Literature Review

Lung–Kidney Interactions: Impact for Systemic Disease

Elvando Tunggul Mauliate Simatupang*[1], Dewi Wijaya[1], Ligat Pribadi Sembiring[2]

[1]Department of Pulmonology and Respiratory Medicine, Faculty of Medicine, Riau University, Arifin Achmad General Hospital, Pekanbaru
[2]Department of Internal Medicine, Faculty of Medicine, Riau University, Arifin Achmad General Hospital, Pekanbaru

Corresponding Author:
Elvando Tunggul Mauliate Simatupang | Department of Pulmonology and Respiratory Medicine, Faculty of Medicine, Riau University, Arifin Achmad General Hospital, Pekanbaru | elvando56@gmail.com

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Abstract

Lung–kidney interaction is increasingly recognized as an important determinant of prognosis in systemic and critical illnesses. This is physiologically based and often occurs in daily medical practice. Evidence shows that dysfunction in one organ may trigger or worsen injury in the other, making this relationship relevant in clinical assessment and therapeutic decision-making. Understanding this bidirectional interaction is essential, as it influences disease severity, treatment response, and mortality. Direct or indirect, lung–kidney interactions are frequently observed in clinical practice. Hypercapnia, hypoxemia, and systemic inflammatory response are among many factors that can induce renal involvement in lung disease. Between lung complications and kidney function abnormalities, there is a correlation, such as pulmonary edema, pleural effusion, chronic kidney disease and acute kidney injury. The patients of acute kidney injury and chronic kidney disease may be more susceptible to lung issues due to several internal risk factors, including uremia, metabolic acidosis, electrolyte imbalances, and volume overload or increased fluid volume. Other external risk factors that also contribute to lung issues include systemic inflammation and oxidative stress. Occupational and environmental exposures may also contribute to lung disease, and indirectly accelerate renal function decline. Despite clinical relevance, lung–kidney interactions remain underrecognized in autoimmune diseases.

Keywords: disease, interaction, kidney, lung, systemic

INTRODUCTION

Despite their anatomical separation, the kidneys and lungs are connected physiologically or pathologically in the human body. Physiologically, the kidneys and lungs are connected to maintain blood pressure, bicarbonate concentration, carbon dioxide partial pressure, pH balance, and body fluid homeostasis.[1]

During the Coronavirus Disease of 2019 (COVID-19) pandemic, a clinically significant association was known between the lung and kidney. In general, the SARS-CoV-2 virus infection process targets the respiratory tract's target organs, advancing from the upper airway to the lung parenchyma. Increased cytokine storms in

response to SARS-CoV-2 viral infection often result in kidney involvement as a complication of COVID-19. Consequently, hypoxemia frequently results in multiple organ dysfunction syndrome (MODS) and leads to mortality from COVID-19.[2]

A study including 5,449 COVID-19 patients treated through all hospitals in New York showed that 36% of patients experienced complications related to acute kidney injury (AKI). This study's results indicate that COVID-19 patients with AKI complications mainly develop respiratory failure, often leading to mechanical ventilation.[2,3] The incidence of AKI in COVID-19 patients was reported to be 0.5-27% of all patients in other studies conducted in China and Europe.[3] According to the previous study, renal involvement is a common side effect in respiratory system diseases, which inhibits the treatment response.

Acute kidney injury can induce abnormalities in other organs, particularly the lungs, due to systemic inflammation, metabolic disturbances, and fluid overload. Acute pulmonary edema itself can be precipitated by acidosis or fluid accumulation as an outcome of AKI in end-stage renal disease (ESRD).[4] An additional potential complication is acute lung injury (ALI), caused by systemic inflammation and oxidative stress.[5] Complications of other underlying diseases are responsible for most of the increase in AKI mortality.

Acute kidney injury is recognized as a major contributor to increased mortality among critically ill patients. Furthermore, Vieira et al reported that acute kidney injury occurred in approximately 57% of mechanically ventilated critically ill cancer patients, and its presence was associated with a significantly prolonged duration of mechanical ventilation. Their findings also demonstrated a markedly higher mortality rate of up to 77% in patients with AKI, compared with those without renal involvement. These results reinforce the clinical significance of lung-kidney interaction, highlighting that deterioration in renal function may negatively influence respiratory outcomes and overall prognosis.[4,5]

Therefore, this review focuses on the physiological and pathological relationships between the lungs and kidneys.

IMMUNOLOGIC MECHANISMS OF LUNG AND KIDNEY

The cross-interaction between the lung and kidney is often overlooked in determining treatment in chronic lung and kidney diseases. Several case studies explain that worsening lung and kidney conditions often occur in patients with chronic obstructive pulmonary disease (COPD) or chronic kidney disease (CKD). A study showed that when there is a progressive decline in kidney function, it will potentially lead to Restrictive Lung Disease with a case incidence of 1-11% of all CKD patients.[6]

The lungs and kidneys are physiologically interconnected through several regulatory mechanisms that maintain systemic homeostasis. Figure 1 illustrates the mechanisms and

interconnected regulatory pathways shared by both organs, including immune response, phosphate metabolism, hormonal balance, acid–base regulation, fluid dynamics, and oxidative stress. These mechanisms explain how dysfunction in one organ may influence the other and contribute to systemic complications.

