Fibrosis

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Review

The Anti-Fibrotic Potential of GLP-1 and GIP Receptor Agonists in Chronic Inflammatory Disorders: Mechanisms and Therapeutic Horizons

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ABSTRACT: Fibrosis, characterised by the excessive deposition of extracellular matrix via activated fibroblasts, is a pathological feature of several chronic inflammatory disorders, which collectively contribute significantly to global morbidity and mortality. Despite this, current anti-fibrotic therapies are of limited efficacy. However, incretin-based therapies, primarily glucagon-like peptide-1 (GLP-1) receptor agonists, are now emerging as candidate drugs for modulating fibrotic signalling pathways. This review synthesises the growing body of preclinical and clinical evidence that incretin receptor agonists exert direct and indirect anti-fibrotic effects. We detail the molecular mechanisms and survey the promising data across hepatic, cardiac, renal, lung, and joint tissues, which underscore the potential for repurposing of this drug class as a therapeutic strategy for fibro-inflammatory conditions.

Keywords: Fibrosis; Incretins; GLP-1; GIP; TGF-β; Myofibroblasts; Synovial fibroblasts; Osteoarthritis; Semaglutide; Liraglutide; Dulaglutide; MASLD; Kidney disease

1. Introduction

Fibrotic diseases, such as metabolic dysfunction–associated steatotic liver disease (MASLD), chronic kidney disease (CKD), heart failure, neoplasms, and pulmonary disease such as idiopathic pulmonary fibrosis (IPF), are estimated to account for around 35% of global deaths [1]. Furthermore, fibrotic remodelling within the synovial joint in rheumatoid arthritis and osteoarthritis [2,3] is considered a major driver of chronic pain and loss of mobility.

The fibrotic process is a dysregulated wound-healing response, driven by the persistent activation of fibroblasts (or myofibroblasts), which results in the deposition of excessive extracellular matrix (ECM) proteins such as collagen [4], a key feature of pathological tissue remodelling in fibrotic disorders [5–8]. These activated fibroblasts also drive chronic persistent inflammation via the secretion and expression of

pro-angiogenic and pro-inflammatory cytokines and chemokines [9], which promote the recruitment of inflammatory immune cells [10].

Despite the profound impact of fibrosis, approved therapeutics that specifically target this pathology are limited. The anti-fibrotic drug pirfenidone [11] (which targets the key fibrotic cytokines TGF-β, TNF-α, and IL-6) and the tyrosine kinase inhibitor nintedanib [12] are both effective in targeting lung fibrosis, such as in IPF. However, these drugs are limited: They slow but do not reverse fibrosis, they are poorly tolerated, and it remains to be established whether they are translatable to other fibrotic inflammatory disorders, highlighting the clinical unmet need for alternative targeted anti-fibrotic strategies.

In seeking to identify existing drugs with anti-fibrotic potential that could be repurposed, incretin receptor agonists, namely the glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP) receptor agonists, are emerging as candidates. The GLP-1 receptor agonists liraglutide and semaglutide are already well-established for their glucoregulatory and weight-loss effects in patients with type 2 diabetes (T2DM) and overweight/obesity [13–15]. However, emerging evidence suggests that their benefits extended beyond glycaemic control, with pleiotropic effects on multiple organ systems, including significant anti-fibrotic effects. Therefore, in this review we detail the direct and indirect molecular mechanisms by which incretin receptor agonists inhibit fibrotic signalling pathways, and critically appraise the evidence for their preclinical and clinical efficacy in fibrotic disorders across diverse tissues, including the liver, heart, kidney, lung, and joints (Table 1; Figure 1), ultimately culminating in an evaluation of their clinical potential for the treatment of fibrotic inflammatory disorders.

