Research in Pharmaceutical Sciences, August 2025; 20(4): 469-484
Received: 21-04-2024
Peer Reviewed: 17-05-2024
Revised: 31-08-2024
Accepted: 01-09-2024
Published: 25-08-2025

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Review Article

Octreotide and direct/indirect lung injury

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Abstract

Background and purpose: Lung injury is one of the most important diseases, which is accompanied by hypoxemia, organ failure, and a high mortality rate. There are several symptoms and causes of lung injuries. In the past years, special attention has been given to investigating the pathophysiology and the treatment of this disease. Octreotide, as an anti-inflammatory, anti-secretory, tissue-repairing, and anti-fibrotic drug, has been considered and administered for the treatment of lung injury. This review article considered the pharmacological effects of octreotide on physiopathological conditions in patients or animal models that have direct or indirect lung injury.

Search strategy and findings: Keywords including "octreotide" OR "sandostatin" AND "lung injury" OR "ARDS" OR "respiratory distress" OR "lung fibrosis" were searched in the database of PubMed, and 44 articles were found. According to the direct or indirect lung injury, the articles were classified.

Conclusion: It appears that octreotide is a protective drug for the treatment of direct and indirect lung injuries, exhibiting anti-inflammatory, anti-hypersecretory, anti-fibrotic, and anti-neutrophil permeability effects, while also increasing endogenous antioxidants. However, there is still room for extensive research to fully clarify the effectiveness of octreotide for direct or indirect lung injury.

Keywords: Acute respiratory distress syndrome; Lung fibrosis; Lung injury; Octreotide.

CONTENT

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Access this article online

Website: http://rps.mui.ac.ir

DOI: 10.4103/RPS.RPS_67_24

1. INTRODUCTION

Lung injury conditions lead to acute pulmonary dysfunctions and a high mortality rate in the clinic. The treatment process for acute lung injury (ALI) and acute respiratory distress syndrome (ARDS) is particularly complicated. In the COVID-19 season, over 661 million people were infected, and 6.7 million of them died by mid-January 2023 (1). During the outbreak of COVID-19, extensive research in the aspects of respiratory diseases, including epidemiology, causes, risk factors (2-6), pathology and treatment approaches were peaked, but unfortunately, they declined again (7). The main importance of the issue is that ALI has a mortality rate of 31-74% (8), which is associated with the severity of ARDS and is accompanied by complications in multiple organs (8-10). The most popular treatment approach for patients with lung injury is the administration of drugs, and octreotide (OCT), an octapeptide analog of somatostatin, is a candidate for this purpose (11). Reportedly, octreotide has effects on direct and indirect lung injuries, such as chylothorax (12,13), severe acute pancreatitis (14,15), or lung injury induced by bleomycin (16,17).

2. SEARCH STRATEGY

To find the effects of octreotide on lung injury, the database of PubMed with keywords including “octreotide” OR “sandostatin” AND “lung injury” OR “ARDS” OR “respiratory distress” OR “lung fibrosis” in the title/abstract field, without any limited time frames, was used. The articles contained various types of clinical trials, preclinical studies, observational studies, *etc*, but cancer studies and scintigraphy articles were excluded. Ultimately, 44 articles were selected. At first, the articles were divided into 2 groups: direct and indirect lung injuries, then, according to the kind of diseases, the articles were categorized. In the database articles, just 3 articles were found about lung fibrosis.

3. DIFFERENTIATION OF ALI AND ARDS

Generally, the clinical symptoms of both ALI and ARDS include acute initiation, bilateral pulmonary edema in chest X-ray images (without clinical signs of heart failure), and wedge pressure ≤ 18 mmHg (10,18). The oxygen partial pressure (PaO2), fraction of oxygen inspired (FIO2), and oxygen saturation (SpO2) were employed to define the level of hypoxemia in patients. Accordingly, the level of hypoxemia for ALI includes PaO2/FiO2 ≤ 300 mmHg, while for ARDS PaO2/FiO2 ≤ 200 mmHg (9,10,19).

3.1. Types of lung injuries: direct and indirect

The causes of lung injuries are classified into extra-pulmonary or indirect causes and pulmonary or direct causes (19), which have different pathophysiological features. The distinction between indirect and direct etiologies is extremely important to reach a better comprehension and select the best treatment approach in patients (20).

3.1.1. Direct lung injury

The features of direct lung injury compared with indirect lung injury include more epithelial damage, disturbed and thicker hyaline membrane, increased blood fibrin and collagen, lung edema, more mortality rate, ground glass opacities (GGO) and more diffusion in chest X-ray, increased lung elastance, more alveolar disturbing, more intra-alveolar neutrophil trapping, and more impaired alveolar fluid clearance (19,21).

