Canagliflozin Possible Roles: A Potential Antifibrotic Agent in Diabetic Idiopathic Pulmonary Fibrosis in comparison with Metformin

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Abstract: Idiopathic pulmonary fibrosis (IPF) is a chronic, progressive interstitial lung disease characterized by extensive fibrosis, leading to respiratory failure and significant mortality. The disease pathogenesis remains poorly understood, but evidence suggests that diabetes mellitus (DM), particularly type 2 diabetes, may exacerbate IPF progression through hyperglycemia-induced oxidative stress, chronic inflammation, and profibrotic signaling pathways. The increasing prevalence of both DM and IPF underscores the urgent need for novel therapeutic strategies targeting overlapping mechanisms of these diseases. Recent studies suggest that metformin has beneficial role as antifibrotic agent in IPF, also certain antidiabetic agent particularly canagliflozin, may exhibit antifibrotic properties beyond its glucose-lowering effects. Canagliflozin, a sodium-glucose cotransporter-2 (SGLT2) inhibitor, has shown potential in reducing inflammation, oxidative stress, and fibrosis in various organ systems, including the kidneys and heart. Its ability to modulate transforming growth factor-beta (TGF-β) and nuclear factor-kappa B (NF-κB) pathways may contribute to its antifibrotic effects. Similarly, metformin, a widely used biguanide, has demonstrated pleiotropic benefits, including antifibrotic properties through activation of AMP-activated protein kinase (AMPK). AMPK activation downregulates TGF-β and connective tissue growth factor (CTGF), both critical mediators of fibrotic processes. Emerging preclinical studies suggest that Canagliflozin may attenuate fibrotic changes in experimental models of lung fibrosis, providing a rationale for its exploration in IPF management. This review highlights the dual benefits of canagliflozin and metformin in the context of DM and IPF, focusing on their antifibrotic mechanisms. We discuss preclinical and clinical evidence, mechanisms underlying fibrosis modulation, and their translational potential in IPF therapy. Additionally, the review explores the safety profile and possible synergistic effects of combining these agents. While promising, the current evidence is preliminary, necessitating robust clinical trials to establish Canagliflozin efficacy and safety in IPF. The therapeutic repurposing of these antidiabetic drugs offers a novel avenue to address the unmet needs of patients with diabetic IPF, providing hope for a disease with limited treatment options.

Keywords: Canagliflozin, Metformin, Diabetic, Idiopathic Pulmonary Fibrosis.

1. Introduction

Idiopathic Pulmonary Fibrosis (IPF) is a chronic, progressive, and ultimately fatal lung disease characterized by fibrosis of the lung parenchyma, which results in progressive respiratory decline. The etiology of IPF remains elusive, with the term "idiopathic" reflecting the lack of a known cause [1]. This disease primarily affects individuals over the age of 60, with a higher prevalence in males compared to females [2]. The median survival time for patients diagnosed with IPF ranges from 2 to 5 years, underscoring the seriousness of this condition [3].

The pathogenesis of IPF is believed to involve an aberrant wound healing response following repeated micro-injuries to the alveolar epithelium. Genetic predisposition, environmental factors, and age-related changes in the lung contribute to this maladaptive response [4]. These micro-injuries stimulate fibroblast proliferation and extracellular matrix deposition, leading to the thickening and stiffening of lung tissue [5]. This results in impaired gas exchange, manifesting as progressive dyspnea and hypoxemia [6].

Clinically, IPF presents insidiously, often with nonspecific symptoms such as chronic dry cough and exertional dyspnea. As the disease progresses, patients may develop clubbing of the fingers, fatigue, and unintentional weight loss [7]. A high index of suspicion is required for early diagnosis, as these symptoms can overlap with other interstitial lung diseases and respiratory conditions [8].

High-resolution computed tomography (HRCT) is the cornerstone for diagnosing IPF, often revealing a pattern of usual interstitial pneumonia (UIP) with reticular opacities, honeycombing, and subpleural basal predominance [9]. When HRCT findings are inconclusive, surgical lung biopsy may be necessary to confirm the diagnosis [10]. Recent advancements in imaging techniques and biomarker research are enhancing diagnostic accuracy [11].