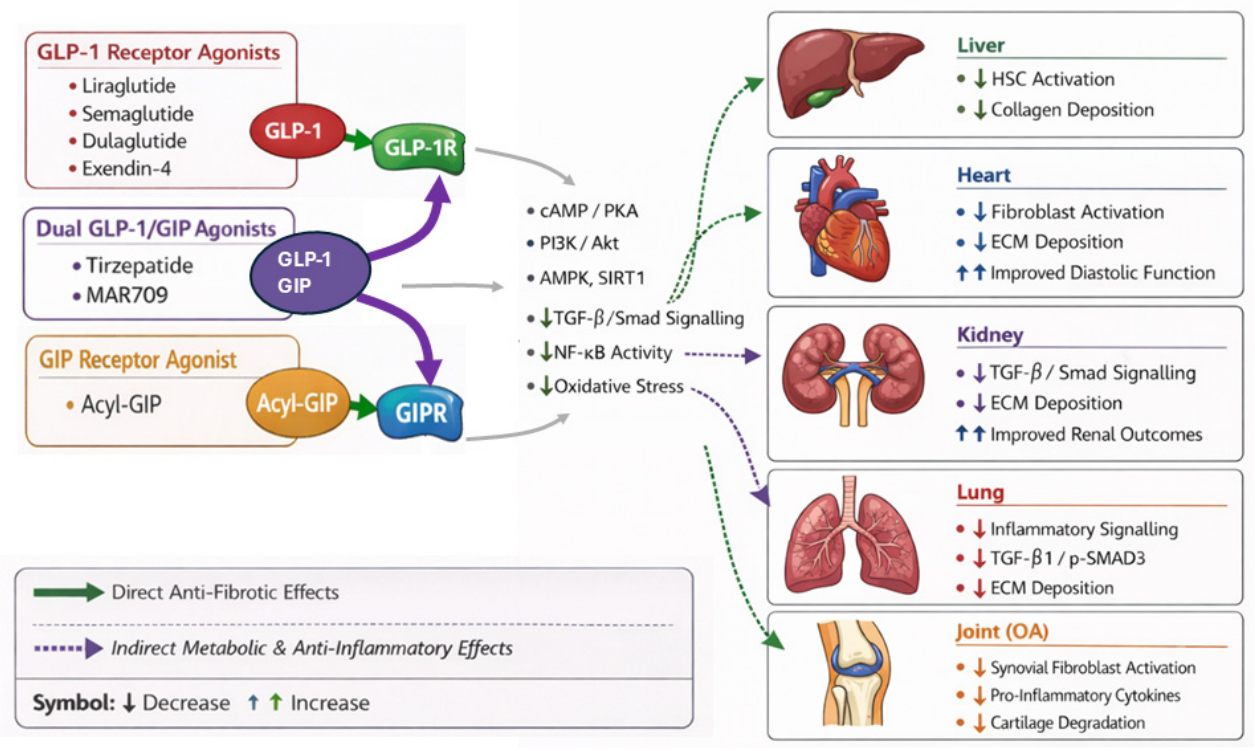

Figure 1. Direct and indirect anti-fibrotic mechanisms of incretin agonists across organ systems.

Table 1. Summary of preclinical and clinical evidence for the anti-fibrotic potential of incretin agonists across organ systems.