The causes of direct lung injury in animals and/or humans are intratracheal lipopolysaccharide (LPS) infusion or infectious organisms, acid aspiration, aggressive mechanical ventilation, bleomycin administration, hyperoxia, surfactant depletion, and inhalation of toxins (22).

3.1.2. Indirect lung injury

The features of indirect lung injury compared with direct lung injury include more endothelial injury, thin and distributed hyaline

membranes, increased blood VIII factor, less edema, impaired alveolar fluid clearance, more centrally located GGO, more interstitial edema, and increased monocytes in circulation (19,21).

The causes of indirect lung injury in animals and/or humans are intravenous LPS, intraperitoneal LPS, cecal ligation and puncture, ischemia-reperfusion (IR) injuries, *etc* (22).

3.2. Phases of lung injury

Both direct and indirect lung injuries usually have 2 distinct phases in the development of lung injury, including early and late phases (23,24). The early phase is exudative, and the late phase consists of proliferative and fibrotic phases. The patients experience the exudative phase approximately 7 to 10 days after the induction of injury. If they survive, the late phase will start. In the early phase, there is widespread neutrophilic recall and accumulation in alveoli due to disruption of the respiration membrane barrier and different pathways of inflammation, apoptosis, necrosis, micro-thrombi, and loss of fibrinolytic/coagulation hemostasis (25). Histologically, the alveolar epithelial barrier integrity is lost, and alveolar epithelial type I cells are extensively necrotized, which ultimately causes dyspnea and hypoxemia (26).

Now, if humans or animals have crossed from the exudative phase, the fibro-proliferative phase would have occurred. In this phase, the restoration of epithelial and endothelial barriers takes place. Then, type II alveolar cells, fibroblasts, and myofibroblasts release fibrotic factors such as transforming growth factor-ß (TGF-ß) and collagen. Ultimately, collagen and extracellular matrix surround epithelial and vascular cells, which induce abnormal integrity and architecture of lung tissue. It seems that the fibrotic phase would be induced by inflammatory lung injury (24).

Following the pandemic and the significant mortality rate from COVID-19, the priority of research in pharmacological approaches increased. Some drugs had improvement or controversial results (27) or harmful effects (24,28).

4. PHARMACOLOGY OF OCTREOTIDE

4.1. Pharmacokinetic

The somatostatin synthetic analog, octreotide, was approved by the Food and Drug Administration and marketed as sandostatin® (50, 100, and 200 μg). Somatostatin receptors are distributed in different tissues, and after binding to somatostatin or their analogs, can induce multiple functions (29). This drug has been modified as long-acting (Sandostatin LAR®) and short-acting release (Sandostatin®), which have the highest affinity to somatostatin receptor subtype 2 ($SSTR_2$) (29).

Octreotide has enzymatic degradation or a plasma half-life of approximately 100 min in humans, which allows for its use in several treatment approaches. It is mainly distributed in the plasma and is highly bound to lipoproteins. In addition, the bioavailability of octreotide subcutaneous injection is about 100%. Also, octreotide has an elimination half-life of approximately 90-110 min. Hepatic metabolism of octreotide is extensive, and some of this is excreted unchanged in the urine (30).

4.2. Pharmacodynamic

According to the pharmacopeia, octreotide is used to treat some diseases including acromegaly, carcinoid tumors, vasoactive intestinal peptide tumors, carcinoid crisis, esophageal varices bleeding, malignant bowel obstruction, glucagonomas, refractory and chylous ascites, liver cirrhosis, diarrhea associated with chemotherapy, sulfonylurea-induced hypoglycemia, thymic malignancies, congenital hyperinsulinism, cushing's syndrome, hypothalamic obesity, post gastrectomy dumping syndrome, small bowel fistulas, zollinger-ellison syndrome, and postoperative chylothorax (29).

The anti-inflammatory and anti-fibrotic effects of octreotide are key points for the possible use of the drug in patients with lung injury. Octreotide can decrease the release of inflammatory factors from immune cells into the blood circulation and/or interstitial spaces. It can decrease the level of necrosing factor-kB, malondialdehyde (MDA) (31), tumor necrosis factor (TNF) α, interleukin (IL) 6 (31), monocyte chemoattractant protein-1 (MCP-1), macrophage inflammatory protein (MIP-2) expression (32), IL-1β, and hepatocyte apoptosis (33). Also, octreotide could inhibit IL-15, increase IL-10 (anti-inflammatory

cytokine) (34), increase the serum levels of myocardial activity of superoxide dismutase (SOD) (31), decrease IL-17 (35), and reactive oxygen species (ROS) such as H_2O_2, OH^-, superoxide anion radicals, and lipid peroxidation products (36-38).