Due to these shared physiological processes, dysfunction in one organ may adversely affect the other and contribute to clinically significant complications. For instance, declining kidney function may predispose patients to restrictive lung physiology, whereas respiratory impairment may alter renal perfusion, gas exchange, and metabolic regulation.[7]

Immune Response

The immune system plays a critical role in mediating interactions between the lungs and kidneys, particularly in the context of chronic disease. Patients with CKD or reduced glomerular filtration rate (GFR) frequently exhibit elevated levels of proinflammatory cytokines such as interleukin-1β (IL-1β), interleukin-6 (IL-6), and tumor necrosis factor-α (TNF-α). Both organs possess extensive capillary networks that facilitate the rapid circulation of these mediators, enabling immunologic crosstalk between pulmonary and renal tissues. Dysregulation of these pathways may result in amplified systemic inflammation, contributing to tissue injury in both organ systems.[7]

Proinflammatory cytokines also play a central role in pulmonary disease progression. TNF-α and IL-6 contribute to COPD pathogenesis by activating inflammatory cascades and promoting exacerbations through Nuclear Factor-κB (NF-κB) signaling. Similarly, elevated IL-1β and TNF-α contribute to extracellular matrix remodelling, angiogenesis, fibroblast proliferation, and the development of lung fibrosis.[7]

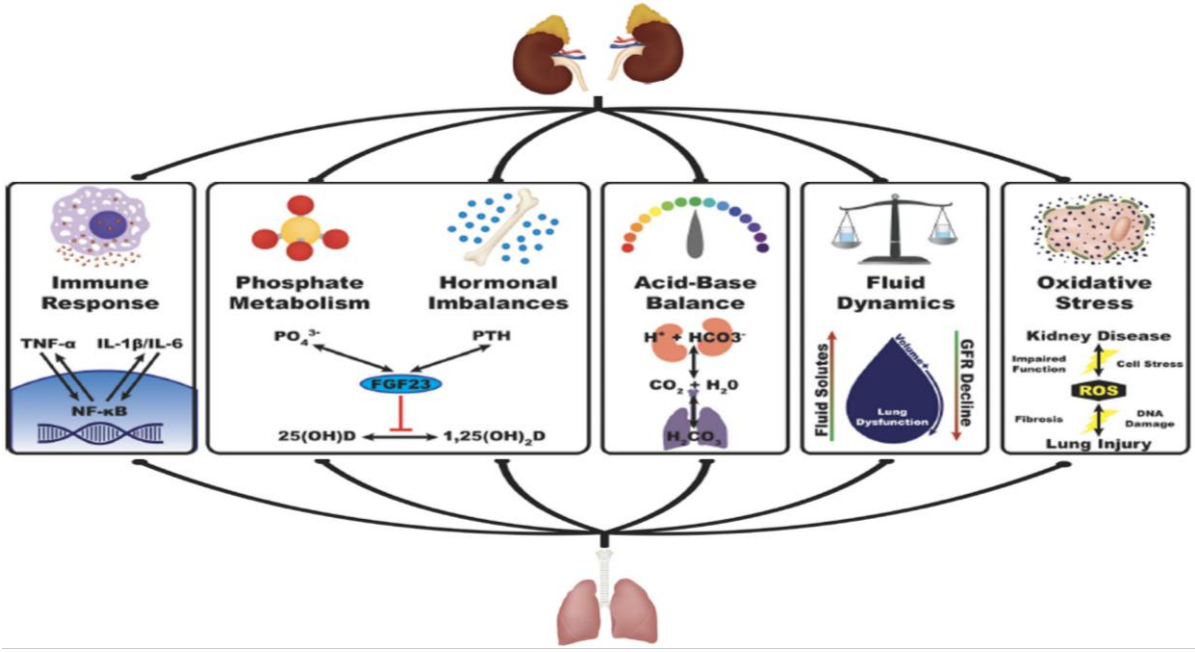

Figure 1. Immunologic Mechanisms of Lung and Kidney[8]

Increasing evidence suggests that immune dysregulation negatively affects the clinical trajectory of CKD. Persistent systemic inflammation may promote endothelial dysfunction and vascular injury due to the shared microcirculatory architecture of the lungs and kidneys, allowing rapid dissemination of inflammatory mediators. This interconnected immune response reinforces the bidirectional pathological relationship between pulmonary and renal disease, highlighting the central role of inflammatory mediators in lung–kidney interaction.[7,9]