Disorder	Preclinical Evidence	Clinical Evidence
Liver fibrosis	*In vivo*: Thioacetamide-induced mouse model; semaglutide reduced α-SMA, oxidative stress, and collagen deposition; downregulated TGF-β/Smad, upregulated SIRT1 and p-AMPK.	MASLD/MASH patients: LEAN study—liraglutide reduced fibrosis progression; Phase 3 semaglutide trial—increased resolution of steatohepatitis and reduced fibrosis. Tirzepatide and semaglutide improved liver steatosis/inflammation.
Cardiovascular fibrosis	*In vitro*: Isolated cardiomyocytes—GLP-1R agonists activated PI3K/Akt, AMPK, cAMP/PKA; reduced NOX4 oxidative stress. Primary cardiac fibroblasts—inhibited TGF-β signalling, COL1A1/COL3A1 expression. *In vivo*: Rodent diabetic or pressure-overload cardiomyopathy—dulaglutide reduced myocardial collagen (~35%) and improved diastolic function; obese HFpEF mouse—semaglutide decreased collagen; MI models—liraglutide reduced adverse remodelling.	Large CVOTs (liraglutide, semaglutide, dulaglutide)—reduced CV events/mortality; SELECT trial—semaglutide reduced HF risk. Smaller T2DM/obesity cohorts—improved diastolic function, LV mass index, exercise capacity (liraglutide, semaglutide). Fibrosis is not directly measured.
Renal fibrosis/CKD	*In vitro*: Tubular epithelial cells—Exendin-4 reduced TGF-β-induced fibronectin/COL1A1 and miR-192; Mesangial cells—GLP-1R agonists suppressed NF-κB/TGF-β, reduced ECM, proliferation via AMPK. *In vivo*: UUO model—liraglutide suppressed TGF-β/Smad3/ERK1/2, reduced collagen; STZ diabetic rats—liraglutide or Exendin-4 reduced α-SMA, collagen I, fibronectin, glomerulosclerosis, oxidative stress.	CKD/T2DM patients (LEADER, SUSTAIN-6, REWIND, FLOW)—liraglutide, semaglutide, and dulaglutide improved renal outcomes (macroalbuminuria, eGFR, composite endpoints), but fibrosis was not directly measured.
Pulmonary fibrosis	*In vitro*: Alveolar macrophages—GLP-1R agonists suppressed NLRP3/IL-1β via histone lactylation; airway/alveolar epithelial cells—reduced IL-33, TSLP; pulmonary artery smooth muscle cells—liraglutide/exendin-4 reduced PDGF-BB-induced proliferation/migration. *In vivo*: Bleomycin lung injury -semaglutide microparticles reduced α-SMA, Col1a1, TGF-β1, p-SMAD3; pulmonary hypertension rodent models—liraglutide/exendin-4 reduced vascular remodelling, inflammation, hypertrophy. GLP-1R knockout reduced injury, highlighting context-dependence.	Meta-analyses in T2DM (77,000+ pts)—lower incidence of pulmonary fibrosis/ILD with GLP-1R agonists; no trials with fibrosis-specific endpoints.
Joint fibrosis/Osteoarthritis	*In vitro*: Rodent primary chondrocytes—liraglutide inhibited IL-1β/AGEs-induced TNF-α, IL-6, iNOS; Human SW1353—dulaglutide inhibited AGEs/NFkB cytokine expression; human primary articular chondrocytes—lixisenatide reduced TNF-α, IL-6, IL-7. *In vivo*: Murine MIA-induced OA—intra-articular liraglutide reduced synovitis and pain; Rat MIA & ACL-transection OA models—subcutaneous liraglutide reduced pro-inflammatory cytokines, cartilage degradation. Effects are partly independent of weight loss.	Knee OA patients with obesity—semaglutide reduced pain (WOMAC); Chinese cohort with T2DM—GLP-1 agonists (liraglutide, semaglutide) reduced cartilage volume loss over 2 years.

2. Molecular Mechanisms of Incretin Receptor Agonism in Fibrosis

The anti-fibrotic actions of incretin receptor agonists are likely mediated through a combination of direct receptor-mediated signalling and indirect systemic effects.

2.1. Direct Anti-Fibrotic Mechanisms

In considering the direct anti-fibrotic mechanisms, it is important to note that the expression of incretin receptors is not confined to the pancreatic islets. In humans, immunohistochemistry using a monoclonal antibody showed that the GLP-1 receptor protein is expressed in the pancreas, in smooth muscle cells of the kidney, lung, and gastrointestinal (GI) tract, and in myocytes of the heart [16]. Furthermore, GLP-1 receptor mRNA and protein have been reported in the brains of adult rodents and macaques [17]. Expression of the GIP receptor appears to be more ubiquitous, with Protein Atlas (proteinatlas.org; accessed on 5 December 2025 [18]) indicating expression of both mRNA and protein across multiple tissue types including brain, liver, kidney, heart, pancreas and gastrointestinal tissues. Furthermore, Protein Atlas indicates that GLP-1 receptor protein (but not mRNA) is present in skeletal muscle, whilst conversely GLP-1 receptor mRNA (but not protein) is detected in adipose tissue. However, data on the expression of either receptor in fibroblasts across different organ systems has not been reported.

Signalling through GLP-1 and GIP receptors involves Gαs-coupled pathways, increasing intracellular cAMP, which, downstream, can modulate the expression and/or activity of several fibrosis effectors. For example, a key fibrotic effector pathway mediated by GLP-1 receptor agonists is AMPK signalling. AMPK activation suppresses key fibrotic signalling pathways, including TGF-β/Smad and NFκB, resulting in inhibition of fibroblast proliferation and reduced ECM protein production [19]. Several studies have demonstrated that the GLP-1 receptor agonists such as extendin-4 and liraglutide can activate AMPK signalling in multiple tissues and cell types, including cardiomyocyte hyperglycaemic [20] or cardiac hypertrophy models [21], in rat INS-1 pancreatic beta cells [22], and in L6 myotubes, resulting in the sensitisation of insulin-stimulated glucose uptake [23].

