Emergent Materials (2021) 4:329–349
https://doi.org/10.1007/s42247-020-00138-6

REVIEW

Combating COVID-19 with tissue engineering: a review

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Received: 30 July 2020 / Accepted: 2 November 2020 / Published online: 20 November 2020

Abstract

The ongoing COVID-19 pandemic triggered by SARS-CoV-2 emerged from Wuhan, China, firstly in December 2019, as well spread to almost all around the world rapidly. The main reason why this disease spreads so many people in a short time is that the virus could be transmitted from an infected person to another by infected droplets. The new emergence of diseases usually may affect multiple organs; moreover, this disease is such an example. Numerous reported studies focus on acute or chronic organ damage caused by the virus. At this point, tissue engineering (TE) strategies can be used to treat the damages with its interdisciplinary approaches. Tissue engineers could design drug delivery systems, scaffolds, and especially biomaterials for the damaged tissue and organs. In this review, brief information about SARS-CoV-2, COVID-19, and epidemiology of the disease will be given at first. After that, the symptoms, the tissue damages in specific organs, and cytokine effect caused by COVID-19 will be described in detail. Finally, it will be attempted to summarize and suggest the appropriate treatments with suitable biomaterials for the damages via TE approaches. The aim of this review is to serve as a summary of currently available tissue damage treatments after COVID-19.

Keywords COVID-19 · SARS-CoV-2 · Tissue engineering · Regenerative medicine · Organ

1 Introduction

In December 2019, an outbreak of a novel coronavirus emerged from Wuhan in China [1]. At first, it was called 2019 novel coronavirus (2019-nCoV), and then it was named severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) [2]. SARS-CoV-2 belongs to the Coronaviridae family. The members of this family are enveloped, non-segmented, and positive-sense RNA viruses [3].

Angiotensin-converting enzyme II (ACE2) is a mediator receptor for SARS-CoV-2 infection. The virus binds to the ACE2 receptors via its' spike glycoprotein (S) and a plasma membrane-associated type II transmembrane serine protease (TMPRSS2) cleaved the S protein for membrane fusion. Then, the virus enters the cell, where it multiplies, thereby causing the cell to become infected and malfunction [4, 5] (Table 1).

SARS-CoV-2 could be transmitted by respiratory droplets or fomites. Therefore, the virus had been able to spread rapidly to almost all over the world in a short time by resulting coronavirus disease (COVID-19). Then, COVID-19 was announced as a global pandemic by the World Health Organization (WHO) on March 11, 2020. Early epidemiological studies indicated that all age groups could be affected by the virus [21].

All reported symptoms for COVID-19 are classified as common and rare symptoms. Although, the WHO announced [22] the most common symptoms like fever, dry cough, and fatigue. Some other symptoms are that muscle pain, nasal congestion, headache, sore throat, diarrhea, loss of taste and smell, skin rashes, swelling of the fingers, and toes. The Centers for Disease Control and Prevention (CDC) stated that

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Table 1 Expression of ACE2 protein in various organs and cells

Organ	Cells	References
Lung	Epithelial cell, lung parenchyma, and type II alveolar cells	[6–8]
Heart	Endothelial, cardiac myocytes	[9]
Arteries	Vascular endothelium	[10]
Brain	Glial cells, endothelial and arterial smooth muscle cells	[11]
Kidney and bladder	Kidney proximal tubule cells and bladder urothelial cells	[12]
Liver	Erythroid, fibroblast, and hepatocyte	[13]
Oral cavity	Epithelial cells, lymphocytes	[8]
Intestine	Intestinal enterocytes	[14]
Colon and ileum	Absorptive enterocytes, cholangiocytes, myocardial cells, endothelium and vascular smooth muscle cells from the blood vessel	[10, 15, 16]
Testis	Adult Leydig cells	[17]
Ovary	Theca-interstitial cells	[17]
Uterus	Epithelial and stromal cells	[18]
Placenta	Cytotrophoblast, syncytiotrophoblast, endothelium and vascular smooth of primary and secondary villi	[19, 20]

these symptoms may be observed between 2 and 14 days [23]. According to the WHO declaration in February, 2020, the initial effects of COVID-19 are non-specific and the disease can develop from no indications (asymptomatic) to serious pneumonia and death. The main symptoms are generally observed after infection, albeit the emergence of other symptoms may vary for individuals depending on gender, age, immunity level, and chronic dysfunctions like high blood pressure, diabetes, cancer, heart, and lung diseases [22].

As known all the systems in the body are interconnected, therefore, dysfunction in an organ is able to cause disorder of another organ or system. Numerous studies indicated that the virus results with acute (temporary) or chronic (permanent) damage in many organs, particularly in the lungs. In addition, drugs used for the treatment may also cause these damages. TE is utilized as a treatment method. It is a multidisciplinary field that is uniquely suited to apply engineering principles to complex clinical problems [24]. These engineering techniques are focused on drug delivery systems, biomaterials, and replacement of damaged tissues and organs [25].

This review will mainly cover tissue damages in several organs such as the lung, cardiovascular system, nervous system, kidney, bladder, liver, gastrointestinal (GI) system, reproductive system and skin, caused by COVID-19, and tissue engineering (TE) approaches by using biomaterials for the treatment of these damages.

2 Symptoms of COVID-19

Compared to other viral respiratory diseases, COVID-19 has not any specific symptoms to differ [26]. All reported symptoms for COVID-19 are classified as common and rare symptoms. Although, the WHO announced [22] the most common symptoms like fever, dry cough, and fatigue (Fig. 1).

Some other symptoms are that muscle pain, nasal congestion, headache, sore throat, diarrhea, loss of taste and smell, skin rashes, swelling of the fingers, and toes. The CDC stated that these symptoms may be observed between 2 and 14 days [23]. According to the WHO declaration in February, 2020, the initial effects of COVID-19 are non-specific and the disease can develop from no indications (asymptomatic) to serious pneumonia and death.

In a meta-analysis study, 80% fever, 63% cough, 46% fatigue, and 40% expectoration were observed as common symptoms among 3.162 patients [27]. In another study involving 53,000 patients, the most common symptoms were fever 79%, cough 58%, and 29% fatigue. The uncommon symptoms are also observed like headache, diarrhea, myalgia, sore throat, shortness of breath, vomiting, chill, nasal congestion/rhinorrhea, dyspnea, anorexia, and dizziness [28] (Table 2).

The main symptoms are generally observed after infection, albeit the emergence of other symptoms may vary for individuals depending on gender, age, immunity level, and chronic dysfunctions like high blood pressure, diabetes, cancer, heart, and lung diseases. According to the WHO, one out of five people get seriously ill and have difficulty in breathing, while 80% of patients recover without any special treatment [22].

As known, the individuals have distinct responses for infections. This situation may be considered as the reason of symptom variability among patients.

In addition to symptomatic patients, lots of asymptomatic cases have been detected. The WHO stated the rarity of asymptomatic patients and stated that they do not appear to be the main driving force of transmission [23].

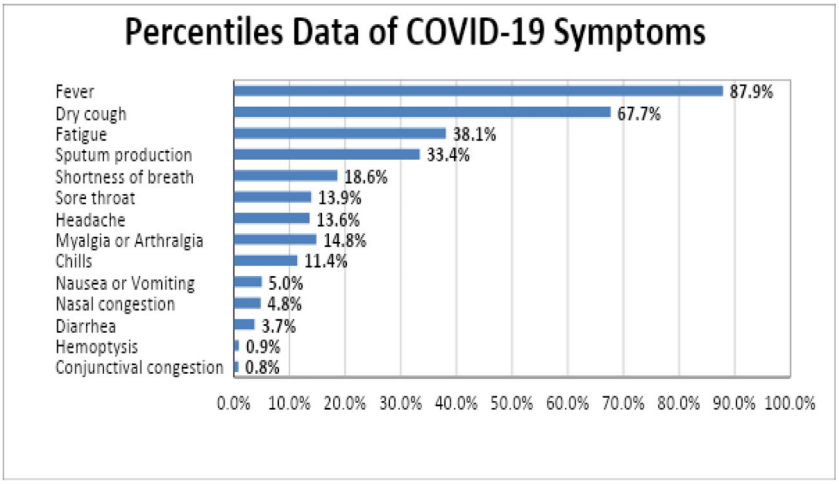

Fig. 1 Commonplace signs and symptoms [22]

3 Organ damages caused by COVID-19

3.1 Lung damages

SARS-CoV-2 causes severe damage to the lower respiratory system as progressed it turns into severe acute respiratory diseases such as bronchitis, pneumonia, and fibrosis [29]. Inflammation in lungs is also reported by Higham et al. [30]. They indicated that as a result of viral infection, the water passes from the circulatory system into the lungs and the inflammation process begins. According to a research conducted in Vienna, pulmonary embolism had been found in severe COVID-19 patients. It has been suggested that if patients are not treated earlier, the death risk will increase [31].