Phosphate Metabolism

Phosphate homeostasis plays a fundamental role in maintaining cellular and systemic function through its involvement in bone mineralization, renal excretion, and gastrointestinal absorption. At the cellular level, phosphate contributes to adenosine triphosphate (ATP) synthesis, nucleic acid metabolism, and intracellular signalling pathways, all of which are essential for energy production, genomic stability, and normal cellular function. Disturbances in phosphate regulation, including hypophosphatemia and hyperphosphatemia, may develop when gastrointestinal absorption or renal phosphate handling becomes impaired.[7]

The primary endocrine regulators of phosphate metabolism include parathyroid hormone (PTH), calcitriol (1,25-dihydroxyvitamin D), and fibroblast growth factor-23 (FGF-23). Within the proximal renal tubules, calcitriol synthesis maintains a physiological balance between PTH and FGF-23. Osteocytes and osteoblasts serve as major sources of FGF-23, which functions as a central hormonal modulator of circulating calcitriol levels and phosphate reabsorption, thereby preserving systemic phosphate equilibrium.[7]

Phosphate regulation requires coordinated signaling between the kidneys, skeletal system, and endocrine pathways. FGF-23 reduces renal phosphate reabsorption and suppresses calcitriol synthesis, while PTH promotes phosphaturia and stimulates renal activation of vitamin D. These tightly integrated hormonal mechanisms ensure adequate mitochondrial bioenergetics, mineral metabolism, and maintenance of physiologic cellular processes.[9,10]

Disturbances in phosphate metabolism are strongly associated with CKD and contribute to progressive hormonal dysregulation between the lungs and kidneys. In the early stages of CKD, reduced responsiveness to FGF-23 leads to compensatory elevation of circulating FGF-23, progressively suppressing calcitriol production and promoting secondary hyperparathyroidism. Persistent hyperphosphatemia in advanced CKD reflects impaired renal responsiveness and ongoing phosphate retention, further destabilizing endocrine balance.[7,9]

Elevated FGF-23 has also been linked to systemic inflammation and impaired pulmonary function, particularly in COPD and in patients experiencing concomitant CKD. Evidence suggests that increasing FGF-23 concentrations are associated with

a progressive decline in lung function in individuals with combined pulmonary and renal impairment.[11]

In COPD and Cystic Fibrosis (CF), elevated FGF-23 further stimulates macrophage proliferation and TNF-α release, amplifying systemic inflammation and hormonal signaling. Cigarette smoke exposure additionally accelerates epithelial injury and airway fibrosis through upregulation of IL-1β and TGF-β, contributing to progressive airway remodeling.[12]

Alterations in vitamin D metabolism further demonstrate the interconnected nature of phosphate regulation and pulmonary disease. Lower serum vitamin D levels have been associated with increased COPD exacerbations, decline in lung function, and higher prevalence of secondary hyperparathyroidism and osteoporosis—findings commonly observed in individuals with CF.[10]

Additionally, dysregulation of the hypothalamic–pituitary–adrenal (HPA) axis exacerbates inflammatory and metabolic imbalance in CKD. Reduced renal filtration prolongs systemic cortisol exposure and promotes metabolic acidosis and hyperphosphatemia. Elevated cortisol levels in CKD have been associated with diabetes mellitus, heart failure, COPD, and unfavorable clinical outcomes, underscoring the systemic implications of disrupted phosphate and hormonal homeostasis.[12]

Hormonal System Imbalance

Hormonal regulation forms a key component of kidney–lung interaction, particularly involving FGF-23, PTH, and vitamin D signaling. Changes in renal function alter endocrine feedback loops, affecting phosphate handling, mineral metabolism, and systemic inflammatory signaling pathways. To maintain phosphate balance, circulating FGF-23 may increase dramatically during early impairment of renal function, leading to reductions in calcitriol and compensatory increases in PTH. As renal disease progresses, hormonal dysregulation may intensify due to reduced renal responsiveness and increased circulating phosphate.[13]

Impaired phosphate metabolism contributes to hormonal imbalance between the lungs and kidneys, particularly in CKD. In early CKD, reduced FGF-23 responsiveness triggers compensatory elevation of circulating FGF-23, reported to increase up to 1.000-fold to maintain phosphate balance. Persistent hormonal resistance leads to decreased vitamin D production, secondary hyperparathyroidism, and progressive hyperphosphatemia.[13]

Elevated FGF-23 has also been associated with persistent systemic inflammation and worsening pulmonary function in chronic lung diseases such as COPD and CF. FGF-23 stimulates macrophages and induces TNF-α, amplifying inflammatory signaling. Cigarette smoking further accelerates this process, promoting epithelial injury and airway fibrosis through increased IL-1β and TGF-β.[12]

Alterations in cortisol regulation additionally contribute to worsening systemic disease in CKD. Reduced renal

clearance prolongs cortisol half-life and promotes hyperphosphatemia, while dysregulation of the HPA axis exacerbates systemic inflammation and metabolic stress. Elevated cortisol levels in CKD are associated with diabetes mellitus, heart failure, COPD, and unfavorable clinical outcomes.[12]

