammatory cytokines such as TNF-α and IL-1β have been investigated for facilitating SARS-CoV-2 invasion in CNS by increasing the permeability of blood–brain barrier. The viral invasion interferes with the nociceptor sensitization inducing pain in COVID-19 patients. Some pieces of evidence of neuronal demyelination have also been reported and is suspected to contribute to fatigue, muscle weakness and development of seizures in infected patients (Zanin et al. 2020). SARS-CoV-2 reaches CNS via systemic circulation. The viral invasion to the central nervous system is followed by different inflammatory mediators and activation of the inflammatory cascade. Neurons and resident glial cells of the nervous system have significant expression of ACE-2 receptors which allows the viral entry into the cell. SARS-CoV-2 RNA was found in the cerebrospinal fluid samples collected from COVID-19 patients confirming viral neuroinvasion (Moriguchi et al. 2020). SARS-CoV-2 invasion in the nervous system typically causes activation of T-cells and other immune effector cells producing high concentrations of IL-6, IFNγ and IL1B proinflammatory cytokines, along with other inflammatory markers such as calcitonin gene-related peptide and D-dimer. Among these, cytokine IL-6, calcitonin gene-related peptide and D-dimer play significant roles in onset of headache and chronic pain (Ashina et al. 2000; De Jongh et al. 2003; Zhou et al. 2016). These cytokines in elevated levels trigger the inflammatory cascade and can cause tissue injury directly to the nervous system. A series of reactions is activated as the hyperactive immune response which often leads to neurotoxicity. The mononuclear cells also cross the blood–brain barrier and produce potent inflammatory mediators which activate of resident immune cells leading to cellular apoptosis and driving nociceptor sensitization (McFarland et al. 2021). Clinical studies have reported manifestation of skeletal muscle incoordination, encephalitis and cerebrovascular diseases were found in late-phase disease (Li et al. 2020b). In a post-mortem report, one-third of COVID-19 patients were found to have inflammation, edema and congestion in their brains (Li et al. 2020b). In a study conducted in Wuhan, China, it was found that impaired consciousness, skeletal muscle injury and acute cerebrovascular disease were some neurological manifestations that were more distinguished in patients with severe conditions (Li et al. 2020b). The development of neurological complications was found to be associated

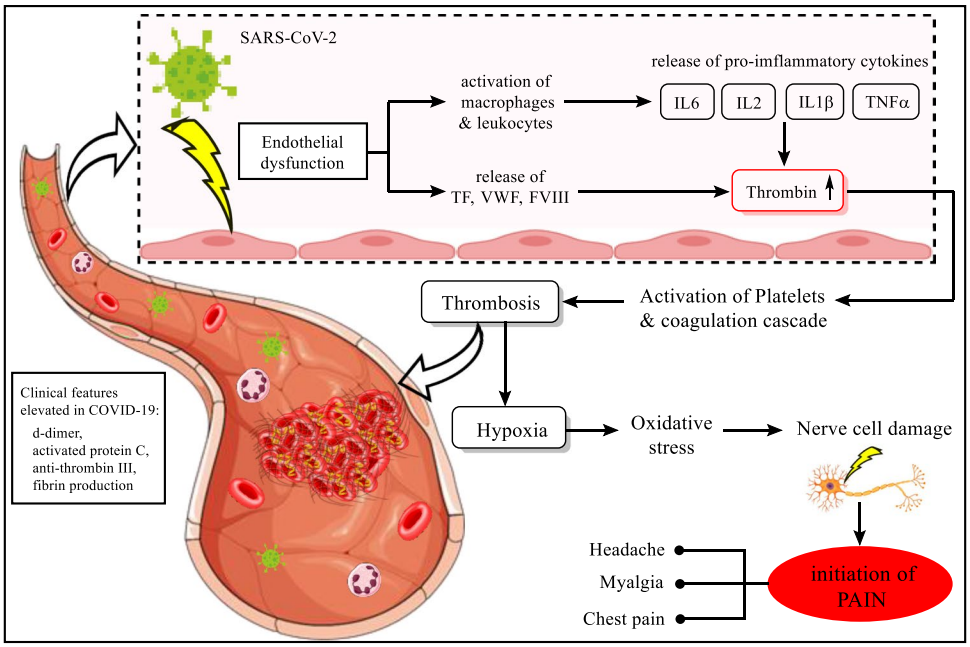

Fig. 2 SARS-CoV-2 virus is responsible for causing either direct endothelial damage or indirect tissue injury by abrupt inflammatory responses, both of which leading to the recruitment of immune cells and production of pro-inflammatory cytokines. The damaged cells trigger the release of tissue factor (TF), von-Willebrand factor (VWF) and factor VIII (FVIII) initiating the coagulation pathway by upregulation of thrombin. Among these, thrombin is the most crucial component of coagulation cascade as it mediates the conversion of fibrinogen to fibrin and activates blood platelets, eventually causing thrombosis at different parts of the body. The clotted blood in the capillaries do not allow the movement of oxygen carrying red blood cells (RBCs) leading to hypoxia. The insufficient oxygen supply to cells causes the production of reactive oxygen species damaging the cells of the body including neurons. Thus, thrombosis in brain causes headache, in muscles causes myalgia and in lungs it causes chest pain. All these types of pain have been found prominent in COVID-19 patients