The management of IPF is challenging, as there is no cure for the disease. Treatment strategies aim to slow disease progression, alleviate symptoms, and improve quality of life. Antifibrotic agents, such as pirfenidone and nintedanib, have shown efficacy in reducing the rate of decline in lung function [12]. These medications target pathways involved in fibrosis and inflammation, offering hope for prolonged survival [13].

Oxygen therapy is a critical component of symptom management in IPF. Supplemental oxygen helps alleviate hypoxemia and improves exercise tolerance, though it does not alter the disease course [14]. Pulmonary rehabilitation programs, including exercise training and education, further enhance functional capacity and quality of life in these patients [15].

Lung transplantation remains the only definitive treatment for IPF, offering a potential cure for selected patients with end-stage disease. However, the procedure is limited by the scarcity of donor organs, comorbid conditions, and the risk of post-transplant complications [16]. Despite these challenges, lung transplantation significantly improves survival and quality of life for eligible patients [17].

Several risk factors have been associated with the development of IPF, including cigarette smoking, environmental exposures (e.g., organic and inorganic dust), and gastroesophageal reflux disease (GERD) [18]. Genetic mutations, particularly in genes associated with surfactant production and telomere maintenance, also contribute to disease susceptibility [19].

The role of GERD in IPF is an area of active investigation. Microaspiration of gastric contents is thought to exacerbate lung injury and fibrosis, prompting the use of proton pump inhibitors in some patients [20]. While the benefits of GERD treatment in IPF remain debated, observational studies suggest a potential protective effect against disease progression [21].

The natural history of IPF is variable and unpredictable, with some patients experiencing rapid decline while others have a more indolent course. Acute exacerbations, defined as a sudden

worsening of respiratory symptoms and lung function, represent a significant cause of morbidity and mortality [22]. The etiology of these exacerbations is poorly understood, but they are often triggered by infections, environmental exposures, or unknown factors [23].

The prognosis of IPF is generally poor, with median survival rates comparable to those of many advanced cancers. Factors associated with worse outcomes include older age, lower forced vital capacity (FVC), and the presence of comorbid conditions such as pulmonary hypertension [24]. Serial monitoring of lung function and symptom burden is essential for assessing disease progression and guiding management decisions [25].

Research efforts in IPF are increasingly focused on understanding the molecular mechanisms driving fibrosis. Targeting pathways involved in epithelial injury, fibroblast activation, and extracellular matrix deposition offers promise for the development of novel therapies [26]. Preclinical studies and early-phase clinical trials are evaluating the efficacy of agents such as antifibrotic peptides, tyrosine kinase inhibitors, and immune modulators [27].

Patient-centered care is a fundamental aspect of IPF management, emphasizing the importance of shared decision-making and psychosocial support. Given the unpredictable nature of the disease, advance care planning and palliative care services should be introduced early in the disease course [28]. These interventions address symptom burden, improve quality of life, and support patients and their families in navigating the complexities of living with IPF [29].

The impact of IPF extends beyond physical health, significantly affecting emotional well-being, social functioning, and financial stability. Patients often experience anxiety, depression, and social isolation due to the progressive and incurable nature of the disease [30]. Multidisciplinary care teams, including pulmonologists, physical therapists, dietitians, and mental health professionals, play a vital role in addressing these multidimensional needs [31].

Public awareness and advocacy efforts are crucial for improving outcomes in IPF. Increased recognition of the disease among healthcare providers and the general population can facilitate earlier diagnosis and access to specialized care [32]. Patient advocacy organizations and support groups provide valuable resources for education, emotional support, and engagement in research initiatives [33].

Idiopathic pulmonary fibrosis is a complex and devastating disease with significant unmet medical needs. While advances in antifibrotic therapies and lung transplantation offer hope, the overall prognosis remains poor. Ongoing research into the molecular underpinnings of fibrosis and the development of targeted therapies is critical for improving outcomes. Holistic, patient-centered care that addresses the physical, emotional, and social dimensions of the disease is essential for enhancing quality of life in this vulnerable population [34].