Chest computed tomography (CT) scan performed in the early stages of the disease revealed interstitial changes and plaques around the lung. Fibrous structures can be seen in the lungs even when the disease disappears [32]. The CT results of another study indicated that the subpleural region of the lower lobes of lungs had ground-glass opacities and consolidation even if treatment completed [33]. In another study conducted with 138 COVID-19 patients, considering the chest CT of patients, consolidations or bilateral ground-glass opacities were detected in almost all patients as shown in Fig. 2 [34].

Table 2 All observed symptoms in the mentioned studies

Symptoms of COVID-19	
Fever	Nausea or vomiting
Dry cough	Nasal congestion
Fatigue	Diarrhea
Expectoration	Hemoptysis
Shortness of breath	Loss of taste and smell
Sore throat	Skin rashes
Headache	Skin color change
Myalgia or arthralgia	Swelling of the fingers and toes
Chills	Dizziness

3.2 Cardiovascular damages

As known, the cardiovascular system provides the required oxygen and nutrients to the cells. Therefore, any damages in this system can cause disorders in all other organs. COVID-19 has effects on the cardiovascular system and causes serious complications. Possible diseases are known myocardial injury

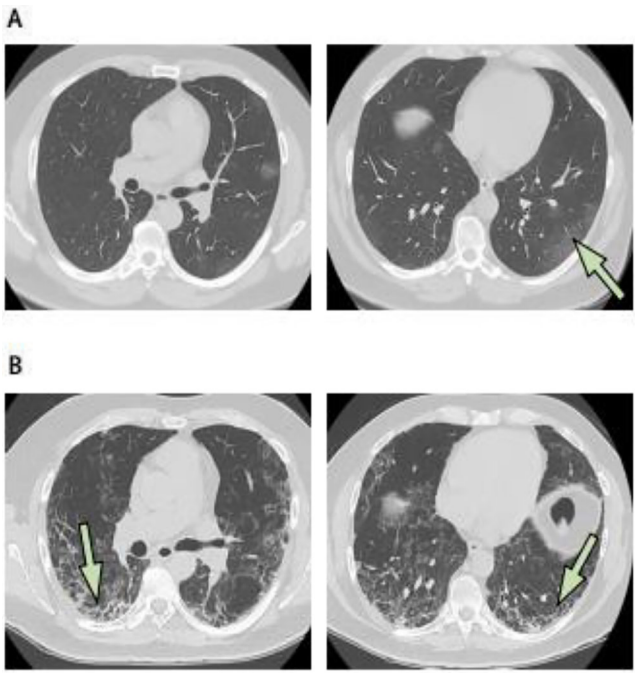

Fig. 2 **a** In the early stages of the disease, soft ground-glass opacities were detected in the area indicated by the arrow in the left lung. **b** Pulmonary damage progressed rapidly in CT scan performed 3 weeks later and fibrosis occurred in the shown regions [34]

[35, 36], acute myocardial infarction [35], dysrhythmias [35], and vascular system damages [35, 37, 38].

Complications of COVID-19 in the cardiac system can be explained by multiple mechanisms; firstly, COVID-19 can indirectly cause cardiac damage by triggering a great immune-inflammatory response and cytokine storm. Secondly, hypoxia from acute respiratory damage caused by COVID-19 can cause myocardial injury [39]. Thirdly, systemic inflammation can disrupt the stability of vascular plaques, causing myocardial infarction and shear stress due to increased blood flow [35]. Also, systemic inflammation increases the risk of a prothrombotic conditions. Finally, drugs used to treat COVID-19 can cause negative effects on the cardiovascular system [40].

3.3 Neural damages

Viruses that can infect the nervous system generally reach the central nervous system (CNS) by hematogenous (via infecting the blood–brain barrier) or neuronal ways [6, 41]. The presence of the ACE-2 receptor in nerve cells leads to the idea that SARS-CoV-2 may also pose a threat to the nervous system [42–46]. Due to both the large size of SARS-CoV-2 and the strong structure of the blood–brain barrier, the virus is more likely to reach the CNS through olfactory nerves [47, 48].

The fact that some COVID-19 patients have symptoms similar to intracranial infections supports the idea that SARS-CoV-2 can infect CNS [6, 49]. Guillain–Barré syndrome, meningitis, and other neuroimmune disorders are also other ailments reported in the context of coronavirus infections [48]. According to autopsy reports of COVID-19 patients, brain tissue edema and partial neuronal degeneration were found in deceased individuals. The first case in this context was reported as a case of viral encephalitis at Beijing Ditan Hospital on March 4, 2020. Xiang and colleagues proved the presence of SARS-CoV-2 in the patient's cerebrospinal fluid by genome sequencing [50]. This study suggests that the blood–brain barrier may be damaged by a pathogenic attack, and symptoms of secondary intracranial infection may occur.

If CNS is infected with SARS-CoV-2, numerous neurological diseases will be triggered by the infection. Possible neurological diseases are known as viral encephalitis [50–52], infectious toxic encephalopathy [41], acute cerebrovascular disease and stroke [49, 53], hypoxia injury [41], and immune injury [41, 54, 55].

3.4 Kidney damages

When urine samples of COVID-19 patients were examined, a high level of blood urea nitrogen and plasma creatinine were detected in the samples [56]. Also, in recent studies, this virus was observed in the patient's urine [57]. The mechanism of the damage has not been precisely determined yet. However, there are multiple possibilities for the viral damage mechanism. One of the supposed mechanisms is cytokine storm which will be discussed in detail in the following sections [58]. Because of the cytokine storm, the kidney is able not to perform its function properly. The second possibility is direct damage that the virus enters and accumulates in the kidney cells. Studies suggest that the ACE2 receptor may be effective in regulating kidney function [59]. Also, in recent studies, nucleocapsid protein has been found in kidney tubules of COVID-19 patients and SARS-CoV-2 antigens have been detected in the kidney. At the same time, it has been seen that kidney tissues examined by electron microscopy have virus-specific residues and these tissues have lymphocyte infiltration. In addition to stimulating macrophages, it also provides complement accumulation and affects kidney function severely. Thus, it was concluded that the virus triggers acute tubular damage by infecting the kidney tubules [60]. The third possibility is that kidney damage occurs due to the pneumonia that reveals after infection. Due to the inflammatory process in the lungs, the oxygen level of blood is insufficient. This issue may cause changes in kidney function. Finally, SARS-CoV-2 has been shown to form blood clot and kidney capillaries may suddenly become blocked with these particles. This prevents the filtering of blood and disrupts the balance of protein, glucose, mineral, and water in the body [61].

Thus, defense systems of immune-deficient patients are not sufficient to overcome the disease, and these patients need an effective treatment. In case of the kidney failure in COVID-19 patients, the dialysis method is applied. There is no exact method known for treating kidney damage from in COVID-19 cases, yet.

3.5 Bladder damages

The SARS-CoV-2 and its genetic material was detected and isolated from the urine of the COVID-19 patients. However, it is not known exactly how the virus passes into the urine. Maybe, it settles into the urine when the cytokine storm damages the kidney function in infected patients [62]. Another possibility is that the virus directly damages the urinary system via ACE2 and TMPRSS2. Bladder cells, like many other organs, have these receptors and could be affected by SARS-CoV-2 [63]. In addition, bladder cancer patients undergoing chemotherapy are more likely to become infected with SARS-CoV-2 due to their weakened immunity [64].

3.6 Liver damages

Numerous studies have been done about liver damages caused by the disease [65, 66]. The high level of alanine aminotransferase (ALT) and aspartate aminotransferase (AST) enzymes in the blood is an indication for severe liver damage [66, 67].

High ALT and AST levels in COVID-19 patients were observed more in male patients than in female patients. Therefore, infected men are assumed to be more susceptible to COVID-19-induced liver abnormalities than female patients [67, 68]. According to the data, liver damage/dysfunction is also observed at a higher rate in adults than children. More studies are required to obtain definite results about gender and age-related liver function disorders [68].