Octreotide has a high affinity for the $SSTR_2$, which inhibits the proliferation of the cell by activating the tyrosine phosphatase pathway (39,40). It can inhibit the secretion of hormones that trigger fibrosis (41). Fortunately, $SSTR_2$ increases in the lung cells, which are involved in idiopathic pulmonary fibrosis (IPF), systemic sclerosis, sarcoidosis, and rheumatoid arthritis (42). On the other hand, octreotide can inhibit the proliferation of fibroblasts as well as inhibit secretion of fibroblast growth factor (FGF) and insulin-like growth factor 1, while fibroblast proliferation and growth factors can significantly increase the risk of fibrosis (16,43-45). Octreotide has the potential to decrease chemokine ligand (CCL2), which is an indicator of growth in IPF patients, as well as CCL-18 and surfactant protein-D, which are linked to the likelihood of fibrosis (46,47).

Interestingly, octreotide can also prevent damage in organs, such as the kidney, brain, and liver (48). Several studies have documented that inhibiting apoptosis in epithelial cells or activating autophagy in macrophages or damaged cells is the most likely way to achieve protective effects against damaged organs (22,33,49-51). Octreotide could inhibit apoptosis *by* increasing B-cell lymphoma 2 (Bcl_2) expression and decreasing Bcl_2-associated X protein (Bax) expression in hepatic cells after hepatic IR (33).

Despite the positive effects of octreotide, there are some adverse effects. The prevalent adverse effects include gastrointestinal signs such as diarrhea, abdominal pain, nausea, vomiting, chronically induced gallstones (3-56% of patients), and effects on glucose homeostasis (52). Also, some uncommon side effects, including sinus bradycardia, headache, pruritus, etc., have been reported (29). However, many articles reported no adverse effects (53-59), but a few of them reported low adverse effects (60,61) or tolerable adverse effects (62). Octreotide also has a wide therapeutic window, and its toxicity has not been reported (60).

Even though more studies have explained the positive effects of octreotide, few of them have been unable to observe the desired effects. Probably, the outcomes may depend on the dreadful state of patients that could not show the advantageous response (63,64) or be due to insufficient dosage (60,65,66).

5. OCTREOTIDE EFFECTS ON INDIRECT LUNG INJURY

5.1. Chylothorax and similar diseases

Chylothorax is a condition with the disruption of the thoracic duct that results in the leakage of lymph fluid from the lymphatic system to the pleural cavity around the lungs. Lung compression leads to abnormal breathing and, finally, hypoxia and dyspnea (67,68). Several etiologies have been explained as chylous ascites, congenital chylous ascites, neoplastic chylothorax, and infectious chylothorax, and the mortality rate of chylothorax was reported to be around 10% (69). Ordinary approaches for the treatment of this disease have been recommended thoracic duct ligation, the administration of sirolimus, or octreotide.

5.1.1. The mechanisms of octreotide effects in chylothorax conditions

Octreotide administration in chylothorax could reduce the splanchnic blood flow, portal pressure, leakage of ascetic fluids into the thorax, intestinal fat absorption, lymphatic flow and production, and pleural effusion (12-14,54-56,59,70-75). Several studies have mentioned the lowering of leakage and secretion of fluids into the thorax (57,58,76-85). In Table 1, the studies related to octreotide effects in chylothorax and similar diseases were tabulated. Totally, octreotide has the potential to improve chylothorax and related conditions through multiple mechanisms, including reducing the drainage of lymphatic and thoracic ducts, volume of pleural effusion, and enhancing respiratory function. Therefore, octreotide can be recommended for administration in chylothorax and similar conditions.

Table 1. Octreotide effects in chylothorax and similar diseases.