Canagliflozin Possible Role among Diabetic Idiopathic Pulmonary Fibrosis

Canagliflozin, an SGLT2 inhibitor, has gained substantial attention for its role in managing diabetes mellitus. Beyond glycemic control, its multifaceted effects have sparked interest in its potential role among diabetic patients with idiopathic pulmonary fibrosis (IPF), a progressive and devastating interstitial lung disease. The intersection of these two conditions poses a significant therapeutic challenge, necessitating an exploration of novel interventions [35].

Canagliflozen has rapid and dose-proportional absorption after oral administration, oral bioavailability of canagliflozin is ≈65% with steady-state plasma concentrations achieved in 4–5 days. Mean peak plasma canagliflozin concentrations (SSC) are achieved 1–2 h after administration. It undergoes extensive metabolism in liver, primarily via glucuronidation by uridine diphosphate glucuronosyl transferase to inactive O-glucuronide metabolites. The pharmacokinetics of canagliflozin are not affected to a clinically significant extent by age, bodyweight, race or gender [35].

Canagliflozen is sodium glucose cotransport 2 (SGLT2) inhibitor acting by a mechanism not dependent on the activity of insulin. SGLT2 is a protein expressed on the proximal renal tubules and is responsible for most (≈90%) of the reabsorption of filtered glucose from the kidneys. Canagliflozin, is a highly selective SGLT2 inhibitor and, as a consequence, inhibits

reabsorption of filtered glucose in the proximal tubules of the kidney and lowers the renal threshold for glucose, thereby increasing urinary glucose excretion The increased urinary glucose excretion also produces a loss of calories associated with a reduction of bodyweight, as well as an osmotic diuretic effect, which leads to modest reductions of blood pressure [35].
Moreover, SGLT2 inhibitors reduce number of myofibroblasts, inflammatory molecules, the extent of myocardial fibrosis and reduce the expression of TGF-β, collagen deposition and cardiac fibrosis also. It also suppresses profibrotic markers such as type 1 collagen and connective tissue growth factor (CTGF) in cultured human cardiac fibroblasts, which suggested that there may be a direct antifibrotic effect of SGLT2 inhibitors [35].
Diabetic individuals are at a higher risk of developing IPF, potentially due to the pro-inflammatory and pro-fibrotic milieu associated with chronic hyperglycemia. Canagliflozin's anti-inflammatory properties provide a theoretical basis for its use in mitigating the fibrotic progression of IPF in diabetic patients. Studies suggest that SGLT2 inhibitors can reduce systemic inflammation and oxidative stress, both of which are implicated in IPF pathogenesis [36].
The mechanism of action of canagliflozin extends beyond glycemic regulation. By promoting glycosuria, it reduces glucose toxicity, which may indirectly attenuate fibrotic pathways. Moreover, canagliflozin has been shown to modulate profibrotic cytokines such as transforming growth factor-beta (TGF-β), a key mediator in IPF. This dual action of glucose control and anti-fibrotic modulation highlights its potential therapeutic advantage [37].
Pulmonary fibrosis is characterized by excessive extracellular matrix deposition and tissue remodeling. Evidence indicates that canagliflozin might mitigate these processes by inhibiting pathways involved in fibrogenesis. For instance, its role in downregulating nuclear factor-kappa B (NF-κB) and reducing interleukin-6 (IL-6) levels could contribute to a less fibrotic pulmonary environment [38].
Canagliflozin's cardiovascular benefits are well-documented, and these effects may also confer pulmonary advantages. Improved cardiac function reduces pulmonary congestion, which might indirectly benefit patients with IPF. Additionally, its diuretic-like effect reduces fluid overload, potentially alleviating pulmonary symptoms in IPF patients with concomitant diabetes [39].
Oxidative stress plays a central role in the pathogenesis of both diabetes and IPF. Canagliflozin has been shown to reduce markers of oxidative damage by enhancing mitochondrial function and reducing reactive oxygen species (ROS) production. These effects may be particularly beneficial in IPF, where oxidative stress accelerates disease progression [40].
Chronic inflammation in diabetes contributes to systemic and organ-specific damage, including lung fibrosis. By reducing levels of C-reactive protein (CRP) and other inflammatory markers, canagliflozin may dampen the inflammatory cascade that exacerbates IPF. This anti-inflammatory effect could be pivotal in managing the dual burden of diabetes and IPF [41].
Recent preclinical studies have highlighted the potential of SGLT2 inhibitors in ameliorating pulmonary fibrosis. Canagliflozin, specifically, has demonstrated efficacy in reducing alveolar inflammation and fibrosis in animal models. These findings provide a promising foundation for future clinical trials to assess its therapeutic efficacy in diabetic IPF patients [42].
In diabetes, hyperglycemia-induced advanced glycation end products (AGEs) play a critical role in fibrosis. Canagliflozin's ability to lower AGE accumulation could translate into reduced fibrotic activity in the lungs. This effect is particularly relevant in IPF, where AGEs exacerbate tissue stiffness and inflammation [43].
Metabolic reprogramming is a hallmark of both diabetes and fibrotic diseases. Canagliflozin's role in improving metabolic efficiency and reducing lipotoxicity may offer a novel approach to managing IPF in diabetic patients. By modulating lipid metabolism, it may reduce pulmonary lipotoxicity and subsequent fibrotic remodeling [44].
The interplay between diabetes and IPF involves complex molecular pathways, including the renin-angiotensin system (RAS). Canagliflozin's inhibition of RAS components could reduce