It has been suggested that liver failure detected in some COVID-19 patients may be due to the hepatotoxicity of the drugs used for treatment [66]. For instance, antipyretic agents are used to reduce the fever of patients. Increased consumption of this drug may cause liver damage and failure. In addition to this drug, although it is not currently an effective antiviral agent for COVID-19, infected patients are administered antiviral drugs such as oseltamivir, umifenovir, and lopinavir/ritonavir that may have hepatotoxic effects [68, 69].

It has been also estimated that cytokine storm during the disease and high inflammation caused by pneumonia can also cause liver damage and liver failure may occur in critical situations. It is suggested that liver damage in COVID-19 patients may be caused by psychological stress as well as systemic inflammatory response [13]. This type of damage has been observed in patients who had severe COVID-19 disease. Among infected patients, those with cirrhosis and/or liver cancer are more susceptible to the disease due to systemic immune deficiency [66].

With pneumonia caused by SARS-CoV-2 infection, shock and hypoxic conditions may occur. It has been suggested that decreased oxygen and increased lipid accumulation in hepatocyte cells in the liver during these conditions may lead to cell death. A significant increase was observed in the reactive oxygen species and their peroxidation products. This increment may cause liver damage by activating redox-sensitive transcription factors and increasing the release of pro-inflammatory factors. Based on all these data, pneumonia-related hypoxia is thought to be one of the important factors causing secondary liver damage in infected patients [68].

3.7 Gastrointestinal system damages

Clinical reports suggest that some parts of the gastrointestinal (GI) tract are also the potential route for SARS-CoV-2 entrance because ACE2 is highly expressed in these cells [70] (Table 1). Twenty to 50% of COVID-19 patients had GI symptoms such as abdominal pain and diarrhea. When the GI symptoms were evaluated individually, it was observed that the rate of nausea and anorexia due to COVID-19 was higher in patients with anosmia and ageusia complaints. Loss of taste and smell is not only associated with nervous system but also associated with upper GI symptoms and is caused by loss of appetite [71].

It was proved that the virus has an ability to replicate itself in human small intestine [14, 72]. The viral RNA was detected in the patient's stool, esophagus, stomach, duodenum, and rectum [71, 73, 74]. SARS-CoV-2 might damage intestinal flora by causing disorders. Furthermore, gut–lung axis and microbiome dysbiosis could impact on the seriousness of disease by altering the microbiota [75, 76].

As a result of the pathological examinations, ischemic enteritis with irregular necrosis and fibrin thrombus were detected in arterioles [77]. The bowel abnormalities and cholestasis could be caused by small vessel thrombosis, so due to the infection.

3.8 Reproductive system damages

Due to ACE2 expression level, the disease is more prominent in the male reproductive system [78]. ACE2 is also expressed in the female reproductive system, mostly in ovaries. The soluble ACE2 level is normally observed to be low, but under certain circumstances, such as large follicles in stimulated eggs, an increase in the level of ACE2 can be observed. In this case, the possible rate of infection with SARS-CoV-2 increases [79]. The damages can be infertility, fetal problems, or menstrual disorders. In addition, the presence of ACE2 in the ovary, uterus, vagina, and placenta suggests that the virus has the potential to be passed to the baby or transmitted sexually [80]. However, there are not enough studies to find out the effects of the virus on oocyte, pregnancy and embryo, and sexual transmission.

The studies to detect damage caused by the virus on the male reproductive system have shown that testis is a potential organ for infection. It has been observed that ACE2 expression in testis varies according to the age range and reduces with increasing age [81, 82]. It is not known exactly whether the virus will cause any loss of function or infertility in males. A study conducted on COVID-19 patients observed the decreased sperm concentrations in male patients during 72–90 days [78]. Consequently, SARS-CoV-2 is thought to cause some functional disorders in both genders' reproductive system.

3.9 Skin damages

Common five skin damage was detected in 375 COVID-19 patients [83]. Acral areas of erythema–edema with some vesicles or pustules (pseudo-chilblain) are one of the damages found in the hand and foot, detected in 19% of COVID-19 patients. Other vesicular eruptions are another damage observed in 9% of patients. It has some blisters filled with blood and was more common in middle-aged patients. The urticarial lesions (19%) and maculopapular (47%) are other damages. The latter is formed in the form of small, flat, and fluffy lumps in the body. It has also seen in the hair follicles. Livedo

(necrosis) is the least common (6%) skin lesion caused by circulatory issues such as vascular narrowing or obstruction. It generally holds in patients who are elderly and have severe disease. However, it was stated that some of the mentioned skin injuries seen in COVID-19 patients are common in healthy individuals and are not sufficient indicators for COVID-19 diagnosis [83]. In Fig. 3, skin lesions observed in a patient with COVID-19 is shown.

3.10 Coronaviruses and ocular effects

Findings from previous coronavirus researches suggested that this virus could also be found in tears and ocular tissues [85]. Wu et al. studied with clinical samples of 38 COVID-19 patients (average age is 65.8). They demonstrated that 31.6% of these patients have ocular abnormalities, and most have more severe systemic symptoms or abnormal observations from blood tests [86]. Besides, the fact that SARS-CoV-1 can be transmitted through unprotected eyes suggests that COVID-19 can also be transmitted through the eyes.

4 Cytokine effect and COVID-19

Cytokines are the first immune defense for external infections. The irregular cytokine/chemokine response is thought to cause an inflammatory cytokine storm and immune damage in the body. In clinical studies, cytokine storm was detected in severe COVID-19 patients [87]. After coronavirus infection, the monocytes, macrophages, and dendritic cells are activated. With activation of the immune system, high levels of pro-inflammatory cytokines (interleukins (IL), IL-6, TNF) and chemokines as well as low levels of interferons (IFNs) are secreted [88]. Qin et al. indicated that the cytokine and chemokine levels are high in the serum of COVID-19 patients [89]. The rapid increase of these chemokines and cytokines attract many inflammatory cells, which causes the apoptosis of the different kinds of cells. Apoptosis of endothelial and epithelial cells of the lung causes damages of cell barrier, alveolar epithelial, and pulmonary microvascular tissues. This issue causes hypoxia and leakage in the vascular system. A schematic representation of cytokine storm in severe COVID-19 patients is shown in Fig. 4.

The high levels of cytokines and chemokines are involved in the formation of acute respiratory distress syndrome (ARDS). This syndrome leads to death in COVID-19 patients. Besides, pro-inflammatory cytokines induction triggers apoptosis of lung epithelium, T cells, and endothelial cells [87]. Increasing of cytokines and chemokines can also cause clotting, immune deficiency, and organ damage [90]. Cytokine levels in the serum of COVID-19 patients are directly proportional to the disease severity.

5 Tissue engineering approaches for organ damages caused by COVID-19

5.1 Tissue engineering approaches for lung damages

Particularly due to the overexpression of cytokines, serious damages may occur in the lungs after COVID-19. Because of its regenerative properties and anti-inflammatory capability, mesenchymal stem cells (MSCs) can repair damaged lung tissue and stabilize endothelial fluid leakage and reduce the alveolar-capillary barrier function, thereby reducing the development of interstitial lung edema [91]. Transplantation of exogenous mesenchymal stem cells can provide the necessary signals to stimulate endogenous lung progenitors and create a synergy between exogenous and endogenous stem cell activities. Several preclinical studies have demonstrated the ability of mesenchymal stem cells to alleviate lung damage in acute respiratory distress syndrome (ARDS), chronic lower respiratory disease (CLRD), cystic fibrosis (CF), bronchopulmonary dysplasia (BPD), and idiopathic pulmonary fibrosis (IPF). Preclinical studies have shown that stem cell therapy can reduce lung tissue damage and improve survival in experimental animal models. Phase 1 clinical trials have proven the safety of mesenchymal stem cell therapy in terms of certain lung diseases [92].