Acid-Base Balance

The balance of hydrogen ions (H^+) represents the body's acid–base equilibrium, a state in which the amount of H^+ produced is proportional to the amount eliminated, thereby maintaining a stable physiological pH. Acids are substances that release H^+ when dissolved in solution, decreasing the pH and increasing the hydrogen ion concentration. Conversely, bases accept H^+, resulting in decreased hydrogen ion concentration and an increase in pH. A buffer is a compound capable of binding or releasing H^+, depending on changes in the surrounding environment, thereby preventing significant fluctuations in pH. The maintenance of physiological pH (7.35–7.45) depends primarily on the coordinated function of the kidneys and the lungs.[14]

According to the Henderson–Hasselbalch equation, pH is determined by the ratio of bicarbonate (HCO_3^-), regulated by the kidneys, to carbon dioxide (PCO_2), controlled by the lungs. This relationship provides the basis for classifying acid–base disorders. Acidosis results from either an accumulation of acid or a loss of alkali and may be metabolic (decreased HCO_3^-) or respiratory (increased PCO_2) in origin. In contrast, alkalosis arises from the loss of acid or a gain of alkali, reflected as increased HCO_3^- in metabolic alkalosis or decreased PCO_2 in respiratory alkalosis. The body's defence against pH disturbances occurs in two stages: a rapid response through the buffering system, followed by longer-term regulation by the lungs and kidneys.[14]

The respiratory system contributes to acid–base regulation by maintaining an appropriate arterial partial pressure of carbon dioxide (PCO_2). Although its primary role is oxygen exchange, the lungs must adjust ventilation in response to CO_2 generated from metabolic processes. Under normal conditions, arterial PCO_2 is maintained at approximately 40 mmHg. Changes in $PaCO_2$ and pH are detected by peripheral and central chemoreceptors, which modulate ventilatory rate and depth. CO_2 produced by cellular metabolism diffuses freely across cell membranes into the bloodstream.[14]

Although only a small fraction remains dissolved, most CO_2 is rapidly converted to carbonic acid by carbonic anhydrase within erythrocytes. Carbonic acid dissociates into H^+, which binds hemoglobin or intracellular proteins, while bicarbonate exits the erythrocyte via chloride exchange, contributing to the plasma buffering system. CO_2 is ultimately transported to the lungs, diffuses across the alveoli, and is exhaled.[14]

Ventilatory control, particularly the elimination of CO_2, plays a key role in compensating for acid–base disturbances. When strong acids enter the extracellular

fluid, free H^+ binds to bicarbonate, shifting the buffer equilibrium toward carbonic acid. A decline in the pH of the cerebrospinal fluid stimulates the respiratory center in the medulla oblongata to increase alveolar ventilation. Peripheral chemoreceptors located in the carotid and aortic bodies also respond to changes in pH and $PaCO_2$.[15]

This respiratory response begins within minutes and represents the body's most immediate compensatory mechanism. Respiratory compensation, however, has limitations. Compensation for metabolic acidosis cannot be sustained without renal regeneration of bicarbonate. Similarly, compensation for respiratory alkalosis is constrained because hypoventilation cannot be allowed beyond a point where tissue oxygenation becomes compromised.[15]

The kidneys provide the third and slowest line of defense in acid–base regulation, responding over several hours to days. Renal compensation involves two interrelated processes: excretion of H^+ and regulation of bicarbonate levels. In acidosis, increased H^+ concentration stimulates enhanced bicarbonate reabsorption and decreased filtration of HCO_3^-, resulting in more acidic urine. In alkalosis, reduced plasma H^+ leads to decreased bicarbonate reabsorption, producing more alkaline urine. Additionally, the kidneys synthesize ammonia (NH_3) in tubular cells. NH_3 readily binds free H^+ to form ammonium (NH_4^+), which is trapped within the tubular lumen and excreted. This mechanism allows for substantial elimination of H^+ when needed.[15,16]

Disruptions in any of the regulatory systems—buffering capacity, respiratory function, renal function, cardiovascular stability, or central nervous system integrity—can result in acid–base imbalances. Severe disturbances typically manifest in an acute phase, characterized by abnormal pH while either PCO_2 or HCO_3^- remains within normal limits. If the imbalance persists, physiological compensatory mechanisms are activated, leading to a compensated state in which pH approaches normal despite persistently abnormal blood gas components.[8,16]

Table 1. Acid-Base Balance Disorders[8]

Abnormality	Respond	pH	PCO_2	HCO_3^-	Base Excess
Respiratory Acidosis (PCO_2 ↑)	Not Compensated	↓	↑	N	N
	Partially Compensated	↓	↑	↑	↑
	Compensated	N	↑	↑	↑
Respiratory Alkalosis (PCO_2 ↓)	Not Compensated	↑	↓	N	N
	Partially Compensated	↑	↓	↓	↓
	Compensated	N	↓	↓	↓
Metabolic Acidosis (HCO_3^- ↓)	Not Compensated	↓	N	↓	↓
	Partially Compensated	↓	↓	↓	↓
	Compensated	N	↓	↓	↓
Metabolic Alkalosis (HCO_3^- ↓)	Not Compensated	↑	N	N	↑
	Partially Compensated	↑	↑	↑	↑
	Compensated	N	↑	↑	↑