pulmonary hypertension and fibrotic progression, making it a valuable therapeutic candidate in this patient population [45].

Microvascular dysfunction is a shared feature of diabetes and IPF. Canagliflozin's vasculoprotective effects, including improved endothelial function and reduced capillary leak, may mitigate vascular contributions to pulmonary fibrosis. These benefits highlight its potential as a comprehensive treatment strategy [46].

The safety profile of canagliflozin further supports its consideration in diabetic IPF patients. Its low risk of hypoglycemia and well-established cardiovascular safety make it a suitable option for long-term use, particularly in a population with complex comorbidities like IPF and diabetes [47].

Emerging evidence suggests that canagliflozin may influence autophagy, a cellular process implicated in both diabetes and fibrotic diseases. Enhanced autophagy may reduce the accumulation of damaged cellular components and attenuate fibrotic signaling pathways, offering additional benefits in IPF management [48].

Fibroblast activation is a key event in pulmonary fibrosis. Canagliflozin has been shown to inhibit fibroblast proliferation and differentiation into myofibroblasts, thereby reducing extracellular matrix deposition and fibrosis. This mechanism aligns with its potential role in IPF therapy [49].

The systemic effects of canagliflozin, including weight loss and improved insulin sensitivity, may indirectly benefit IPF patients by reducing the metabolic burden and inflammatory state associated with obesity and insulin resistance. These benefits could enhance overall disease management [50].

In IPF, epithelial-mesenchymal transition (EMT) contributes to disease progression. Canagliflozin's ability to inhibit EMT-related pathways, such as TGF-β signaling, may slow the progression of pulmonary fibrosis, offering hope for improved outcomes in diabetic IPF patients [51].

Diabetes is associated with increased fibroblast growth factor-23 (FGF-23) levels, which are linked to pulmonary fibrosis. Canagliflozin's ability to modulate FGF-23 levels could provide an additional pathway to mitigate fibrotic progression in IPF [52].

Preclinical studies have shown that SGLT2 inhibitors can reduce pulmonary artery pressure and improve right ventricular function. These effects may alleviate symptoms and improve quality of life in IPF patients with concurrent diabetes and pulmonary hypertension [53].

The role of canagliflozin in reducing systemic inflammation and oxidative stress has implications for its use in IPF. By targeting common pathogenic mechanisms, it may offer a dual benefit for diabetic patients with this devastating lung disease [54].

Emerging research highlights the potential of combining canagliflozin with antifibrotic therapies like nintedanib or pirfenidone. Such combinations may provide synergistic effects, enhancing efficacy while minimizing disease progression in diabetic IPF patients [55].

The metabolic and anti-inflammatory effects of canagliflozin extend to improved skeletal muscle function and reduced sarcopenia. These benefits may enhance physical capacity and quality of life in IPF patients, who often experience debilitating muscle weakness [56].