Notably, TGF-β is considered the master regulator of fibrosis, and its downstream signalling is transduced primarily through the phosphorylation and activation of receptor-associated Smads (R-Smads), Smad2 and Smad3. These activated Smads form a complex with Smad4, which translocates to the nucleus and promotes the expression of pro-fibrotic genes [24], such as Type I Collagen alpha 1 (COL1A1) and Fibronectin and Connective Tissue Growth Factor (CTGF). Importantly, GLP-1 receptor agonism has been demonstrated in several fibrotic models to lead to inhibition of TGF-β signalling. In rodent H9C2 cardiomyocytes, liraglutide inhibited TGF-β signalling and reduced collagen production [25]. In a rat model of diabetes-induced testicular dysfunction, liraglutide reduced testicular TGF-β and Smad2 mRNA expression levels [26], whilst in HUVECs, liraglutide attenuated high glucose and IL-1β-induced TGF-β signalling (via inhibition of Smad2 phosphorylation), leading to reduced endothelial-to-mesenchymal transition (EndMT) marker expression [27].

2.2. Indirect Anti-Fibrotic Mechanisms

Incretin agonists likely also exert anti-fibrotic activity by indirect mechanisms. Firstly, metabolically, both hyperglycaemia and hyperinsulinemia are potent pro-fibrotic stimuli. High glucose levels lead to the creation of advanced glycation end products (AGEs), which contribute to fibrotic tissue formation [28], and both AGEs and excess insulin can promote fibroblast proliferation and ECM production [29,30]. Thus, by improving glycaemic control and improving insulin resistance, incretin receptor agonists may reduce fibrosis indirectly.

Secondly, significant weight loss and the resultant change in the inflammatory phenotype of obese adipose tissue would reduce the release into the circulation of key pro-fibrotic pro-inflammatory

cytokines/adipokines such as TNF-α, IL-6, leptin [31], visfatin and resistin, and increase levels of anti-fibrotic adipokines such as adiponectin [32]. For example, resistin-stimulated cardiac fibroblasts show increased expression of ECM proteins, including α-smooth muscle actin (α-SMA), COL1A1, CTGF, and fibronectin [33]. Thus, incretin receptor agonist-induced weight loss would be expected to create a tissue environment that is less conducive to fibrosis [34].

3. Efficacy of Incretin Receptor Agonists in Tissue-Specific Fibrotic Inflammatory Disorders

3.1. Liver Fibrosis

Liver fibrosis, with activation of hepatic stellate cells (HSCs) driving ECM deposition and progressive pathological changes to the liver architecture, is a central determinant of morbidity and mortality in MASLD. Thus, therapeutic strategies that can slow, halt, or reverse fibrotic change are a major clinical priority. As such, liver fibrosis has been a major focus of incretin receptor agonist research.

Several clinical studies have shown that GLP-1 receptor agonists, including semaglutide and liraglutide, and the dual GIP/GLP-1 receptor agonist tirzepatide, reduce liver steatosis and inflammation in MASLD patients [35]. In the LEAN clinical study in MASLD patients, liraglutide was found to reduce the incidence of fibrosis progression compared to placebo [36]. Similarly, in an ongoing phase 3 trial in patients with Metabolic Dysfunction–Associated Steatohepatitis (MASH; a subset of MASLD), resolution of steatohepatitis and reduction in liver fibrosis were reported in a greater proportion of patients in the semaglutide group compared to the placebo group [37].

A growing number of preclinical studies suggest that incretin receptor agonists may modulate core pathways involved in hepatic fibrogenesis, though whether these effects are direct or secondary to metabolic improvements remains an area of active investigation. *In vivo* data from rodent fibrosis models support a potential anti-fibrotic action. For example, in a thioacetamide-induced mouse model, semaglutide reduced biochemical and histological markers of liver injury, attenuated α-SMA expression, decreased oxidative stress, and downregulated the canonical TGF-β/Smad signalling pathway while upregulating SIRT1 and phosphorylated AMPK. These changes were accompanied by a significant reduction in collagen deposition and overall fibrosis severity, suggesting that GLP-1 receptor agonism can modify established fibrogenic signalling cascades within the liver [38].