Animal or human	Model of lung disease	Combined treatment or octreotide alone	Results	Article type	Year	Reference
Human	Chylothorax	Combined	↓Drainage output volume, ↑respiratory improvement, and no adverse effects	Case report	2023	(53)
Human	Chylothorax	Combined	Drugs could not control the chylothorax	Case report	2023	(63)
Human	Congenital hyperinsulinemia/hypoglycemia	Combined	No response due to the KCNJ11 mutation and the severe condition of the patient.	Case report	2022	(64)
Human	Mucopolysaccharidosis	Combined	↓Drainage of the lymphatic and thoracic ducts and ↑respiratory	Case report	2021	(111)
Human	Luteinized thecomas with sclerosing peritonitis	Combined	↓Drainage of the lymphatic and thoracic ducts and ↑respiratory	Case report	2021	(72)
Human	Congenital chylous ascites	Combined	↓Drainage output volume, ↑respiratory improvement, and no adverse events, normal growth and neurodevelopment over the last 5 years	Case report	2020	(54)
Human	Congenital chylothorax	Combined	After 48 h: stopped drainage output volume, ↑respiratory improvement, and ↓pleural effusion	Case report	2019	(82)
Human	Pleuro-pancreatic fistula and chylous ascites	Combined	↓Drainage of lymphatic and thoracic duct, ↓pleural effusion, ↑respiratory improvement, and ↓pancreatic secretions	Case report	2019	(83)
Human	Congenital chylothorax	Combined	↓Drainage output volume, ↑respiratory improvement, and no adverse	Case report	2017	(55)
Human	Congenital chylothorax	Alone	With chest X-ray and ultrasound: ↓drainage of the lymphatic and thoracic duct, ↓pleural effusion, ↑respiratory improvement, no adverse effect	Case report	2015	(56)
Human	Chylous ascites	Alone	↓Drainage of lymphatic and thoracic duct, ↓pleural effusion, and ↑respiratory improvement	Case report	2011	(85)
Human	Congenital chylothorax	Combined	↓Drainage of lymphatic and thoracic duct, ↓pleural effusion, ↑respiratory improvement, ↓invasive procedures (entering chest tubes, surgery), and no adverse effect	Case report	2011	(73)
Human	Chylo-pericardium	Combined	↓Production of pericardial fluid and no adverse effect	Case report	2011	(57)
Human	Idiopathic congenital chylothorax	Combined	↓Drainage of lymphatic and thoracic duct, ↓pleural effusion, ↑respiratory improvement, and no adverse effect	Case report	2010	(58)
Human	X-linked myotubular myopathy and chylothorax	Combined	↓Drainage of lymphatic and thoracic duct, ↓pleural effusion, and ↑respiratory improvement	Case report	2008	(74)
Human	Hepatic hydrothorax	Combined	↓Drainage of the lymphatic and thoracic duct, ↓pleural effusion, and ↑respiratory improvement	Case report	2001	(112)
Human	Congenital chylous ascites	Combined	↓Drainage of the lymphatic and thoracic duct, ↓pleural effusion, and ↑respiratory improvement	Case report	1996	(75)

5.2. Severe acute pancreatitis

There is an important association between ARDS and pancreatitis. In severe acute pancreatitis, the damaged pancreas releases activated enzymes into the blood circulation. Lipase and phospholipase can induce fat necrosis. Also, proteases and elastases can induce proteolysis and hemorrhage, respectively (86). It is common for severe acute pancreatitis to cause multiple organ dysfunctions, such as lung dysfunction, which leads to hypoxia, respiratory distress, and pleural effusion (87). Hypoxemia was reported in 75% of cases (88).The mortality rate of acute pancreatitis in the condition of normoxia is about 3% to 5.9%, but in uncontrollable hypoxemia is about 45% (89,90). ARDS has been introduced as the cause and effect of pancreatitis (91).

Numerous pathological mechanisms were explained in acute pancreatitis. The mechanisms include burst release of inflammatory cytokines, circulating trypsin, chemoattractants such as TNF α, IL-1, IL-6, IL-8, phospholipase A2, platelet-activating factor, free fatty acids, *etc*. The factors can promote multiple organ failure (61,92-95).

5.2.1. The mechanisms of octreotide effects in severe acute pancreatitis

Investigators detected the anti-inflammatory effects of octreotide in pancreatitis *via* decreasing serum levels of TNFα, IL-1, IL-6, IL-8, diamine oxidase, and endotoxin. Octreotide plus ulinastatin could significantly improve blood amylase, white blood cell (WBC), C-reactive protein (CRP), IL-6, and MDA (48,61,92-94). Also, decreasing the plasma level of amylase, TNFα, and protection of multiple organs were detected in the sodium taurocholate-induced severe acute pancreatitis experimental animal model (95). In patients with severe acute pancreatitis, the administration of octreotide plus ulinastatin versus the administration of octreotide alone could potently reduce blood amylase, WBC, CRP, IL-6, and decrease ARDS complications (13.3% versus 33.3%) (61). In addition, the sepsis, ARDS, and mortality rates were significantly higher in patients with severe acute pancreatitis than in octreotide treated with octreotide (14,15). Table 2 presents studies revealing the octreotide effects in severe acute pancreatitis. Consequently, the therapeutic effects of octreotide on acute pancreatitis conditions may be involved in decreasing inflammatory factors, lowering secretion of enzymes and fluids from the injured pancreas, enhancing tissue repair, lowering the mortality rate, and septic conditions. Accordingly, octreotide administration in severe acute pancreatitis is recommended for improving lung injury.