Studies indicate that SGLT2 inhibitors can influence extracellular matrix turnover. Canagliflozin's role in reducing matrix metalloproteinase activity may further contribute to its anti-fibrotic potential in IPF [57].

In diabetic patients, chronic kidney disease (CKD) often coexists with IPF. Canagliflozin's renoprotective effects, including reduced albuminuria and slowed CKD progression, may offer additional benefits in managing this complex patient population [58].

The anti-inflammatory effects of canagliflozin may extend to modulating immune cell activity in the lungs. By reducing macrophage activation and pro-inflammatory cytokine release, it may create a less fibrotic pulmonary microenvironment [59].

Hyperglycemia-induced mitochondrial dysfunction contributes to oxidative stress and

inflammation in IPF. Canagliflozin's ability to improve mitochondrial efficiency and reduce ROS production may offer a novel therapeutic approach [60].
The role of canagliflozin in improving glycemic control and reducing systemic inflammation is particularly relevant in IPF, where metabolic dysregulation exacerbates disease progression. Its dual action offers a comprehensive approach to managing these interconnected conditions [61].
Canagliflozin's ability to reduce inflammatory markers such as tumor necrosis factor-alpha (TNF-α) may have direct implications for its use in IPF, as TNF-α is a key mediator in fibrotic pathways [62].
Emerging data suggest that canagliflozin may influence the gut microbiome, leading to reduced systemic inflammation. This gut-lung axis interaction could provide additional benefits in managing IPF [63].
The potential role of canagliflozin in managing pulmonary hypertension, a common complication in IPF, adds to its therapeutic appeal. By reducing vascular remodeling and improving hemodynamics, it may offer symptomatic relief and slow disease progression [64].
Canagliflozin's ability to enhance nitric oxide bioavailability and reduce endothelial dysfunction may further contribute to its potential benefits in IPF. These effects are particularly relevant given the vascular component of this disease [65].
The anti-fibrotic effects of canagliflozin may also extend to reducing lung stiffness, a hallmark of IPF. By modulating extracellular matrix composition, it could improve lung compliance and respiratory function [66].
In diabetic patients with IPF, canagliflozin's ability to improve insulin sensitivity and reduce systemic inflammation may offer a holistic approach to disease management, addressing both metabolic and fibrotic pathways [67].
The therapeutic potential of canagliflozin in diabetic IPF patients underscores the need for clinical trials to evaluate its efficacy and safety in this unique population. Such studies could pave the way for new treatment paradigms in interstitial lung diseases [68].
Metformin's Role in Diabetic Idiopathic Pulmonary Fibrosis (IPF)
Metformin, a first-line treatment for type 2 DM, has demonstrated antifibrotic effects in preclinical studies. Its ability to modulate adenosine monophosphate-activated protein kinase (AMPK) activity and suppress profibrotic signaling pathways, such as transforming growth factor-beta (TGF-β), makes it a candidate for managing fibrotic disorders. This has prompted investigations into its therapeutic role in patients with IPF [70].
Metformin has an oral bioavailability of 50–60% under fasting conditions and is absorbed slowly. Peak plasma concentrations (Cmax) of metformin tablet are reached at around 3 hours after administration. The plasma protein binding of metformin is negligible, as reflected by its very high apparent volume of distribution. [70].
Metformin has acid dissociation constant values (pKa) of 2.8 and 11.5. It shows low lipophilicity, and rapid passive diffusion of metformin through cell membranes is unlikely. As a result of its low lipid solubility, it requires the transporter solute carrier family 22 member 1 (SLC22A1) to enter cells. Metformin is not metabolized and is cleared from the body by tubular secretion, being excreted unchanged in the urine. It is undetectable in blood plasma within 24 hours of a single oral dose. The average elimination half-life in plasma is 6.2 hours. Metformin is distributed to and appears to accumulate in red blood cells, with a much longer elimination half-life: 17.6 hours.[70]. The oral absorption, hepatic uptake, and renal excretion of metformin are mediated largely by organic cation transporters (OCTs). Metformin is excreted unchanged in urine, with an elimination half-life reported to be between 1.5 to 1.7 hours.[70].
Metformin lowers both basal and postprandial glucose levels. It works mainly by suppressing excessive hepatic glucose production through a reduction in gluconeogenesis. Other effects of metformin include an increase in glucose uptake, enhanced insulin signaling, a decrease in fatty acid and triglyceride synthesis, and an increase in fatty acid β-oxidation. Metformin may also increase glucose utilization in peripheral tissues, and possibly reduce food intake and intestinal

glucose absorption. Since metformin does not stimulate endogenous insulin secretion, it does not cause hypoglycemia or hyperinsulinemia.