In contrast, cell-based studies in human hepatic stellate cells and hepatocytes provide a more nuanced picture. Using both immortalised and primary human cells, liraglutide, acyl-GIP, and a dual GLP-1/GIP receptor agonist (MAR709) failed to produce measurable effects on lipid accumulation, fibrogenic gene expression, or CREB phosphorylation at physiologically relevant concentrations. Importantly, these compounds did not prevent TGF-β-induced HSC activation or reduce expression of ECM genes, including α-SMA and COL1A1 [39]. Thus, these *in vitro* findings indicate that the beneficial effect of incretin receptor agonists on fibrosis progression in MASLD patients is likely to be mediated indirectly through improvements in body weight, inflammation, and insulin resistance, rather than through the direct action on hepatic parenchymal or non-parenchymal cells.

In summary, incretin receptor agonists demonstrate consistent anti-fibrotic effects *in vivo*, reducing hepatic stellate cell activation, oxidative stress, and collagen deposition in animal models, and improving fibrosis outcomes in clinical MASLD and MASH studies. However, evidence from human cell-based experiments suggests that these benefits are unlikely to result from direct actions on hepatocytes or HSCs, instead reflecting indirect metabolic and anti-inflammatory mechanisms. Together, these data highlight the therapeutic potential of incretin receptor agonism in slowing or reversing liver fibrosis, while emphasising the need for further mechanistic studies in human-relevant systems to delineate direct versus indirect effects fully.

3.2. Cardiovascular Fibrosis

Cardiovascular fibrosis is a hallmark of pathological cardiac remodelling and a key mediator of the progression from metabolic or ischemic injury to overt heart failure. Chronic stress signals, including hyperglycaemia, inflammation, neurohormonal activation, and mechanical overload, promote the activation of cardiac fibroblasts and the accumulation of extracellular matrix within the myocardium. This stiffening and structural distortion impair diastolic and eventually systolic function, making fibrosis a central determinant of adverse cardiovascular outcomes. As a result, interventions capable of attenuating or reversing fibrotic remodelling hold significant therapeutic promise in cardiometabolic disease.

Clinical studies of incretin receptor agonists provide evidence of cardiovascular benefit, but they do not directly demonstrate anti-fibrotic effects, as fibrosis has not been measured as a primary outcome in major trials. Large cardiovascular outcome trials with liraglutide [40], semaglutide [41], and dulaglutide [42] have shown reductions in adverse cardiovascular events and cardiovascular mortality, while the SELECT trial demonstrated a reduction in heart failure with semaglutide [43]. Despite these benefits, these trials assessed cardiovascular clinical endpoints rather than myocardial structure or ECM collagen deposition, and thus do not establish a fibrosis-mediated mechanism.

Smaller cohort mechanistic studies provide indirect evidence that is suggestive of favourable fibrotic cardiac remodelling. In a prospective study of T2DM patients, six months of liraglutide therapy improved diastolic function and reduced left ventricular mass index [44], while additional echocardiographic studies have reported improvements in global longitudinal strain and left ventricular mass with GLP-1 receptor agonists [45]. Similarly, in patients with obesity-related HFpEF (Heart Failure with Preserved Ejection Fraction), semaglutide produced substantial improvements in symptoms and exercise capacity [46]. These findings are consistent with reduced myocardial stiffness and remodelling, but remain surrogates rather than direct measurements of fibrosis. Moreover, liraglutide trials in patients with HFrEF provided no clinical benefit, underscoring that the efficacy of incretin receptor agonism does not uniformly extend across heart-failure phenotypes and that remodelling mechanisms may differ by disease context [47].

Preclinical *in vivo* models have demonstrated anti-fibrotic effects of incretin receptor agonism in the heart. In rodent models of diabetic or pressure-overload cardiomyopathy, dulaglutide reduced myocardial collagen content by approximately 35% and improved diastolic function [48]. Semaglutide similarly decreased collagen deposition and improved diastolic indices in an obese mouse model of HFpEF [49]. In experimental myocardial infarction, liraglutide activated cardioprotective signalling pathways and reduced adverse ventricular remodelling [50].

In vitro studies provide mechanistic support for the anti-fibrotic actions of incretin receptor agonists in the cardiovascular system. In isolated cardiomyocytes, GLP-1 receptor agonists activated PI3K/Akt, AMPK, and cAMP/PKA pathways while reducing NOX4-mediated oxidative stress, signalling cardioprotective effects by alleviating ER stress-induced apoptosis [51]. Similarly, in primary cardiac fibroblasts, GLP-1R agonism inhibited TGF-β signalling activity and expression of ECM proteins, including COL1A1 and COL3A1 [25]. Together, these cellular studies highlight multiple convergent mechanisms, namely anti-inflammatory, anti-oxidative, pro-survival, and TGF-β/Smad inhibitory, through which incretin receptor agonists may modulate cardiac fibrogenesis.