5.3. Cecal ligation and puncture and sepsis

Cecal ligation and puncture (CLP) is one of the experimental animal models to study indirect acute lung injury (96-98). In this model, the animal undergoes laparotomy, and a needle below the ileocecal valve is used to puncture the cecum. The content of the cecum, which is full of bacteria, enters the abdomen and bloodstream, resulting in peritonitis, septicemia, lung injury, and multiple organ dysfunction. Some features of CLP include hypoxia, neutrophilic inflammation, interstitial inflammation, and ultimately, respiratory dysfunction (96-98).

5.3.1. The mechanisms of octreotide effects in CLP and sepsis

Bora *et al*. reported that octreotide could improve oxygenation and the repair of lungs in the model of CLP (99). Gul *et al*. also showed that octreotide decreased the plasma level of IL-6 and MDA in the lung tissue (60)**.** Table 3 lists studies performed on octreotide effects in CLP and sepsis. Consequently, octreotide affects CLP and sepsis by decreasing inflammatory factors, increasing oxygenation, and enhancing lung repair (60,99). Because there are few studies about sepsis and octreotide, further studies, especially animal models, are needed to explain the effects on growth and accumulation of microorganisms in the pneumonic lung.

Table 2. OCT effects in severe acute pancreatitis.

Animal or human	Model of lung disease	Combined treatment	Results	Article type	Year	Reference
Human	Acute necrotizing pancreatitis	Combined	↓Drainage of the lymphatic and thoracic ducts and ↓the Severity of necrotizing pancreatitis and pulmonary failure	Original	2022	(113)
Human	Severe acute pancreatitis	Combined	↓TNF-α, ↓IL-1, IL-6, and IL-8, ↓diamine oxidase, ↓endotoxin, ↓D-lactic acid, and ↔ mortality rate between groups	Original	2019	(94)
Animal	Acute pancreatitis induced by caerulein	Combined and alone	Combined with diclofenac: ↓lung edema, ↓neutrophil inflammation, ↓mononuclear inflammation, and ↓scores of lung, liver, stomach, and kidney injuries	Original	2018	(48)
Human	Severe acute pancreatitis	Alone and combined	In combination with ulinastatin: ↓amylase in circulation, ↓white blood cell, ↓C-reactive protein, ↓ IL-6, ↓incidence of ARDS, ↓incidence of acute renal failure, ↓incidence of shock, and the adverse effects of OCT are low, and the safety is high.	Original	2015	(61)
Animal	Severe acute pancreatitis	Alone	↓Pathological injuries of multiple organs, endotoxin, ↓TNF-α in blood, ↓mortality rate, ↑expression of Bax protein in lymph nodes and spleen	Original	2009	(92)
Animal	Severe acute pancreatitis	Alone	↓Pathological injuries of multiple organs, ↓endotoxin, ↓TNF-α in blood, ↓serum malondialdehyde, ↓mortality rate, ↔plasma amylase, and ↔serum nitric oxide contents	Original	2008	(93)
Human	Severe acute pancreatitis	Alone	↓Mortality rate, ↓hospitalization, ↓rate of sepsis, and ↓rate of ARDS	Original	2000	(15)
Human	Necrotizing pancreatitis	Alone	↓Drainage of the lymphatic and thoracic ducts and ↓severity of necrotizing pancreatitis and pulmonary failure	Original	1996	(70)
Human	Severe acute pancreatitis	Alone	↓Mortality rate, ↓hospitalization, ↓rate of sepsis, ↓rate of ARDS	Original	1995	(14)

TNF, Serum tumor necrosis factor; IL, interleukin; OCT, octreotide; ARDS, acute respiratory distress syndrome.

Table 3. OCT effects in cecal ligation and puncture and sepsis**.**

Animal or human	Model of lung disease	Combined treatment or OCT alone	Results	Article type	Year	reference
Animal	Sepsis model of cecal ligation and puncture	Alone	↑Arterial pressure of O_2/fraction of inspiration O_2, ↓score of lung injury	Original	2022	(99)
Animal	Sepsis	Alone	↓Interleukin 6, ↓the level of malondialdehyde in the lung, and a wide margin of OCT and less adverse reaction	Original	2007	(60)

OCT, octreotide.