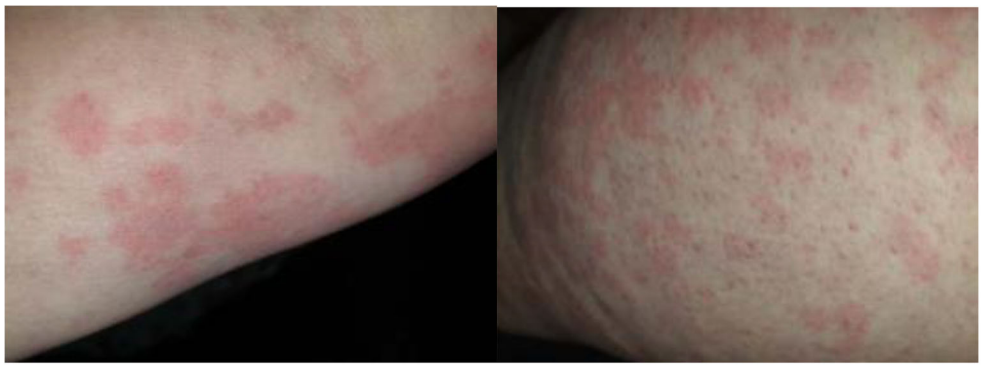

Fig. 3 Skin lesions observed in a patient with COVID-19 [84]

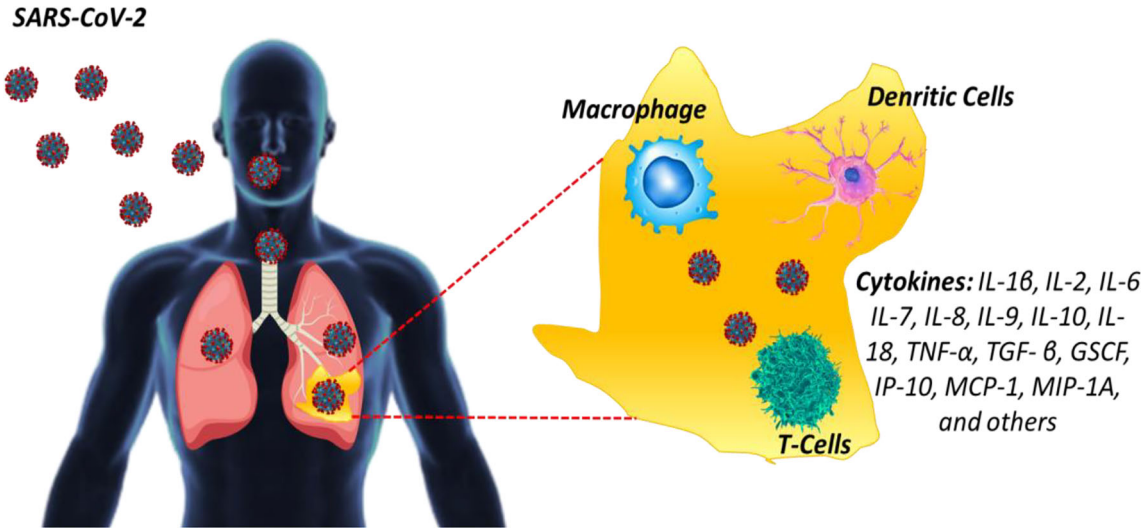

Fig. 4 The cytokine storm in severe COVID-19 patients

In human studies, an implantable airway was produced with TE strategies [93]. Human bone marrow-derived mesenchymal stem cells (hBMMSCs) and human adipose tissue-derived mesenchymal stem cells (hATMSCs) were prepared to be cultured on a cell-free scaffold under favorable conditions, and obtained results showed that these cells were suitable for cell-free lung regeneration and treatment. Based on this study, it can be said that damaged lung tissues could be regenerated after COVID-19.

The therapeutic utilization of lung progenitor cells, which are appropriate for vascularization of lung tissue, derived from human embryonic stem cells/induced pluripotent stem cells (ESC/iPSC) for the regeneration of injured lungs has been found to have an enormous clinical effect [94, 95]. Current seeding strategies allow all lung scaffolds to be evenly distributed across the endothelial cells (ECs), and after a few days of cultivation, 75–80% coverage has been achieved [96]. Based on these studies, it can be stated that lung damages caused by COVID-19 could be eliminated by using these progenitor cells. Petersen et al. produced the functional lung using the rat model system by TE [97]. Firstly, the natural lung was decellularized to remove all immunogenic cellular components and then the extracellular matrix was cultivated in a bioreactor designed to mimic the properties of the normal lung environment. The function of the designed lung tissue was tested by implanting it in a syngeneic rat model for short periods. Designed lungs ventilated with oxygen and blood flow was restored. However, many issues need to be considered and resolved before long-term engineering lung function could be performed. The decellularization method is shown in Fig. 5.

In 2004, a porcine jejunum patch which is decellularized and seeded with autologous primary fibroblasts and muscle cells was implanted in a 58-year-old male patient. Epithelization and 80% cellular density were achieved in the patient's lungs 5 days after implantation. In 2008, a 5-cm-long decellularized cadaver left bronchus made from a human trachea was implanted in a 30-year-old female patient with late phase bronchomalacia. The implanted left bronchus was cultured 96 h in the bioreactor with autologous epithelial cells and mesenchymal stem cells. In 2011, a nanocomposite trachea implanted into a 36-year-old patient with late tracheal cancer. This synthetic trachea which is made of polyhedral oligomeric silsesquioxane-poly(carbonate-urea) urethane (POSS-PCU) was created using a glass mold of the trachea of a patient. The artificial trachea containing U-shaped polymer strips was seeded with mononuclear cells derived from autologous bone marrow and incubated in the bioreactor for 36 h. Then the synthetic trachea was then implanted to the patient. One week after implantation, the analysis showed that the trachea was covered with cells and that lung function improved at 4 months compared to before surgery [98].

5.1.1 Biomaterials used for lung damages

Synthetic and natural polymers that can be modified by the cultivation of various cells are frequently studied in lung tissue engineering [99]. Synthetic biomaterials such as polycaprolactone (PCL), polylactic acid (PLA), polyglycolic acid (PGA), and poly(lactic-co-glycolic) acid (PLGA) are often used in lung tissue engineering as they can be easily modified to have various desired features. Natural biomaterials such as keratin, silk, collagen, and elastin provide easy adhesion and differentiation of cells as they contain special proteins [100]. Natural materials such as Matrigel and Gelfoam are generally used for lung tissue regeneration. These natural scaffolds have been shown to support lung tissue growth in various studies, but there are some limitations in the use of synthetic or natural ECM [99]. PGA and poly-D,L-lactide (PDLLA) are used as scaffolds in lung tissue engineering

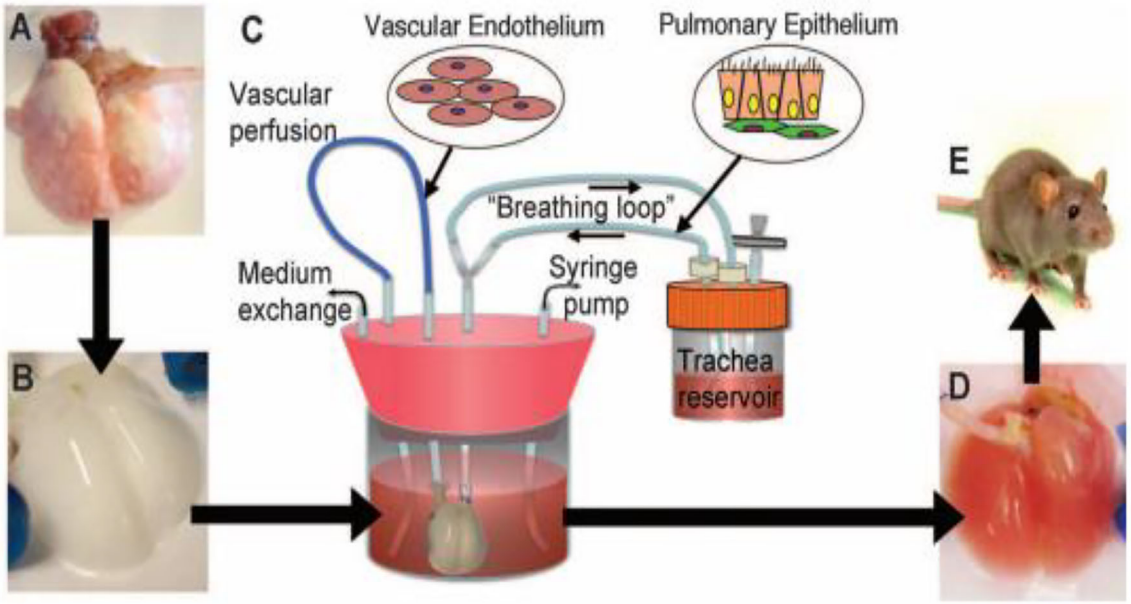

Fig. 5 The lung TE scheme. (**a**) Infusion of decellularization solutions by cannulating natural adult rat lungs in the pulmonary artery and trachea. (**b**) Acellular lung matrix lack of cells after 2 to 3 h of treatment. (**c**) Acellular matrix, insertion into a biomimetic bioreactor and seeding the pulmonary epithelium into the trachea and vascular endothelium into the pulmonary artery. (**d**) The designed lung is removed from the bioreactor after 4 to 8 days of culture. (**e**) Implantation [97]

due to their properties. PGA seeded with adipose tissue-derived stem cells was used as a patch in a mouse model lung. The results obtained showed that the alveolar and vascular tissues of the mouse were regenerated [101]. Decellularization of whole lungs from human cadavers or pigs are generally used in lung tissue engineering as acellular scaffolds [102]. There are several biomaterials that are used in lung tissue engineering. Ling et al. showed that gelatin/microbubble skeleton seeded with mouse pulmonary stem/progenitor cells (mPSC) have alveolar structure can support lung cell proliferation, differentiation, and angiogenesis, and this material can be used in lung tissue engineering [103]. Horváth et al. reported the in vitro human air blood tissue barrier resembling native lung tissue by using the 3D bioprinting method. The system consists of printing two-cell layer endothelial cell model onto the Matrigel ECM-bioprinted layer [104].