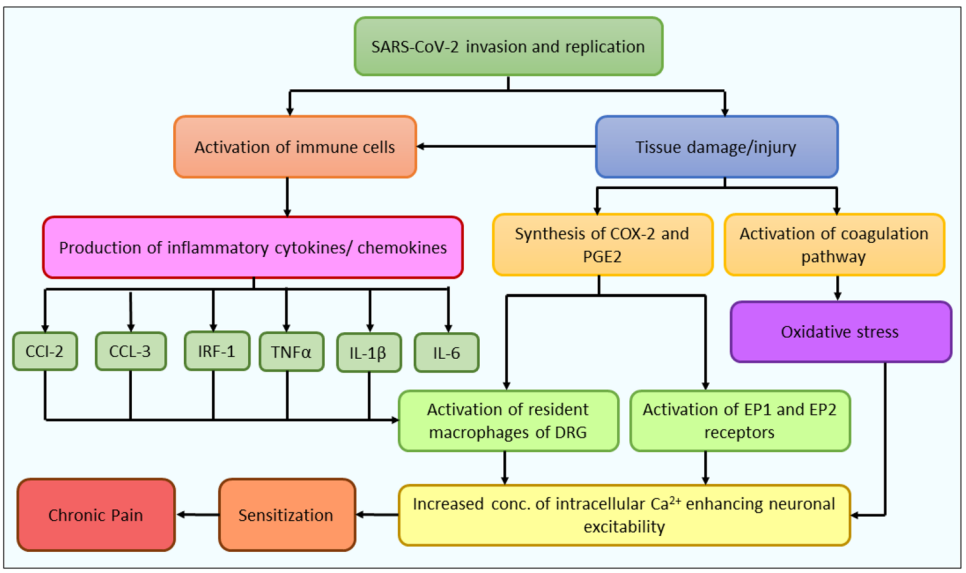

Fig. 3 Schematic representation of the distinguished molecules involved in the activation of pain pathway during SARS-CoV-2 infection

with the severity of COVID-19 infection. Along with the exacerbated immune response, hyper-coagulopathy also follows in COVID-19 pathophysiology. Upregulation of D-dimer expression in later stages of disease increases the chances of cerebral venous thrombosis and stroke (Abou-ismail et al. 2020). In such cases, headache has been

reported to the earliest and most common symptom. All the previously discussed mechanisms drive sensitization of nociceptive signaling resulting in pain.

Post-infection risks of developing chronic pain in COVID-19 patients

Post-viral symptoms are common in many virus-related diseases just as hepatitis (Berelowitz et al. 1995), chikungunya (Tritsch et al. 2021) and chickenpox (Garry et al. 2005). SARS outbreak in 2003 has also presented the potential role of this virus in causing chronic post-infection syndrome which lasted for almost 2 years (Moldofsky and Patcai 2011). A virus when enters the body, it influences a series of reactions whose effects can be seen even after the virus is gone from the body. Such post-infection symptoms can include, diffuse chronic pain, fatigue, sleep disturbance and depression. Many attributes of the COVID-19 pandemic can potentially increase the risk of development and prevalence of chronic pain. The SARS-CoV-2 virus has been investigated to disrupt and sensitize the pain signaling pathway. Chronic pain results from dynamic yet complex interplay of various molecular and biological factors. Chronic pain can be of different forms, among which neuropathic pain has been observed in COVID-19 patients. People already living with any chronic pain conditions have reported to experience exacerbation in pre-existing pain during SARS-CoV-2 infection. Whereas in other cases, COVID-19 infection acts a trigger for chronic pain. SARS-CoV-2 virus can damage central and/or peripheral nervous system directly by neuro-invasion causing activation of immune cells leading to neuroinflammation and neurotoxicity, increasing the risk of manifestation of any of the following neurological conditions such as meningitis and stroke. In all these neurological conditions, neuropathic pain is the most common complication. So, this also increases the chances of developing neuropathic pain in COVID-19 patients. About 2% of patients with SARS-CoV-2 infection admitted into hospitals have presented a possible prevalence of neuropathic pain (Mao et al. 2020). Dysregulation of the immune system is another factor that contributes to the development of chronic pain conditions. Though not confirmed, the SARS-CoV-2 virus is also suspected to cause demyelination of neurons. Guillain-Barré syndrome is another neurological condition seen in COVID-19 patients. The hyperactivity of the immune system can result in auto-immunity attacking the neurons (Caress et al. 2020). Moreover, in severe cases, many patients of COVID-19 require ICU care for their treatment (Andrews and Benken 2020). Such patients often suffer from severe functional limitations for a longer period of time leading to persistent psychological distress, weakness and chronic pain (Capdevila et al. 2017). Post-traumatic experience from ICU can also be one of the important driving factors of neuropathic pain in COVID-19 patients.