The molecular mechanism of metformin is incompletely understood. Multiple mechanisms of action have been proposed, including inhibition of the mitochondrial respiratory chain (complex I), activation of AMP-activated protein kinase (AMPK), inhibition of glucagon-induced elevation of cyclic adenosine monophosphate (cAMP) with reduced activation of protein kinase A (PKA), and inhibition of mitochondrial glycerophosphate dehydrogenase. .[70].

Activation of AMPK is required for metformin's inhibitory effect on liver glucose production. AMPK is an enzyme that plays an important role in insulin signaling, whole-body energy balance, and the metabolism of glucose and fats..[70].

Metformin increases insulin sensitivity, enhances peripheral glucose uptake by inducing the phosphorylation of glucose transporter 4 (GLUT4) enhancer factor, decreases insulin-induced suppression of fatty acid oxidation, and decreases absorption of glucose from the gastrointestinal tract. Metformin directly exerts antifibrotic effects by inhibiting TGF-β1 production and subsequently decreasing the phosphorylation and nuclear translocation of Smad2/3..[70].

Additionally, some studies suggest that metformin exerts antifibrotic effects by blocking the phosphorylation of Smad2/3. Metformin treatment and subsequent AMPK activation inhibit the phosphorylation and nuclear translocation of Smad3. Decreased reactive oxygen species (ROS) generation induced by metformin treatment modulates TGF-β1-induced Smad2/3 phosphorylation and myofibroblast differentiation. ROS-sensitive regulation of tyrosine kinases and protein tyrosine phosphatases accounts for a decrease in Smad2/3 phosphorylation. Furthermore, metformin has also been shown to directly interact with TGF-β1 at its receptor-binding domain, thus suppressing the binding of TGF-β1 to its receptor and resulting in decreased activity of downstream signaling .[70].

AMPK activation by metformin inhibits key mediators of fibrosis, including TGF-β and the mammalian target of rapamycin (mTOR). This inhibitory action on the TGF-β pathway reduces fibroblast differentiation into myofibroblasts, a critical step in the pathogenesis of IPF. By attenuating myofibroblast proliferation, metformin helps mitigate the excessive extracellular matrix deposition that characterizes IPF [71].

Oxidative stress is a hallmark of IPF and contributes to tissue damage and fibrosis progression. Metformin’s antioxidant properties, achieved through AMPK-dependent and AMPK-independent mechanisms, can reduce reactive oxygen species (ROS) levels in lung tissue. These actions may protect against oxidative damage and slow fibrosis progression in diabetic IPF patients [72].

Chronic low-grade inflammation is another contributor to both DM and IPF. Metformin’s anti-inflammatory effects, mediated by its ability to inhibit nuclear factor kappa B (NF-κB) signaling, can attenuate inflammatory cytokine production. This dual anti-inflammatory and antifibrotic action positions metformin as a therapeutic option for patients with diabetes and concurrent IPF [73].

Hyperglycemia in diabetic patients is associated with increased production of advanced glycation end products (AGEs), which contribute to fibrosis through AGE-receptor interactions. Metformin’s ability to improve glycemic control may indirectly reduce AGE formation, thereby mitigating their profibrotic effects in diabetic IPF patients [74].

Preclinical studies have provided evidence supporting metformin’s efficacy in experimental models of pulmonary fibrosis. In vitro studies have shown that metformin can reduce fibroblast proliferation and extracellular matrix deposition, while in vivo studies demonstrate its to ameliorate lung fibrosis in animal models [75].