Note: (↑=increased; ↓=decreased; N=normal)

If the underlying causes are not corrected, compensatory mechanisms eventually fail to counteract the disturbances, leading to an uncompensated state. The major patterns of acid–base imbalance are summarized in Table 1, which outlines characteristic abnormalities for each disorder.[8,15]

Respiratory acid–base disturbances arise from an imbalance between the production of CO_2 in peripheral tissues and its elimination by the lungs, resulting in either elevated or reduced PCO_2 levels. In contrast, metabolic acid–base disturbances occur when bicarbonate concentrations in the extracellular fluid decrease or increase in response to the accumulation of fixed or organic acids or the loss of base.[8,15]

Changes in Body Fluid Volume

The human body is composed of approximately 60% water, and both the respiratory system and the kidneys serve as key regulators of fluid homeostasis. The kidneys maintain extracellular fluid volume primarily through glomerular filtration and the modulation of sodium handling. When extracellular fluid volume increases, renal sodium excretion is enhanced to restore osmotic balance. Conversely, in conditions of low blood pressure or volume depletion, the kidneys increase sodium reabsorption to promote fluid retention. Glomerular filtration rate (GFR) naturally declines with age and further deteriorates in CKD, resulting in reduced filtration capacity and subsequent expansion of circulating fluid volume.[16]

Excess fluid accumulation can affect the lungs by altering the integrity of the alveolar–capillary membrane. When fluid shifts into the interstitial or alveolar spaces, gas exchange becomes impaired due to decreased alveolar compliance and increased diffusion distance. This mechanism is frequently observed in critically ill patients, particularly during the recovery phase, where studies have demonstrated a strong association between fluid overload and pulmonary complications. Patients experiencing significant fluid excess often develop restrictive ventilatory impairments and may require mechanical ventilation to support adequate oxygenation.[17]

In individuals with AKI or CKD, persistent fluid overload further contributes to chronic pulmonary dysfunction. Evidence indicates that fluid excess in these patients is associated with pulmonary edema, restrictive lung disorders, and in some cases, obstructive physiological changes. These abnormalities arise from increased hydrostatic pressure, impaired lymphatic drainage, and altered sodium–water handling within the pulmonary microenvironment.[17]

Overall, disturbances in renal fluid regulation exert significant effects on pulmonary physiology. Fluid overload not only reduces lung compliance and compromises gas exchange, but also increases the workload of the respiratory system. In turn, impaired pulmonary function can exacerbate renal injury through mechanisms such as hypoxemia, sympathetic activation, and systemic

inflammation, underscoring the bidirectional interaction between the kidneys and the lungs.[16,17]

Oxidative Stress

Oxidative stress arises when the production of reactive oxygen species (ROS) exceeds the capacity of antioxidant defense mechanisms, resulting in damage to essential cellular structures such as membranes, proteins, and nucleic acids. ROS may originate from exogenous sources—including cigarette smoke, air pollutants, and ozone exposure—or from endogenous processes such as chronic inflammation, ischemia, immune cell activation, and age-related metabolic decline.[18]

The lungs are particularly vulnerable to oxidative injury due to their continuous exposure to the external environment and inhaled oxidants. Conversely, the kidneys are exposed predominantly to endogenous ROS. Renal tubular cells, which contain a high density of mitochondria to support solute reabsorption, are major generators of intracellular ROS. When antioxidant defenses become overwhelmed, excessive ROS disrupt mitochondrial function, induce lipid peroxidation, and promote apoptosis and fibrosis.[18]

Accumulating evidence indicates that oxidative stress contributes to a range of pulmonary and renal abnormalities, including restrictive lung dysfunction, DNA damage, pulmonary fibrosis, and progressive renal injury. These shared mechanisms highlight a bidirectional relationship between kidney and lung pathology.[18]

In conditions such as CKD, reduced renal clearance of oxidative metabolites and increased systemic inflammation exacerbate pulmonary oxidative stress. Similarly, oxidative injury originating in the lungs can amplify systemic oxidative burden and aggravate renal dysfunction. The intertwined oxidative pathways between these organs underscore the importance of addressing oxidative stress as part of comprehensive management in diseases that concurrently affect the lungs and kidneys.[18]

SYSTEMIC IMPACTS ON THE LUNG AND KIDNEY

The immune system mediates the effects of numerous systemic diseases on the kidneys and airways. Systemic disorders in autoimmune diseases are influenced by the relationship between the lungs and kidneys. Figure 2 illustrates the bidirectional pathological mechanisms linking kidney dysfunction and pulmonary impairment, including volume overload, altered sodium transport, pulmonary vascular permeability, circulating inflammatory mediators, autoimmune activation, hypoxemia, excessive cytokine production, and resulting pulmonary edema and respiratory dysfunction.[19]