5.2 Tissue engineering approaches for cardiovascular damages

5.2.1 Tissue engineering approaches for heart damage

COVID-19 can cause numerous heart damages which are previously mentioned. Myocardial tissue does not have a regenerative capability to replace the lost/injured cells. TE provides an alternative approach in restoring the function of myocardial tissue that has lost functionality [105, 106].

There are three main cell types used in cardiac tissue engineering studies: smooth muscle cells, endothelial cells, and cardiomyocytes. These cells are obtained from either allogenic (cardiomyocyte, human umbilical cord, embryonic stem cells) or autologous sources (adipose stem cells, skeletal stem cells, induced pluripotent stem cells, bone marrow-derived cells) [107]. The use of muscle-derived stem cells for cardiovascular tissue engineering studies is promising. In this field, MyoCELL® is a skeletal muscle myoblast cell therapy developed by BIOHEART. It takes part in phase II/III trials (MARVEL NCT00526253) with MyoCATH and MyoSTAR delivery catheters in the USA [108].

Myocardial regeneration is the method by which the damaged myocardium is restored to its fundamental form. After myocardial infarction that tissue damage leads to structural changes in the left ventricular. With an engineered cardiac patch that consists of natural or synthetic polymers, it helps to remodel in the left ventricle [105]. For the purpose of producing 3D tissue-like patches to treat myocardial tissue damage, Chen et al. synthesized cardiac patch material using poly(glycerol sebacate) (PGS) [106]. PGS is a biocompatible polymer that has shown potential applications in nerve and vascular tissue engineering. In the study, it was stated that elastomeric PGS covers the passive stiffness range of the heart muscle and can be adapted for the repair of myocardial damage. Artificial heart patches are produced to mimic the natural extracellular matrix (ECM) and provide mechanical support and cell delivery to the infarction area. Cardiac patches help reduce cardiomyocyte apoptosis by narrowing the area of infarction.

The other method is to use acellular scaffolds. These scaffolds (e.g., SynerGraft®, AlloDerm®, DermaMatrix®) can be

applied immediately [105]. It is used in decellularization technique for repairing myocardial damage. This aims to regenerate the heart tissue by decellularizing the whole or part of heart and reseeding it with heart cells [109].

The injectable materials such as fibrin, collagen, alginate, self-harvesting peptides, and chitosan could become potential therapies for myocardial infarction alone or in combination with cells [109, 110]. Dong et al. developed self-conductive injectable hydrogels based on chitosan–graft–aniline tetramer (CS-AT) and dibenzaldehyde-terminated poly(ethylene glycol) (PEG-DA) as a cell delivery vehicle for myocardial infarction [111]. It is stated that the conductivity values of these injectable hydrogels are close to the heart tissue. These hydrogels are the biomaterials that can be used to repair cellular damage caused by myocardial infarction due to their regeneration capability. TE offers different strategies for repairing myocardial damages. By improving these strategies and increasing the number of studies on clinical applications, the treatment of COVID-19 disease-induced myocardial damage can be performed.

5.2.2 Tissue engineering approaches for vascular damage

COVID-19 can cause embolic events, which cause various clinical results according to the related organ, in the vessels [37]. Vascular diseases are treated with the use of bypass, stent replacement, and anticoagulation treatments. Bypass surgery generally aims to treat the occluded vessel using autologous arterial and venous grafts, but to obtain these grafts is difficult. To solve these problems, studies are carried out on synthetic grafts. However, the synthetic grafts cause thrombus formation and are not suitable for small vessels [112, 113].

In this case, treatment may be possible by using vascular grafts to be developed by using TE approaches. Damages caused by COVID-19 in the veins can be treated with the use of autografts. Matsumura et al. obtained autografts by seeding bone marrow cells (BMCs) on biodegradable scaffolds (PGA + P(CL/LA)) and (PLLA + P(CL / LA)). After the application of autografts, any problem was not observed. They have not any rejection risk, albeit they have a low incidence of calcification and reduced long-term anticoagulation therapies [114]. This promising method can be successful in solving potential problems due to COVID-19.

There are many tissue engineering studies for the development of small-scale vascular grafts. Syedain et al. have developed a new bioreactor system to produce grafts similar to natural arteries from dermal fibroblasts in fibrin gel. Two- to 4-mm-thick grafts were produced by this bioreactor and they gave successful results in animal models. This is a promising research for the production of grafts that can be used for TE applications [115].

Smith et al. designed small diameter grafts using the electrospinning method to utilize in the treatment of vascular occlusions. They successfully produced polydioxanone (PDO) and elastin tubes reinforced with sutures for potential usage in vascular TE [116]. In another study, Williamson et al. developed a scaffold compatible with small vascular grafts [117]. In this study, composite scaffolds consist of polycaprolactone (PCL) produced by wet spinning and polyurethane (PU) produced by electrospinning to support the vessel wall. PCL surface supports the formation of stable functional endothelial cell monolayers. These properties, combined with the controlled release of bioactive molecules, indicate the potential of this material as a suitable scaffold for vascular TE. In addition to these methods, bioprinting method can be used in the development of vascular grafts. Norotte et al. applied the bioprinting method for vascular tissue engineering. In the study, scaffold-free vascular grafts were produced. Bioprinting technique is a significant approach for the development of vascular grafts in that it provides fast and easy scalable approach [118].

5.2.3 Biomaterials used for cardiovascular damages

Natural polymers that have biodegradability, renewability, and low toxicity used in cardiovascular tissue engineering studies are fibrin gel, collagen, gelatin, chitosan, alginate, and Matrigel [105, 119]. PLA, PGA, PLGA, PEG, PU, PCL, and poly (*N*-isopropyl acrylamide) are synthetic polymers used in cardiovascular tissue engineering applications. Synthetic biodegradable polymers are considered as potential materials for cardiac tissue engineering due to their strong mechanical properties, controlled structure, great processing flexibility, and non-immunological response. In some cardiovascular tissue applications, natural/synthetic composites are used to combine the advantages of both polymers [119].

5.3 Tissue engineering approaches for neural damages

Since almost all neurodegenerative diseases are characterized by nerve cell loss, studies on neural regeneration-enhancing treatments are of great importance. Concordantly, cell applications are one of the important methods for treating different nerve damage. As a result of in vivo studies conducted by Oh et al., it was found that MSC application in animal models of Alzheimer's disease (AD) increased hippocampal neurogenesis and differentiation of NPCs into mature neurons [120]. In a study conducted by Pollock et al., it has been reported that stem cell application for brain-derived neurotrophic factor (BDNF) release may be a positive treatment for neurodegenerative disorders such as Alzheimer's, juvenile Huntington's, ALS, spinocerebellar ataxia (SCA), and Parkinson's diseases [121].

In clinical trials for the treatment of neurodegenerative diseases, the stem cell strategy is applicable. Fetal tissue

transplantation is a strategy to repair the nervous system. In the study conducted by Gallina and colleagues, four patients with Huntington's disease had human fetal striatal tissues transplanted [122]. New tissue formation was observed connecting transplanted grafts with the frontal cortex and ventral striatum. This study provides evidence that in humans, neuroblasts of the striatal primordium can develop after neurotransplantation and pass into the brain. Besides, the study also revealed the results that support the reconstructive potential of fetal tissue. Some studies provide evidence that transplantation of human embryonic dopamine–neurons into the brains of patients with Parkinson's disease may be an appropriate treatment method. Transplantation of human embryonic dopamine neurons into the brains of patients with Parkinson's disease has been shown to be beneficial in clinical trials [123]. Cultured mesencephalic tissues from 4 embryos were implanted in the transplant group. Fiber growth from transplanted neurons was observed in 17 of the 20 patients in the transplantation group. The study provides evidence that the embryonic dopamine–neuron transplantation provides clinical benefits in relatively young patients with Parkinson's disease. In another study, Li and colleagues explained the histological analysis of a Parkinson patient who underwent unilateral cell transplantation with human embryonic mesencephalic tissue 24 years ago [124]. Major motor improvement in striatal dopaminergic function was observed in this patient after transplantation. As a result of histological analysis, it was revealed that dopaminergic reinnervation produced from the vaccine could be maintained for 25 years without creating an immune response. In vivo and clinical studies are encouraging the use of fetal and stem cell-derived therapies for neurodegenerative diseases such as Parkinson's disease in the future.