3.3. Renal Fibrosis and Chronic Kidney Disease

Renal fibrosis is a major driver of progressive kidney function loss in CKD. Chronic metabolic, inflammatory, and hemodynamic stresses lead to myofibroblast activation, ECM deposition, and distortion of glomerular and tubulointerstitial architecture. As fibrotic scarring accumulates, nephron function declines irreversibly, underscoring the importance of targeting fibrosis as a central pathway in developing therapeutics for CKD.

Clinical evidence supporting the renoprotective effects of incretin receptor agonists primarily derives from large cardiovascular outcome trials, where kidney outcomes were secondary endpoints. These studies consistently report favourable renal outcomes (e.g., eGFR, macroalbuminuria, or serum creatinine levels) with GLP-1 receptor agonists. For example, in LEADER, liraglutide reduced the composite renal endpoint, driven mainly by a lower incidence of new-onset macroalbuminuria [52]. Similar findings were observed with semaglutide in SUSTAIN-6 [53] and dulaglutide in REWIND [54] clinical trials, where reductions in nephropathy events were reported. However, none included a direct assessment of renal fibrosis. Similarly, the recent FLOW trial demonstrated that semaglutide significantly reduced the risk of major kidney outcomes in patients with type 2 diabetes and CKD. However, these benefits were based on clinical endpoints and did not include direct measures of renal fibrosis, such as histology or fibrosis-specific biomarkers [55].

In contrast, preclinical *in vivo* studies provide more direct evidence that incretin receptor agonism attenuates renal fibrogenesis. In the unilateral ureteral obstruction model, liraglutide suppressed TGF-β expression and downstream Smad3 and ERK1/2 signalling, resulting in reduced tubulointerstitial collagen accumulation and improved histological fibrosis scores [56]. Similar anti-fibrotic effects of liraglutide have been reported in a streptozotocin (STZ)-induced diabetic model, where liraglutide reduced α-SMA, collagen I and fibronectin expression and altered the renal proteome consistent with decreased oxidative stress and attenuated ECM deposition [57]. In addition, Exendin-4 in STZ diabetic rats attenuated albuminuria and glomerulosclerosis by inhibiting the activation of NFκB and subsequent oxidative stress pathways [58]. Importantly, these effects were independent of the glucose lowering effect of the incretin receptor agonist.

Furthermore, across several cellular models, incretin receptor agonists have been reported to suppress pro-fibrotic signalling pathways, including TGF-β/Smad signalling, and NFκB activation, leading to reduced expression of ECM proteins. For example, in tubular epithelial cells exposed to high glucose, Exendin-4 reduced TGF-β-induced fibronectin and COL1A1 expression and decreased secretion of the microRNA miR192, which is implicated in kidney fibrosis, pro-fibrotic microRNA-192, a mediator implicated in renal fibrosis [59]. Similarly, in mesangial cells, GLP-1 receptor agonists have been shown to suppress either high-glucose-induced or AGEs-induced pro-fibrotic signalling pathways, including NF-κB activation and TGF-β1 expression, leading to reduced ECM deposition [60,61], and to suppress their proliferation via AMPK activation [62].

Collectively, while clinical trials of GLP-1 receptor agonists consistently demonstrate renoprotective effects, these studies have not directly assessed renal fibrosis. By contrast, preclinical *in vivo* and *in vitro* studies both indicate that incretin receptor agonism can attenuate fibrogenic signalling in models of kidney disorders, and thus the positive clinical trial data on kidney function outcome measures may, in part, be mediated by inhibition of fibrosis.

3.4. Pulmonary Fibrosis

Fibrosis of the lung disrupts alveolar architecture and impairs gas exchange, representing a central pathological feature of fibrotic interstitial lung diseases. Given the limited efficacy of current anti-fibrotic therapies and the substantial morbidity associated with progressive pulmonary fibrosis, identification of novel pathways capable of modulating fibroblast activation and ECM remodelling remains a major therapeutic priority. In this context, interest has emerged in incretin receptor agonists as potential modulators of pulmonary fibrotic pathways, although the supporting evidence remains preliminary.