Pulmonary renal syndrome (PRS) or pulmonary kidney syndrome is a clinical condition that is characterized by the simultaneous occurrence of crescentic glomerulonephritis (CGN) and intra-

alveolar hemorrhage. PRS is an emergency condition that results in kidney and lung dysfunction. Clinical symptoms of hemoptysis without a distinct cause, such as pneumonia, bronchiectasis, or malignancy, may suggest the presence of PRS. Anemia, proteinuria, and hematuria are among the conditions in which clinical manifestations of PRS in the kidneys are identified.[19]

Dysregulation of inflammatory cytokines contributes to the worsening of chronic lung diseases, including COPD, bronchial asthma, and pulmonary fibrosis, particularly among individuals with CKD. PRS is prototypically caused by Goodpasture Syndrome, which targets the kidney and lung, as well as other autoimmune disorders like systemic lupus erythematosus (SLE), eosinophilic granulomatosis with polyangiitis (EGPA), post-streptococcal glomerulonephritis (PSGN), rheumatoid arthritis (RA), and systemic sclerosis (SSc).[20]

The Lungs and Kidneys as Target Organs of Autoimmune Diseases

Goodpasture Syndrome is a specific autoimmune disease that concurrently impacts the kidneys and lungs. Goodpasture Syndrome is a rare disease with an annual incidence of 1 in 1 million cases, as determined by epidemiological methods. Regardless of a low incidence, Anti-glomerular basement membrane (anti-GBM) is responsible for 20% of cases of rapidly progressive glomerulonephritis (RPGN).[21]

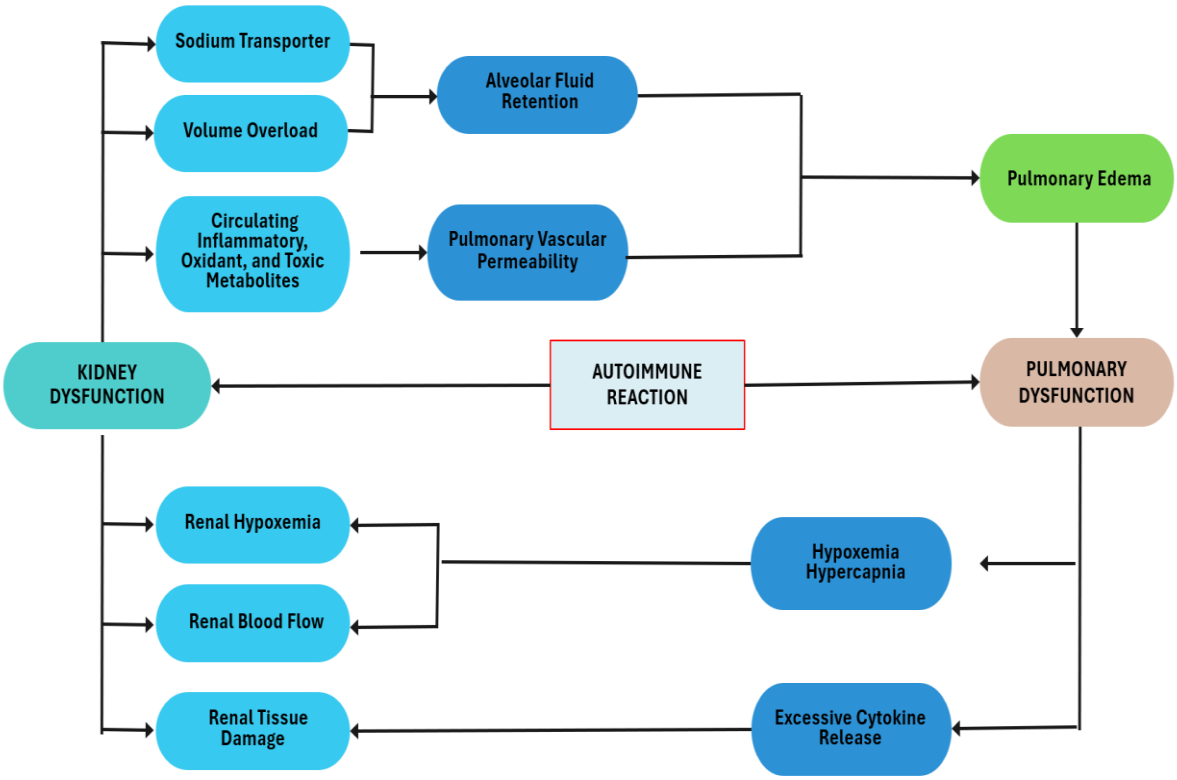

Figure 2. Pathological Relationship between Lungs and Kidneys[22]

The kidneys and lungs experience pathophysiological damage simultaneously in Goodpasture Syndrome. The diagnosis of Goodpasture Syndrome is dependent on serum antibody testing that yields positive anti-GBM results, as the syndrome's mechanism is mediated by anti-GBM. Positive results for target antibodies on the 28 kD monomer subunit derived from the Non-collagenous domain of the Alpha 3 Chain of type IV Collagen (alpha3[IV]NC1) in the glomerular basement membrane are observed in the majority of patients with Goodpasture Syndrome.[23]