Due to some adverse effects and ethical issues in cell applications, researchers have investigated the effects of polymeric structures on neural regeneration through in vivo studies. In a study, the therapeutic effect of hydrogel consisting of polyphenol, tannic acid, polypyrrole was investigated for the treatment of spinal cord damage, and in vivo studies showed that this hydrogel activates endogenous NSC in the lesion region and improves locomotor function [125]. Naseri-Nosar et al., found that PLA and cellulose acetate 3D scaffolding containing citalopram, produced by coaxial electrospinning, significantly increased nerve regeneration in the wound site in an animal model of sciatic nerve defect [126].

Fan et al. presented a clinical study of the chitosan/PGA artificial nerve graft designed to eliminate sciatic nerve damage [127]. In this study, this graft was used to repair a 35-mm-long median nerve defect in the elbow of a patient. The results showed that artificial nerve graft could be used to repair major peripheral nerve defects in patients. He et al. developed a human acellular nerve graft (hANG) as an alternative to autogenous nerves [128]. Clinical trial results of this developed graft reveal that hANG is a safe and effective method for repairing nerve defects of 1–5 cm size.

As a result of the studies, it is understood that treatment methods of both cell and biomaterial origin can be used to eliminate neurodegenerative diseases and nerve losses that may occur after the COVID-19 pandemic. A treatment method that includes both systems may be a more effective treatment method for eliminating nerve damage.

5.3.1 Biomaterials used for neural damages

The most commonly used structures for repairing neural damages are hydrogels and solid scaffolds. Properties such as biocompatibility, non-immunogenic, allowing the diffusion of matter (nutrients, oxygen etc.), and promoting cell migration and proliferation are provided to the scaffold by biomaterials [129, 130]. dECM, scaffolds, and hydrogels made from natural and synthetic polymers are used for CNS regeneration [130–133]. Each material used has superior features. For example, acellular scaffolds facilitate axonal regeneration, accelerating functional recovery [134]. It also offers the closest 3D structure to the natural ECM structure [130]. Collagen, hyaluronic acid (HA), chitosan, gelatin, agarose, alginate, and fibrin are the most commonly used natural polymers [130–132]. Collagen, chitosan, alginate and fibrin promote axonal growth [131]. HA is the structural backbone of the CNS and provides decreased glial scar formation [132]. Synthetic polymers are also used to repair nerve defects. PLA, poly-ε-caprolactone, PGA, PEG, PU, polipirol, PVA, and co-polymers (i.e., PLGA, polylactic-co-caprolactone) that are used in neural tissue engineering are synthetic polymers [130–133]. PLA promotes axonal expansion, while PCL promotes cell differentiation and neuronal expansion. PLGA provides more NCS viability than PCL and PLA [131]. Unlike these, PEG provides repair of the damaged neuron membrane [131]. Scaffolding and hydrogels can be produced using a combination of several polymers [133]. Stem cells, drugs, or other auxiliaries (such as growth factors) can be added to scaffolds and hydrogels. The use of these auxiliary materials makes tissue regeneration more effective.

5.4 Tissue engineering approaches for kidney damages

Since there is not any special method for the treatment of kidney damages seen in COVID-19 patients, dialysis is the most used method for the treatment of renal function. Treatment can be provided by selecting an appropriate TE method according to acute or chronic dysfunctions.

New generation cellular treatment methods used in kidney treatment include integrating nephrons into the kidney, using embryonic or adult stem cells, creating tissues

compatible with nuclear transplantation (therapeutic cloning), and obtaining artificial kidneys [135, 136]. By integrating new nephrons into the kidney, it is aimed to restore the functional properties of the kidney that had lost its function. It is thought that the addition of nephrons under the kidney capsule or into the tunnels shaping the cortex and the development of the host kidney over time may help the kidney to perform its functions [135, 137]. This targeted study includes transplantation of kidney metanephros derived from embryos. This method was performed on mouse by Woolf et al. [137, 138]. It was seen that the nephrons developed in the kidneys to which they were transferred. As a result of the transplantation of metanephros with ureteric buds, it was seen that metanephros developed and got the shape of kidney. The development of metanephroses and taking the shape of kidney shows that this method can be subjected to clinical studies. The differentiation ability of stem cells is one of the best options for creating functional tissue. The transplanted ureter buds also replaced the ureter. Thus, new kidney formation was observed in situ [138]. In a study conducted by Bruno et al., the effect of microvesicles on cell proliferation was investigated [139]. In this study, mice were injected with human mesenchymal stem cells and microvesicles derived from mesenchymal stem cells. It was observed that it accelerated the healing in acute kidney injury by inducing tubular proliferation. In human body, it was concluded that microvesicles obtained from bone marrow mesenchymal stem cells can stimulate in vitro proliferation and apoptosis resistance. At the same time, utilization of stem cells for organ production reduces the possibility of the body rejection. Also, scaffold systems and all cellular treatment methods derived from biomaterials are promising TE methods for kidney regeneration in COVID-19 triggered kidney disease.

5.4.1 Biomaterials used for kidney damages

Cell-based TE approaches using nephrons and kidney stem cells are generally used in the treatment of kidney damage. Besides, there are various studies [140, 141] for the treatment of kidney problems with natural polymers such as chitosan and synthetic polymers such as PEG.

In hemodialysis, cellulose, celluloses modified with natural polymers and synthetic counterparts from polysulfone (PSu), polyacrylonitrile (PAN), polyamide (PA), and polymethylmethacrylate (PMMA) polymers are used.

For other applications, many polymers such as polyarylethersulfone (PES), polycarbonate, PA, polyvinyl chloride (PVC), polyether, polypropylene (PP), polyetherimide (PEI), polyvinyl-pyrrolidone (PVP), PU, PAN, and PEG can be used [142].

5.5 Tissue engineering approaches for bladder damages

Acute or chronic dysfunction and tissue damage may occur in the bladder due to the SARS-CoV-2 attack. Investigations have shown that tissues or organs produced in vitro can be used for the treatment of the bladder damages [143].

Organs produced from the patient's own cells with ex vivo regeneration ability are called neo-organs [144]. The urothelial and smooth muscle cells taken from natural bladder biopsies were seeded on polymer scaffolds designed as bladder by Oberpenning et al. to produce the bladder with TE [145]. This neo-organ created with TE was implanted into dogs. As a result of the investigations, it was observed that the bladder neo-organ was able to perform mechanical functions, maintain the histological architecture, and retain urine. This study has shown that autonomous and hollow organ can reconstitution successfully. In another study, Atala et al. isolated the autologous bladder urothelial and smooth muscle cells, seeded them on PGA-collagen-based bladder-shaped scaffolds, and implanted the obtaining tissues that wrapped with the omentum in patients [146]. Through this study shown in Fig. 6, it has been demonstrated that the bladder obtained by TE can be implanted in patients. These bladders provided positive results when transferred to the patient and can be utilized as a reference for the treatment of bladder dysfunction in COVID-19 patients. This method allows obtaining transferable, customized, and controlled organs.

Reconstruction of the bladder with TE methods has successful results. However, ischemic fibrosis can be developed during maturation. This is undesirable, and it is necessary to limit this issue. Baumert et al. used the omentum as an in vivo bioreactor for seeded scaffolding [147]. As a result of this study, the omentum showed intense vascularization to prevent fibrosis. At the same time, maturation was observed on the seeded scaffold. Thanks to the induction of vascularization of in vivo bioreactors, the scaffold can be transferred to the bladder replacement site without blocking blood flow [148]. Another development in tissue technology is 3D printing which is rapidly growing with decreasing cost. Especially, nanocellulose is a preferred polymer for 3D print applications [149]. The increase in the number of 3D printers and thus their widespread use, decreasing their costs, has paved the way for obtaining personalized organs with cell culture techniques. This rapidly developing technology can be used as an alternative method for the production of organs for treatment in the next years [150].