Clinical studies exploring the role of metformin in IPF are limited but promising. Retrospective analyses have indicated that metformin use in diabetic patients with IPF is associated with

improved lung function and reduced disease progression. However, these findings require validation in prospective, randomized controlled trials [76].
The safety profile of metformin is well-established in diabetic populations, but its safety and tolerability in non-diabetic patients with IPF require further investigation. side effects, such as lactic acidosis in patients with impaired renal function, must be carefully considered when exploring its use in IPF management [77].
IPF's pathogenesis involves aberrant epithelial repair and activation of fibroblasts. Metformin's role in restoring epithelial cell homeostasis and inhibiting fibroblast activation highlights a therapeutic strategy for this devastating disease [78].
The interplay between diabetes and IPF is complex, with hyperglycemia, insulin resistance, and systemic inflammation contributing to fibrosis. Metformin's ability to target multiple pathological mechanisms simultaneously makes it an attractive candidate for addressing this interplay in diabetic IPF patients [79].
In addition to its antifibrotic properties, metformin has shown to improve endothelial function and reduce vascular remodeling. This may have implications for IPF, where abnormal angiogenesis and vascular dysfunction play a role in disease progression [80].
The impact of metformin on mitochondrial function is another area of interest. Mitochondrial dysfunction is a hallmark of IPF pathogenesis, and metformin's ability to enhance mitochondrial biogenesis and reduce mitochondrial oxidative stress may contribute to its protective effects in IPF [81].
Fibroblast senescence and telomere shortening are key features of IPF. Recent studies suggest that metformin may delay fibroblast senescence by activating AMPK and enhancing autophagy, thus reducing fibrosis severity in diabetic IPF patients [82].
Autophagy, a cellular process that removes damaged organelles and proteins, is impaired in IPF. Metformin's ability to restore autophagic activity through AMPK activation may help mitigate fibrotic changes in the lungs, providing another avenue for its therapeutic [83].
The pro-inflammatory microenvironment in IPF involves various cytokines, including interleukin-6 (IL-6) and tumor necrosis factor-alpha (TNF-α). Metformin's suppression of these cytokines through AMPK-dependent pathways can reduce lung inflammation and fibrosis progression [84].
Emerging evidence suggests that gut-lung axis dysbiosis may play a role in IPF pathogenesis. Metformin's effects on gut microbiota composition and its ability to promote beneficial microbial metabolites may contribute to its antifibrotic effects in IPF [85].
Studies have shown that diabetic patients with IPF often experience accelerated lung function decline compared to non-diabetic patients. Metformin's ability to improve systemic metabolic and inflammatory parameters may provide a protective effect against this accelerated decline [86].
In addition to its direct antifibrotic effects, metformin has demonstrated the ability to modulate extracellular matrix remodeling by inhibiting matrix metalloproteinases (MMPs), enzymes involved in tissue fibrosis. This adds another dimension to its role in IPF management [87].
Advanced imaging studies have revealed that metformin may reduce radiological markers of fibrosis progression in diabetic IPF patients. These findings, while preliminary, suggest that metformin's impact on structural lung changes warrants further investigation [88].
An emerging area of research is the synergistic effects of metformin when combined with current IPF treatments such as nintedanib and pirfenidone. Preliminary findings suggest that metformin's AMPK activation can enhance the antifibrotic efficacy of these therapies, providing a combinatorial approach to managing IPF [89].
Furthermore, metformin's role in improving insulin sensitivity may have indirect benefits on pulmonary health in diabetic IPF patients. Improved insulin signaling may reduce the systemic inflammation and oxidative stress associated with insulin resistance, attenuating fibrosis progression [90].

The effect of metformin on alveolar epithelial cells, a key player in IPF pathogenesis, has been explored in preclinical studies. By protecting these cells from injury and apoptosis, metformin may support epithelial repair mechanisms and reduce the fibrogenic signaling cascades that lead to IPF [91].

Emerging biomarkers of IPF, such as Krebs von den Lungen-6 (KL-6) and surfactant proteins, have been investigated in the context of metformin therapy. Studies suggest that metformin may reduce the levels of these biomarkers, reflecting a reduction in epithelial injury and fibrosis [92].

Recent studies have highlighted the role of extracellular vesicles (EVs) in IPF progression. Metformin's ability to modulate the release and composition of EVs may represent another mechanism through which it exerts antifibrotic effects in diabetic IPF patients [93].

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