5.4. IR conditions

When reperfusion is performed in the ischemic tissue, ischemia-induced detrimental factors enter the blood circulation and affect different organs, including the production of ROS by endothelial cells, the release of inflammatory cytokines, activation of immune responses of macrophages and neutrophils and the accumulation in damaged organs, endothelial dysfunction, apoptosis, and ultimately organ failure (51). The damaging effects of IR on the lungs are hypoxia and acute initial lung injury (100). The scientists tend to induce ischemia in one organ and evaluate the pathological and pharmacological effects of a specific drug on other organs in response to IR injury.

5.4.1. The mechanisms of octreotide effects in IR conditions

Reportedly, octreotide could decrease the release of endotoxin and proinflammatory cytokines (66). Also, it could prevent IR injuries by activation of the autophagy pathway in damaged cells (32,33). After hepatic IR, octreotide could reduce the plasma levels of TNF-α, IL-6, MCP-1, and expression of MIP-2 in the kidney, as well as suppress apoptosis of cells (32). Also, octreotide induces a decrease in levels of endotoxin and the proinflammatory cytokines, TNF-α and IL-1β, and the inhibition of hepatocellular apoptosis (33).

About lung tissue, octreotide could decrease free radicals (65) and inflammatory factors, increase glutathione as an antioxidant in lung tissue, decrease MDA as an end product of lipid peroxidation, decrease myeloperoxidase as an index of neutrophilic infiltration (100). In Table 4, studies about octreotide effects in IR conditions were presented.

Consequently**,** octreotide decreased inflammatory factors and the histology score of lung injury in the IR model (33,100). However, one study mentioned that octreotide has no improving effect on the lung histology score (65). The reason may be low dosage and/or only a single administration in normal rats for evaluating the preventive effects. According to these results, there is a need to perform human studies about octreotide effects in IR.

6. OCTREOTIDE EFFECTS ON DIRECT LUNG INJURY

According to the literature, the effects of octreotide on direct lung injuries, including severe thoracic trauma (13), pulmonary fibrosis (16,46,62), lipopolysaccharide (101), or paraquat-induced lung injury (102) in patients and animal models have been studied.

6.1. The mechanisms of octreotide effects in direct lung injury

Several treatment effects of octreotide include anti-inflammatory, increasing endogenous antioxidant, anti-hypersecretion, decreasing neutrophil accumulation and permeability of the lung, anti-fibrotic, decreasing apoptosis, and enhancement of autophagy (101). In Table 5, studies about octreotide effects in direct lung injury conditions were presented. According to studies and results, the effects of octreotide in direct lung injuries can be divided into aspects, which were presented in Fig. 1.

6.1.1. Octreotide effects on the immune system

Some prominent anti-inflammatory enzymes include SOD (converts superoxide anions to H_2O_2), catalase (converts H_2O_2 into O_2 and H_2O), and glutathione peroxidase (reduction of H_2O_2) (103). There are some non-enzymatic anti-inflammatories with antioxidant effects, such as selenium and vitamins A, E, and C (17). These anti-inflammatory factors reduce free radicals to prevent damage to cells. Some inflammatory products can suppress the activity of anti-inflammatories, and tremendously induce deleterious disease (104). Some protective effects of octreotide are associated with effects on the immune system. Intratracheal bleomycin injection can decrease anti-inflammatories; however, octreotide can recover and improve them (103,105). It can decrease inflammatory factors, increase enzymatic and non-enzymatic anti-inflammatory factors (17), refuse neutrophil migration and accumulation in alveoli (100,101,106). It could prevent the permeability of lung tissue and hypoxemia induced by LPS plus mechanical ventilation (107) or sepsis (108).

Table 4. OCT effects in ischemia-reperfusion conditions.

Animal or human	Model of lung disease	Combined treatment or OCT alone	Results	Article type	Year	reference
Animal	IR graft injury	Alone	↓Free radicals, ↓portal inflammation, and ↔ lung histology score	Original	2020	(65)
Animal	IR	Alone	↓Endotoxin, ↓tumor necrosis factor-α, ↓interleukin 1β, ↓hepatocellular apoptosis, ↓hemodynamic changes, and ↓score of lung and kidney injury	Original	2013	(33)
Animal	IR injury	Alone	↓Malondialdehyde in the lung and kidney, ↓myeloperoxidase in the lung and kidney, and ↑glutathione in the lung and kidney	Original	2003	(100)

IR, Ischemia-reperfusion.

Table 5. OCT effects in direct lung injury conditions.