As the tissue damages and dysfunctions that may occur in the bladder are not yet known, a definite treatment method cannot be recommended. However, based on these successful studies, it can be said that the structures that are very similar to bladder or bladder tissues may be obtained through TE and it

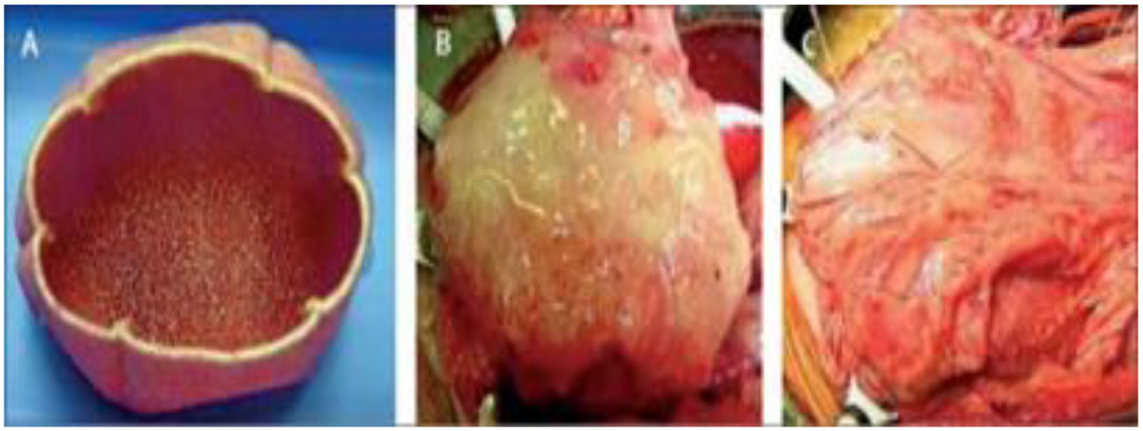

Fig. 6 Bladder formation by TE. **a** Cells are seeded on the scaffold. **b** The scaffold that is seeded with cells and is anastomosed to the native bladder with polyglycolic sutures. **c** The obtained implant is covered with fibrin glue and the omentum [146]

can be implanted for the treatment of the bladder disorders in COVID-19 patients.

5.5.1 Biomaterials used for bladder damages

Generally, studies for the treatment of bladder injuries consist of a combination of natural bladder cells and polymeric scaffolds [146]. In the construction of biological scaffolds, natural biomaterials such as collagen, alginate, and acellular tissue matrices are used due to the advantages of good biodegradability and good biocompatibility; synthetic polyesters such as PLA and PGA are used due to their non-toxicity, biodegradability, and high processability advantages; silk-based materials are used due to their advantages such as high strength, biocompatibility, and flexibility; and materials such as silicone and teflon, although they are rarely used in studies. Generally, synthetic materials are more preferred because they provide more physical intervention to the produced scaffolds. The cells chosen to be planted in scaffolds are autologous cells, with good tissue integration and regeneration and also do not create an immunological response, and stem cells with differentiation ability [151].

5.6 Tissue engineering approaches for liver damages

Liver TE is thought to be a promising treatment for COVID-19 patients who had liver injuries. Hepatocyte-based treatments are promising for clinical applications. Ohashi et al. produced hepatocyte tissue using a special cell culture dish coated with the temperature-sensitive polymer, poly(*N*-isopropyl acrylamide) (PIPAAm) [152]. The produced hepatic tissue was placed in the subcutaneous region of mice and successfully designed an ectopic liver system that had all functional activity during liver regeneration. Clinical applications of hepatocyte cell transplantation therapy based on liver injuries have yielded desirable long-term results [153]. As a result of clinical studies, it was determined that hepatocyte transplantation is less invasive than orthopic liver transplantation and can be performed safely in severe patients [154]. In hepatocyte-based studies, the encapsulation technique is generally used to increase cell viability and proliferation rate [155]. Such a system can be used for congenital liver injuries for COVID-19 patients.

Stem cell transplantation was clinically performed in individuals with serious diseases such as liver cirrhosis, tumor, and liver failure. To date, multiple clinical studies have been conducted on the effects and side effects of stem cell transplantation. In 2012, Shi et al. conducted a case control study on patients with chronic failure. In this study, the effect on patients was examined using mesenchymal stem cells obtained from the umbilical cord (UC-MSC). As a result of the studies, it was determined that UC-MSC transplantation increased the survival rate in patients [156]. In another study in which MSC transplantation was performed, it was found that liver function improved, the incidence of severe infection decreased, and survival rate increased [156].

Lee et al. developed a dECM bioink for 3D bioprinting of the liver [157]. Stem cell differentiation and functionality of HepG2 cells were investigated on this bioink. An increase in cell functions was observed in the study. According to this study, the artificial liver can be designed and produced by bioprinting with the liver biopsy obtained from COVID-19 patients. The transplantation of the produced liver can be performed. Since it is produced from the patient's own tissue, tissue rejection does not occur.

In the study of Bai et al., 3D graphene scaffolds made by nanotopography were studied by imitating ECM [158]. Graphene scaffolds can create real ECM conditions as a result of their structural, chemical, and biological properties. It is a promising tool for the cultivation of hepatocytes in that it has a porous structure and supports cell–cell interactions and cell adhesion/proliferation. Therefore, hepatocyte cells can be grown in graphene-based scaffolds and can be implanted into the damaged area to repair.

In another dECM production study, decellularization was performed based on high g-force oscillation/high shear stress [159]. Then, human acellular liver tissue cubes (ALTCs) were produced by 3D printing, and both parenchymal and non-parenchymal liver cells grown in these tissue cubes showed high gene expression. Disease pathophysiology, pharmacological target discovery, and drug toxicity assessment can be easily performed using this scaffold. In guidance of this study, such a scaffold can be produced to prevent liver damage from antiviral drugs used for COVID-19.

Lastly, the treatment method that can be recommended is bioartificial liver systems (BAL) consisting of functional hepatocytes. More than 30 cell-based support systems have been on the market since 1987 and 14 BAL systems have been used in clinical studies. It has been clinically established that such support systems are effective to treat existing liver damage [160].

5.6.1 Biomaterials used for liver tissue engineering

In liver TE, natural or synthetic, biocompatible, biodegradable, decellularized matrices, polymer-based materials, and surface-modified nanofibers are used. Usually in hepatocyte TE studies, polydimethylsiloxane (PDMS), poly(D,L-lactic acid) (PLLA), PLGA, and polyurethane-acrylate (PUA), which are biodegradable polymers, are used to create scaffolds like natural ECM. Apart from these polymers, alginate, a natural polysaccharide, chitosan, a linear amino polysaccharide, and poly-terephthalate (PET) films are also used in liver TE. Hydrogels are used as biodegradable scaffolds for cell transplantation, as they promote cell proliferation. In addition to hydrogels, collagen-based scaffolds are used for hepatocyte cell transplantation [161]. In some studies, gelatin and chitosan, agarose and chitosan, and agarose and collagen have been used to develop liver-specific bionics [162]. Biodegradable and biocompatible HA, which has high water retention capability, is used as a viscoelastic material in drug delivery systems and liver TE. It has been found that it promotes cell division in the presence of collagen during tissue repair [163].

5.7 Tissue engineering approaches for gastrointestinal system damages

The greatest damages of COVID-19 left in the GI tract appear to be ischemia and necrosis. The purpose of TE applications for the GI tract is to aid in repairing the structure and function of all damaged GI segments.

Intestinal damages caused by SARS-CoV-2 should be treated to prevent other diseases or damages. Although mild intestinal damage can be remedied due to the gut's regeneration capability, the major intestinal damages may not be cured. For this reason, the treatment methods supporting bowel regeneration are remarkable. The effect of small intestine submucosa (SIS) on intestinal regeneration has been investigated for this purpose. In vivo studies demonstrated that SIS structure facilitates regeneration of intestinal tissue layers such as mucosa and smooth muscle [164, 165]. Denost et al. compared pig SIS structure and chitosan hydrogels with in vitro and in vivo experiments [166]. The results of this experiment showed that chitosan hydrogels were superior to SIS structure in healing wounds in the colon wall. Finkbeiner et al. compared the effects of intestine and artificial PGA/PLLA scaffolds on intestinal regeneration [167]. Experiments have shown that SIS is not successful in both tests, while polymeric scaffolding may develop a small intestinal mucosal component.