Goodpasture Syndrome's autoantibody process specifically targets the basal membrane of the alveoli and glomerulus. As of the present time, the pathophysiology of this condition appears unknown. It is believed that the specific binding of autoantibodies in Goodpasture Syndrome may be influenced by the accessibility of epitopes on the basal membrane of alveoli and glomeruli and other factors.[19] The entry pathway of antibodies is facilitated by the conformational structure of alpha3[IV]NC1 in the alveoli and glomerulus. The propensity for Goodpasture Syndrome to develop can also be increased by genetic factors in individuals with specific types of human leukocyte antigen (HLA).[24]

Approximately 10% of patients with Goodpasture Syndrome experience pathological changes in the lungs that are not accompanied by pathological changes in the kidneys.[19] The initial symptoms of Goodpasture Syndrome are non-specific, including fatigue and lethargy. These symptoms may progress gradually or rapidly to AKI, which is accompanied by pulmonary edema and bleeding.[25]

The kidney biopsy examination discovered renal lesions in Goodpasture Syndrome, which is a characteristic of CGN.[26] The renal immunofluorescence staining demonstrated compatibility with IgG on the GBM. The CT scan indicated significant bilateral ground glass opacities (GGO), and the chest of the CT-scan examination found bilateral parenchymal consolidation with the appearance of infiltrates consolidating in both hemithorax.[19]

The definitive treatment for Goodpasture Syndrome is still not known to this day. Nevertheless, a study has demonstrated that the response to treatment is significantly affected by immunosuppressive management.[26]

Non-Specific Autoimmune Diseases of the Lungs and Kidneys

The term "Goodpasture Syndrome" was initially used to identify a group of patients who showed combined alveolar and glomerular hemorrhage. The role of anti-GBM was identified in many cases and has been suggested to be among the primary pathogenic mechanisms that explain the progression of the syndrome. The term "Goodpasture Syndrome" has been restored and has been referred to as "Pulmonary Renal Syndrome (PRS)" due to the discovery of multiple pathogenic mechanisms in several studies. In general, PRS is a life-threatening condition that can be recognized by the combination of RPGN and diffuse alveolar hemorrhage (DAH).[27]

Systemic autoimmune conditions with anti-neutrophil cytoplasm antibodies (ANCA) – associated vasculitides (AAV) are commonly linked with as many as 20% of PRS cases. ANCA-AAV is a rare form of vasculitis that is characterized by ANCA and is detected through immunofluorescence examination. It's an outcome of immune complex mediation.[22]

The clinical course of ANCA-AAV can have an impact on a variety of target organs, including the heart, kidneys, lungs, skin, and nervous system. The autoantibody process in ANCA-AAV will target Proteinase-3 (PR3) and Myeloperoxidase (MPO), which will associate with ANCA to form PR3-ANCA [Cytoplasmic ANCA (C-ANCA)] or MPO-ANCA [Perinuclear ANCA (P-ANCA)]. The cytoplasm of neutrophils and monocytes frequently contains PR3 and MPO. C-ANCA and P-ANCA formation induce neutrophil degranulation, which leads to the release of oxidative stress and endothelial disruption, thereby causing vasculitis in small blood vessels.[22]

Most of PRS cases are diagnosed in comparison to autoimmune conditions that involve ANCA test results and are differentiated based on the underlying pathological processes (Table 2). Along with the differential diagnosis of PRS, serological assays are employed as parameters. The management of PRS is determined by the underlying cause, as indicated by the ANCA serological test results (positive or negative) (Figure 3).

Many studies showed that the use of immunosuppressants and glucocorticoids is appropriate for the management of PRS with positive or negative ANCA serology results.

Table 2. Differential Diagnosis of PRS with Serological Examination Results[27]

Diagnosis of PRS	Serological Examination Results
Vaskulitis-related ANCA (ANCA-AAV)	
1. Granulomatosis with Polyangiitis (GPA)	1. ANCA (+) 90%; PR3 (+) 75%
2. Microscopic Polyangitis (MPA)	2. ANCA (+) 60%; MPO (+) 65%
3. Eosinophilic Granulomatosis with Polyangiitis (EGPA)	3. ANCA (+) 30–70%; PR3 (+) 5%; MPO (+) 45%
Disease with Anti-GBM Abnormalities	Antibody anti-GBM → Sensitive (95–100%); Specific (90–100%)
Vasculitis with Negative ANCA Results	
1. Disease with IgA Abnormalities	1. No Specific
2. Cryoglobulinemia	2. Hepatitis Serology → Serum of Cryoglobulin (+)
Autoimmune Connective Tissue Disease (ACTD)	
1. Systemic Lupus Erythematosus (SLE)	1. Anti-dsDNA, anti-Smith, anti-C1q antibodies
2. Antiphospholipid Syndrome (APS)	2. Anti-cardiolipin, Lupus Anticoagulant Antibodies
3. Rheumatoid Arthritis (RA)	3. Rheumatoid factor, Anti-cyclic Citrullinated Peptides
Mixed Connective Tissue Disease (MCTD)	
1. Polymyositis and Dermatomyositis	1. Anti-Jo1, anti-Ro antibodies
2. Systemic Sclerosis (SSc)	2. Anti-centromere, anti-Scl70

Note: Positive results on serological tests narrow down the differential diagnosis of PRS. ANCA serological testing (Positive/Negative) is the first step in identifying the underlying cause.