Animal or human	Model of lung disease	Combined treatment or OCT alone	Results	Article type	Year	Reference
Human	Human pulmonary epithelial cells damaged by lipopolysaccharide (*in vitro*)	Alone	↓TNF-α, ↓IL-1β, ↓IL-6, ↓lactate dehydrogenase activity, ↓apoptotic capacity such as ↑Bcl-2 protein, ↓Bax and caspase3; ↑autophagy, such as inhibiting the AKT/mTOR signaling	Original	2022	(101)
Human	Portal hypertension and COVID-19	Combined	↓Splanchnic pooling, ↓postprandial hypotension, and ↓COVID-19 complications	Case report	2021	(49)
Human	Lung adenocarcinoma with ARDS	Combined	↓Respiratory secretions, gradually from 1 L-100 mL/day, ↑PaO2/fraction of inspiration O2 ratio	Case report	2019	(12)
Human	Severe thoracic trauma	Combined	↓Chylothorax output from 2000 to 1000 mL/day	Case report	2018	(13)
Human	Refractory bronchospasm in interstitial lung disease	Combined	↓Wheezing, ↓chromogranin-A (from neuroendocrine tumors)	Case report	2015	(80)
Animal	Interstitial pulmonary fibrosis	Alone	↓Parenchymal fibrosis and structural deformities	Original	2013	(16)
Human	Idiopathic pulmonary fibrosis	Alone	Functional vital capacity improved, diffusion lung capacity of carbon monoxide improved; the adverse effects were tolerable.	Original	2011	(62)
Animal	Intra-tracheal bleomycin	Alone	↓Malondialdehyde, ↓glutathione peroxidase, ↑antioxidant vitamins, ↑selenium, and ↓free radicals	Original	2010	(17)
Human	Ectopic corticotropin-releasing hormone production	Combined	↓Secretions of the adrenal gland of Cushing's syndrome, ↓ARDS symptoms, and hypophosphatemia were managed	Case report	2008	(77)
Human	Idiopathic pulmonary fibrosis	Alone	↓Progression of lung fibrosis, ↓ fibroblast cell progression	Original	2006	(46)
Animal	ARDS by paraquat	Alone	↓Inflammatory response, ↑pulmonary improvement, ↑PaO_2, ↓$PaCO_2$, ↓TNF-α level of plasma and BALF, and ↓IL-6 level in BALF	Original	2006	(102)
Human	Pneumocystis carinii pneumonia	Combined	↓Serum cortisol, ↑risk of *Pneumocystis carinii* pneumonia in Cushing's syndrome	Case report	2000	(81)

TNF, Tumor necrosis factor; IL, interleukin; OCT, octreotide; ARDS, acute respiratory distress syndrome; Pa, arterial pressure; BALF, bronchoalveolar lavage fluid.