The desired recovery rate could not be achieved by using solely scaffolding biomaterials for intestinal damage due to some limitations. Therefore, researchers have investigated the combination of cells and intestinal organoids together with scaffolds. For example, Nakase et al. reported the application of seeded collagen scaffolding with autologous smooth muscle cells (SMC) ensures that the luminal surface is covered by a well-developed epithelial layer with the numerous villus [168]. In another study, organoid units obtained from pigs were implanted into the autologous host after being loaded into biodegradable scaffolds [169]. The intestinal structure which has the characteristics of a robust stem cell niche and smooth architecture was obtained. In addition to SIS and polymeric scaffolds, the effect of ECM scaffolds on intestinal repair has also been investigated. A study in this context showed that the ECM hydrogel structure applied to colitis model mice accelerated the change of the colonic mucosal barrier, resulting in rapid improvement in damaged areas [170].

Although the mentioned studies are promising for the treatment of COVID-19-induced damages, the main obstacle of transferring the techniques to the clinical trials is the layered structure of GI tissues. Combined therapies that include undifferentiated cells, specialized equipment, biomaterials, and surgery methods should be applied to overcome this complexity [171]. Up to now, there is not any successful clinical study in TE applications for GI tract [172].

5.7.1 Biomaterials used for gastrointestinal system damages

While it is common to use collagen and chitosan as natural polymers in TE treatment of GI tract injuries, PLLA, PLGA, PLLC, and poly-ε-caprolactone are preferred among synthetic polymers. Collagen has the effect of increasing the regeneration of the smooth muscle layer [173]; however, it may need to be combined with other ingredients to do this effectively. Although chitosan shows high biocompatibility, its biodegradation occurs too quickly [174]. Combination with synthetic polymers may be considered to overcome the disadvantages of natural polymers. Thus, some undesirable properties of

synthetic polymers such as poor cell attachment can be avoided [175].

5.8 Tissue engineering approaches for reproductive system damages

SARS-CoV-2 is thought to cause some functional disorders or infertility in the female and male reproductive systems, although it is not known in definite. Novel methods that developed to treat dysfunctions in the reproductive system using TE methods can guide the treatment of damages in COVID-19 patients [176].

5.8.1 Tissue engineering approaches for female reproductive system damages

In cases of oocyte loss, ovarian failure, or deficiency of hormones in COVID-19 patients, TE methods can be carried out. Successful results have been obtained with the human ovarian transplantation study conducted by Silber et al. and this study may be an option for ovarian treatment [177, 178]. Ovarian transplantation is a method that is used today and provides a baby. In another study, it was studied on the delivery of hormones to eliminate disorders that occur in the deficiency of ovarian hormones [179]. In this study, the cell encapsulation technique with alginate was used to deliver hormones to the body. As a result, an ex vivo tissue that secretes sex steroids and peptide hormones and responds to gonadotropins were obtained.

Another issue is in vitro maturation of egg follicles. For the treatment, Xu et al. cultured the ovarian tissue and separated the somatic cells from the oocytes and developed a 3D culture medium using hydrogels [180]. A natural ovarian environment has been provided for egg follicles through this study. It may be a treatment guide for ovarian damage that may occur in COVID-19 patients.

The bottleneck for vaginal treatment is the lack of natural tissue for the structuring of the vagina. To solve this problem, rabbit epithelium and smooth muscle cells were seeded on the PGA scaffold and then implanted in mice by De Filippo et al. [181]. Vagina-like tissue formation has also been observed with their experiments. The appearance of vaginal tissue formation in mice has shown that there is a potential for vaginal tissue formation to be observed in clinical studies. These works are accelerated and this reference can be utilized for the treatment of vagina injuries in COVID-19 patients.

The uterus is considered as a target organ for SARS-CoV-2 due to its receptors. Since the availability of uterine transplantation is limited, De Filippo et al. studied on the production of tissue with autologous cells [181]. Therefore, they seeded the rabbit epithelium and smooth muscle cells on biodegradable polymer scaffolds. Then, obtained tissue was used for tissue replacement in animals, and a uterus-like structure formation was observed. In another study, collagen targeting a fibroblast growth factor (bFGF) delivery system was created by bFGF-loaded collagen membrane. bFGF delivery system were tested on rats with uterine damage and the studies showed that the system's ability to regenerate the cells of muscle cells increased, vascularization was improved, and pregnancy was supported [182]. For the treatment of cervix, House et al. developed collagen-covered silk scaffolds in 3D structure and seeded the cervical fibroblasts isolated from premenopausal women on the scaffold [183]. The seeded scaffolds were cultured for 8 weeks and then cervical cells were developed, biochemical components resembling natural tissue, and an ECM were synthesized. Based on these studies, it may be said that similar strategies can be applied for the treatment of uterus damages in COVID-19 patients.

5.8.2 Tissue engineering approaches for male reproductive system damages

As a result of damage, in cases requiring testis prosthesis or hormone supplementation, in vivo cartilage formation can be used. In a study, Raya-Rivera et al., developed scaffolds in the form of testis from PGA [184]. The scaffolds were seeded with chondrocytes isolated from the hyaline cartilage from the joint of the bull shoulder. The results have shown that the cartilage testis can be implanted successfully and secrete testosterone for a long time. This study may be a reference for the treatment of COVID-19 patients with testicular dysfunction and can be used as a treatment method due to the success of the results obtained.

Besides, there is a possibility that SARS-CoV-2 can affect fertility and spermatogonial stem cell (SSC) can be used in such cases. These cells can differentiate to germ cells and maintain fertility [178]. The studies on SSCs reveal the possibility of translation from non-human primate models to human fertility clinics [185]. All these studies can be developed and used for the treatment of SARS-CoV-2-induced reproductive system damage.

5.8.3 Biomaterials used for reproductive system damages

In studies conducted for the treatment of reproductive system damage, a scaffold made of biomaterials and seeded cells are generally used [8]. Studies are carried out with many natural and synthetic materials for the treatment of diseases in the reproductive system; for example, fibrin is especially shown to have an important role for preservation of fertility with tissue engineering studies [186]. Thanks to its biological structure, fibrin provides a great advantage for cell attachment, proliferation, and differentiation. Also, it provides support for biochemical signaling and fibrin can be cross-linked by a variety of factors for the formation of new vessels and tissues.

Natural polymers such as agarose, alginate, chitin and chitosan, cellulose and methyl cellulose, collagen, decellularized ovary, decellularized adipose tissue, elastin, keratin, fibrin, gelatin, silk, and hyaluronic acid are used. PCL, Polydimethylsiloxane, polyethylene glycol, copolyester, oligo-(polypropylene fumarate), poly(2-hydroxyethyl methacrylate), poly(*N*-isopropylacrylamide), PU, and silica as synthetic materials are used for female reproductive system studies [187, 188].

For the treatment of tissues in the male reproductive system, studies were carried out using materials such as cavernosal and acellular collagen matrices, bladder matrices, hydroxyapatite-coated collagen sponges, silk fibroin, tubular shaped PGA and PLGA scaffolds, and non-woven PGA fibers, and finally, structures similar to natural tissues were obtained [188].

6 Conclusion

The novel outbreak, COVID-19, caused by SARS-CoV-2, which affects the whole world, seems likely to damage many organs and systems. Given the diversity of these cells and organs considered, the treatment is significant with appropriate TE approaches. In the presented review, after brief explanation about specificities and symptoms of COVID-19, the damages in each organ were described in detail with reported studies. Then, the cytokine storm which is considered to trigger many damages is outlined and finally the most appropriate treatment approaches in terms of TE were tried to be reviewed and suggested.

Treatments of the damages caused by COVID-19 are vital for enhanced life quality. Particularly, scaffolds made of synthetic or natural polymers can be used in the treatment of organ damages. After seeding of stem cells and signaling molecules to these biodegradable and biocompatible scaffolds, damage can be treated by transplantation of the scaffold to the related region. To sum up, TE strategies mentioned in this review are quite promising to get rid of and heal the damages caused by COVID-19.

Data Availability Data sharing is not applicable to this article as no new data were created or analyzed in this study.

Authors' contributions CBU and OG conceived the review topic and outlined the manuscript draft. AA, GC, ZED, HE, AK, MO, and LS performed the literature search and data analysis. CBU, OG, and SA edited, revised the draft critically, and approved the final version of the manuscript.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval Not applicable

Consent to participate Not applicable

Consent for publication Not applicable

Code availability Not applicable

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