Clinical data directly evaluating the impact of incretin receptor agonists on pulmonary fibrosis are limited. In a meta-analysis of large randomized controlled trials of GLP-1 receptor agonists in type 2 diabetes, the incidence of pulmonary fibrosis and interstitial lung disease events was lower in treated patients compared with controls, although absolute event rates were extremely low and differences did not

reach statistical significance [63]. A larger meta-analysis encompassing over 77,000 participants similarly reported a reduced overall risk of respiratory diseases with GLP-1 receptor agonist treatment, but pulmonary fibrosis was not analysed as a discrete outcome, and no fibrotic endpoints were prospectively assessed [64]. Importantly, none of these studies incorporated imaging, physiological, or histopathological measures of lung fibrosis, precluding conclusions regarding anti-fibrotic clinical efficacy of GLP-1 agonists in pulmonary fibrosis.

Preclinical *in vitro* evidence for the efficacy of incretin receptor agonists is derived primarily from epithelial, immune, and vascular cellular models rather than from direct studies of lung fibroblasts. As such, the data suggest that incretin receptor agonists may modulate cellular pathways that initiate and amplify fibrotic remodelling in the lung. For example, in alveolar macrophages, GLP-1 receptor agonism suppressed activation of the NLRP3 inflammasome and reduced production of IL-1β [65], an effect in part mediated by the disruption of histone lactylation, a recognised regulator of pro-fibrotic gene expression [65]. In immortalised human airway epithelial cell lines (including bronchial epithelial cells) and human alveolar epithelial–like cells, GLP-1 receptor agonists reduced epithelial stress and inflammatory signalling, including downregulation of epithelial-derived cytokines, including IL-33 and thymic stromal lymphopoietin (TSLP), both of which are implicated in epithelial–mesenchymal crosstalk and fibroblast recruitment in fibrotic lung disease [66–68]. Additionally, liraglutide and exendin-4 inhibited platelet-derived growth factor BB (PDGF-BB)-mediated proliferation and migration of pulmonary artery smooth muscle cells [69,70].

In vivo, studies directly modelling pulmonary fibrosis remain sparse and have shown converse results. In murine models of bleomycin-induced lung injury, genetic deletion of the GLP-1 receptor was associated with reduced inflammatory injury, and pharmacological GLP-1 receptor activation exacerbated pulmonary inflammation [71]. In contrast, multiple rodent pulmonary hypertension models demonstrate that GLP-1 receptor agonists, including exendin-4 and liraglutide, reduce vascular remodelling, inflammation, and ventricular hypertrophy via endothelial nitric oxide signalling and suppression of endothelin-1 pathways [68,69,72,73]. Furthermore, a recent study using a dual-sensitive, gelatin-coated chitosan microparticle formulation for pulmonary delivery of semaglutide significantly attenuated bleomycin-induced lung fibrosis *in vivo*, with reductions in inflammatory signalling (TLR4/NF-κB), fibrogenic mediators (TGF-β1, p-SMAD3), and markers of ECM deposition α-SMA and Col1a1 [74].

In summary, evidence supporting a therapeutic role for incretin receptor agonists in pulmonary fibrosis is promising but inconclusive. Clinical studies suggest a favourable respiratory safety profile and a possible reduction in fibrotic events, but lack fibrosis-specific endpoints. Preclinical data indicate modulation of inflammatory and pro-fibrotic signalling pathways relevant to lung fibrosis, yet direct demonstration of reduced fibroblast activation or collagen deposition in established pulmonary fibrosis models is currently lacking. Therefore, further targeted *in vivo* and human-relevant mechanistic studies are required to determine whether incretin receptor agonism can meaningfully modify fibrotic progression in pulmonary disease.

3.5. Osteoarthritis and Synovial Joint Fibrosis

The potential for incretin receptor agonists as therapeutics for disease modification and/or pain in OA is supported by epidemiology and by both clinical and preclinical studies, which suggest direct and indirect mechanisms of efficacy. Firstly, epidemiologically, obesity is an established risk factor for the development of OA; individuals with obesity are 3–5 times more likely to develop OA [75], and most OA patients undergoing total joint replacement surgery for end-stage OA have obesity or are overweight [76].