Management of pain associated with COVID-19 infection

Pain management is a very important aspect of the treatment of any disease as it helps in improving patient's compliance to the therapy (Shanthanna et al. 2020). COVID-19 is a global pandemic affecting millions of lives around the world. Healthcare systems are being continuously challenged to control this pandemic situation as fast as possible. Understanding various mechanisms responsible for the occurrence of pain in COVID-19 can assist in deciding the suitable care for patients. Paracetamol is one of the common and safer analgesics used to treat pain in COVID-19. About 40% of infected patients showed relief especially in headaches, myalgia and fever (Şahin et al. 2021). Paracetamol has shown good pain management and can also be taken as an over-the-counter medication of mild pain symptoms in COVID-19. As we have seen till now, the immune system has a very big role in the pathology of pain in COVID-19 patients (McFarland et al. 2021). NSAIDs can be considered as one of the options for managing pain with additional immunomodulatory effects. NSAIDs work by inhibiting the COX-1 and/or COX-2 enzyme, preventing the synthesis of prostaglandins (Micallef et al. 2020). Ibuprofen which is an NSAID has been reported to worsen the disease condition in COVID-19 patients (Quaglietta et al. 2021). It is postulated that use of Ibuprofen upregulates the expression of ACE-2 receptors in the patients making the infection more severe. But in a large cohort study conducted in Denmark and in Saudi Arabia, this hypothesis is denied as no significant changes were seen in severity of disease with respect to ibuprofen use (Kragholm et al. 2020; Abu Esba et al. 2021). However, in a pre-clinical study, evidences supporting the given hypothesis have been presented. Ibuprofen treatment in a rat model with cardiac fibrosis showed elevation in the expression of ACE-2 receptor (Qiao et al. 2015). Regulation of ACE-2 expression is vital for the treatment of SARS-CoV-2 infection, thus the increased level of ACE-2 expression can lead to worsening of infection posing a serious threat. Apart from this, the use of NSAIDs has some limitations of its own such as it can increase the risk of cardiovascular, renal and gastrointestinal problems. Gastric ulcers, drowsiness and allergic reactions are some of the common side-effects of NSAIDs. Immunosuppressants are another therapeutic approach in pain management. Opioids are reported to act on the HPA axis by interfering with innate as well as adaptive immunity. Opioids are preferably used in elderly patients (Schimmel and Manini 2020; Shanthanna et al. 2020). Buprenorphine is one of the

safest choices of opioids that can be used especially for the management of chronic pain associated with COVID-19 (Franchi et al. 2019). For patients with even more severe conditions such as those with refractory shock, the steroid may be suggested (Kemp et al. 2020). It should be noted that unnecessary and/or excessive steroid use should be avoided as it can lead to the manifestation of other diseases such as hypertension and liver damage.

Discussion and conclusion

COVID-19 pandemic has traumatized the lives of people all around the world. People are forced to live in quarantine for several months to a year. This not only affects the physical health but also the mental health of the patients and their families. People tend to be more afraid of things when they have less knowledge about. The emergence of this unknown virus has caused a state of panic among people. Extensive research is being conducted in order to settle down the current condition. The government, healthcare workers and citizens are working in harmony to end this pandemic as soon as possible. More than one year has been passed and experts are still struggling and are faced with new challenges every day. Pain is one such challenge that has emerged with SARS-CoV-2 infection. Pain management is highly subjective to patients and can have multiple complex reasons for its manifestation. In COVID-19, multiple types of pain have been reported. Headache, myalgia and chest pain being the most common ones. Pain management is a very important aspect that has to be considered for the successful treatment of any disease. COVID-19 pathophysiology involves an interplay of series of molecules. Several molecular mechanisms are suspected to contribute to the initiation and prevalence of pain. There have been no resolute studies focussing on the impact of the SARS-CoV-2 virus on the nociceptor sensitization. Still some studies, has shown viral RNA to be involved in the modulation of sensory neurons during SARS-CoV-2 infection. The SARS-CoV-2 neurovirulence can be postulated from the neurological symptoms that have been presented by the infected patients. The cytokinetic impact can be considered to be one of the vital mediators of pain in COVID-19. It not only damages the tissue directly but also facilitates indirect injury via activated macrophages and the coagulation system. The SARS-CoV-2 invasion in the human body elevates the synthesis and activation of the immune response, which acts a driving force for the development of pain. The cytokinetic storm is a well-researched topic in the COVID-19 pathophysiology. The elevated immune response activates many molecules inside the body which further contributes to neuronal hypersensitivity. In this review article, we have suggested and discussed different mechanisms involved in the pain pathology associated with COVID-19 which can help to find a potential target for the management of pain.

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