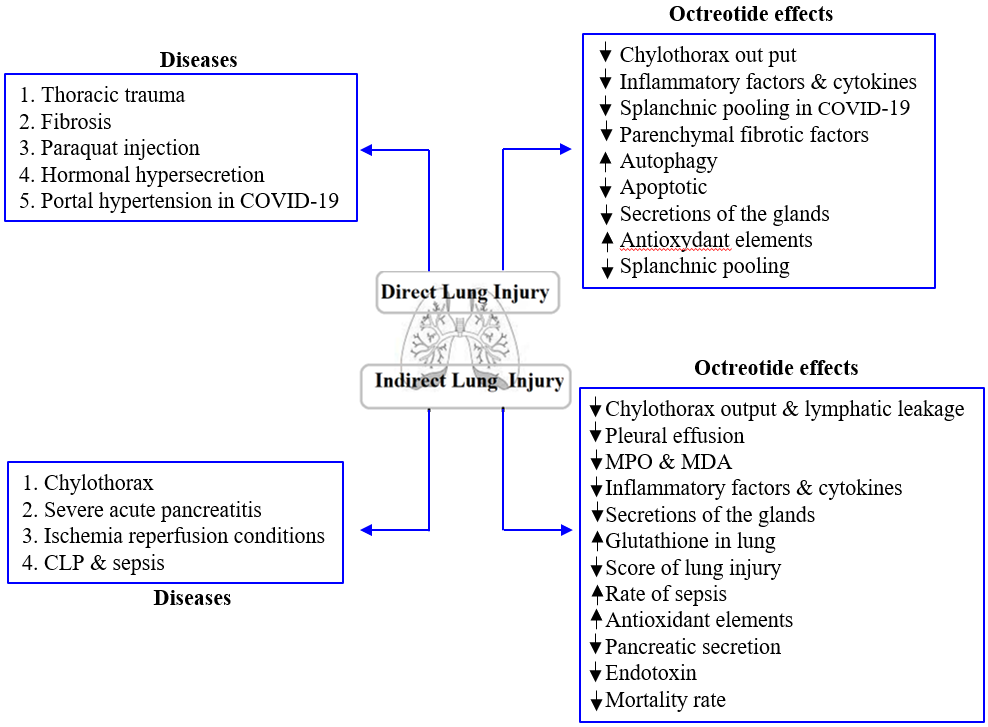

Fig. 1. OCT effects on direct and indirect lung injury subtypes. According to several studies, OCT with the induction of beneficial effects could improve the disease. For each disease, a different number of articles (i.e., 21 studies for chylothorax and 1 study for COVID-19) was found.

6.1.2. Octreotide effects on cell survival

There are reports about cell signaling and cell-molecular mechanisms of octreotide. Octreotide affects cell survival by inhibiting cell apoptosis (32,33,101) and enhancement of the cell autophagy (32,101,109). Cell apoptosis is one of the important mechanisms that increases damage and induces organ failure (32,33,101), and inversely the inhibition of apoptosis can increase cell survival. Octreotide can inhibit apoptosis by several pathways, which include decreasing inflammation, increasing Bcl_2 (an anti-apoptotic factor), and decreasing Bax (an apoptotic factor). This pathway is validated with the administration of 3-methyladenine (3-MA), while 3-MA induces apoptosis by increasing Bax and decreasing the anti-apoptotic effect of octreotide (32,33,101). It was reported that the activation of autophagy in injured tissues is a mechanism for preventing progressive damage in direct and indirect lung injuries (101,110). The enhancement effect of octreotide on the autophagy pathway provided a protective mechanism in injured tissues. This mechanism may be induced by increasing the expression of light chain 3-II/I and beclin 1, which would inhibit the pathway of PI3K/AKT/mTOR/S757-ULK1, ultimately inducing autophagy in pulmonary epithelial cells, and could alleviate damage in the animal model (32,109) and an *in vitro* experiment (101).

6.1.3. Effects of octreotide on the secretion of growth factors

Lung cells, including epithelial, fibroblast, and macrophage cells, release several factors such as IGF_1, vascular endothelial growth factor, FGF, platelet-derived growth factor, epidermal growth factor, and TGF-β into the peripheral and blood circulations. TGF-β is the most potent profibrotic factor that can be decreased by octreotide (41). Fortunately, the $SSTR_2$ may increase in the lungs of fibrotic patients, which consequently increases the antifibrotic effects of octreotide can increase (29). Three articles have investigated the antifibrotic effects of octreotide in direct lung injury conditions in patients (62,46) and animal model (16).

6.2. The prospects of octreotide in lung injury investigations

According to these studies, octreotide has several beneficial effects on lung injury, but further studies including tissue repair, genetic effects, cell signaling, and histological changes are needed. It seems that different studies about octreotide effects will be predictable in clinical trial studies on septic patients and IR conditions, as well as animal studies on direct lung injury, such as acid aspiration, *etc*.

7. CONCLUSION

In this review study, several articles that administered octreotide in different diseases accompanied by lung injury were considered. These diseases were chylothorax, acute severe pancreatitis, sepsis, IR, and direct lung injuries. For chylothorax conditions and acute severe pancreatitis, the outstanding and beneficial effects of octreotide for the treatment of patients or animal models were explained. Therefore, octreotide can be recommended for these diseases. But, the number of studies about sepsis, IR, and direct lung injuries in humans is few. Therefore, more investigations should be done to verify the octreotide effects in these diseases.

In summary, the beneficial effects of octreotide include anti-inflammatory, increasing endogenous antioxidants, anti-hypersecretion, decreasing neutrophil permeability into the lung, anti-fibrotic, decreasing apoptosis, and enhancement of autophagy. Yet, further studies on tissue repairing, genetic effects, histological changes in sepsis, IR, and direct lung injuries are needed.

Acknowledgments

This research was financially supported by Isfahan University of Medical Sciences (Grant No. 3401651).

Conflict of interest statement

All authors declared no conflict of interest in this study.

Authors' contributions

G. Zarei and M. Nematbakhsh participated in study conception and design; G. Zarei performed literature review and found the respective articles; G. Zarei, M. Nematbakhsh, S. Choopani, and Z. Pezeshki prepared the tables; M. Nematbakhsh designed the figure. G. Zarei, S. Choopani, and Z. Pezeshki wrote the first draft of the manuscript; M. Nematbakhsh edited and reviewed the first draft of the manuscript. All authors read and approved the final version of the manuscript.

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