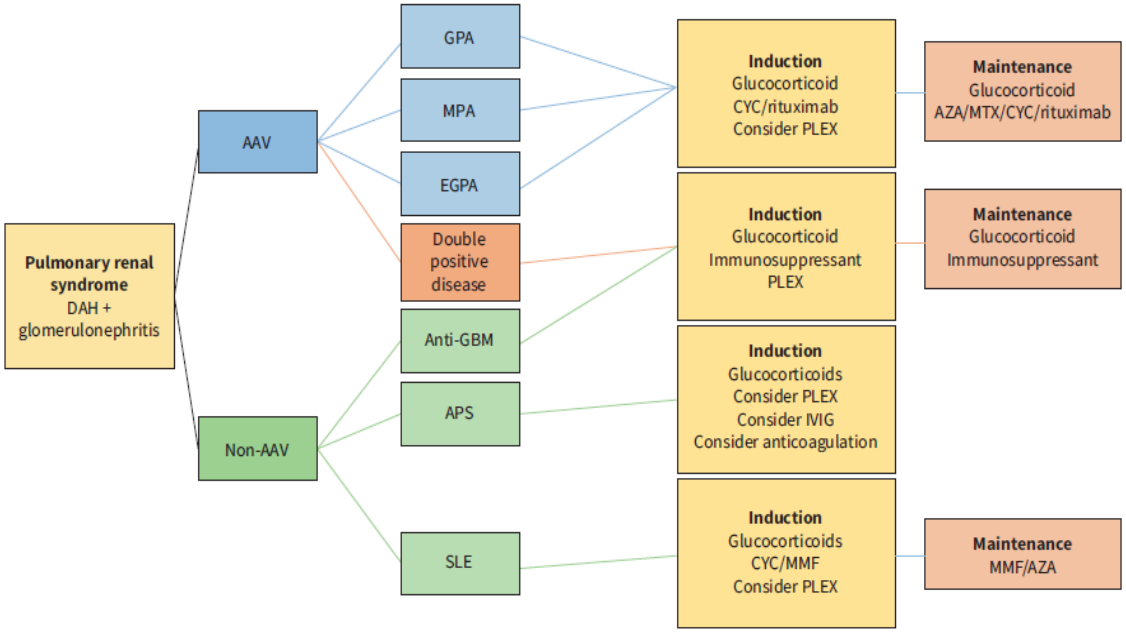

Figure 3. Algorithm for the Management of Pulmonary Renal Syndrome[27]

Note: DAH=Diffuse Alveolar Hemorrhage; ANCA=Anti-neutrophil Cytoplasm Antibodies; AAV=ANCA-associated Vasculitis; GPA=Granulomatosis with Polyangiitis; MPA=Microscopic Polyangiitis; EGPA=Eosinophilic Granulomatosis with Polyangiitis; GBM=Glomerular Basement Membrane; APS=Antiphospolipid Syndrome; SLE=Systemic Lupus Erythematosus; CYC=Cyclophosphamide; PLEX=Plasmapheresis; IVIG=Intravenous Immunoglobulin; MMF=Mycophenolate Mofetil; AZA=Azathioprine; MTX=Methotrexate.

The dose of high-dosage methylprednisolone is given for 3-5 days as the initial treatment induction, and the dose is subsequently tapered by 1 mg/kg body weight each month. Methotrexate, Azathioprine, Cyclophosphamide, and Rituximab are immunosuppressants that can be given in combination with glucocorticoids. Furthermore, plasmapheresis is recommended as an induction treatment for secondary PRS caused by AAV with RGPH or DAH.[27]

CONCLUSION

The kidneys and lungs have functional connections that are both physiological and pathological. From a physiological perspective, the relationship between the lungs and kidneys includes immune response mechanisms, phosphate metabolism, hormonal system imbalances, acid-base balance, fluid excess changes, and oxidative stress. Pulmonary Renal Syndrome is an example of a condition that simultaneously relates lung and renal dysfunction, such as autoimmune disorders. Fluid excess and non-cardiogenic pulmonary edema are kidney disorders that typically have implications for the lungs from a pathological perspective. Conversely, hypoxemia and hypercapnia are respiratory disorders that have an impact on the kidneys. Associated conditions that affect lung and kidney dysfunction include inflammatory conditions with acute and chronic onset. The fundamental principle of treatment for lung and kidney disorders is the management of the underlying causes of dysfunction.

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