In clinical studies, once-weekly administration of the GLP-1 agonist semaglutide in knee OA patients with obesity reduced patient-reported pain scores (WOMAC) over 68 weeks compared with placebo. With both groups receiving counselling on physical activity and a reduced calorie diet [77]. Furthermore, a retrospective analysis of a Chinese cohort of knee OA patients with type 2 diabetes, those patients who had

been prescribed a GLP-1 agonist (including liraglutide, semaglutide or other), exhibited reduced cartilage volume loss after 2 years, compared to those patients who had not been prescribed a GLP-1 agonist [78]. Given that both of these studies were in patients with OA of the knee (a load-bearing joint), it is likely that a significant proportion of the efficacy observed was due to the significant loss of body weight, reducing pathological joint loading. Indeed, diet-induced weight loss in knee or hip OA patients has previously been shown to slow disease progression, improve joint function, and reduce joint pain [79]. Furthermore, the reduction in adipose tissue mass likely reduced obesity-associated systemic inflammation by reducing the release of pro-inflammatory adipokines, which can drive cartilage degeneration [80] and abnormal subchondral bone remodelling [81].

However, emerging evidence suggests that incretin receptor agonists may also have direct effects on the activity of diseased synovial joint cells. Historically, OA was considered purely a "wear and tear" degenerative disease of the cartilage. However, in recent years, it has been increasingly recognised as a disease involving significant synovial inflammation (synovitis) [82,83]. In OA, the synovial joint lining tissue (synovium) undergoes a fibrotic transformation, with TGF-β a key regulator driving an influx of inflammatory immune cells and the activation of resident synovial fibroblasts. Latent and active forms of TGF-β are detected in OA synovial fluid [84], but are present at much lower levels, or are undetectable, in healthy non-arthritic synovial fluid [85]. Intra-articular injection of C57Bl/6 mice with an adenovirus vector overexpressing active TGF-β [86] or repeated in-articular injections of recombinant TGF-β induced hyperplasia of synovium with increases in inflammatory immune cells, including macrophages [87]. Interestingly, the activated fibroblast phenotype, which is more proliferative and pro-inflammatory, is particularly pronounced in OA patients with obesity [88–90], even in non-load bearing joints *i.e.*, hands [91]. This inflammatory synovial fibroblast phenotype exacerbates cartilage degeneration, via the induction of matrix metalloproteases (MMPs) and aggrecanases (ADAMTS4/5), and sensitises the growth and activity of joint nociceptors [92–94]. Thus, synovial fibrosis is likely a central mediator of both progression in the loss of joint integrity, and patient's perception of joint pain.

Critically, preclinical evidence supports direct benefits of incretin receptors in modulating OA synovial fibrosis. *In vivo*, in a murine monoiodoacetate (MIA)-induced model of OA, a single intra-articular injection of liraglutide reduced synovitis severity, whilst weekly intra-articular injections attenuated behaviour pain responses [95]. Importantly, no difference in weight was observed between the liraglutide and vehicle control groups. In a rat MIA model, Que et al. [96] found that sub-cutaneous administration of for 28 days liraglutide reduced pro-inflammatory cytokines in cartilage, whilst in a surgically induced (ACL transection) rat model of OA, subcutaneous Liraglutide reduced histological signs of cartilage degradation [97].

These findings are supported by *in vitro* studies using either murine or human cells. Predominantly, these studies have been conducted in chondrocyte cells rather than synovial fibroblasts. Nevertheless, the available data indicate that incretin receptor agonism exerts direct immunomodulatory effects, which would be expected to reduce synovial inflammation and fibrosis. In rodent primary chondrocytes, Liraglutide inhibited AGEs- or IL-1β-induced expression and release of pro-inflammatory cytokines, including iNOS, TNF-α and IL-6 [95,98]. Similarly, in the human chondrocyte SW1353 cell line, dulaglutide inhibited AGEs-induced activation of NFkB and the expression of pro-inflammatory cytokines [99], whilst in human knee OA primary articular chondrocytes, lixisenatide reduced mRNA ad protein expression of TNF-α, IL-6 and IL-7 [100].

Therefore, incretin receptor agonists likely exert a multimodal therapeutic effect in OA. Although substantial weight loss can reduce pathological joint loading and systemic inflammation, the direct pharmacological effects on synovial fibroblasts—attenuating their inflammatory signalling and fibrotic activation may offer an additional, disease-modifying and analgesic mechanism that targets the local synovial environment, driving pain and structural progression. Collectively, these findings provide a strong

rationale for the therapeutic repurposing of incretin receptor agonists to address the unmet clinical need for treatments that modify disease and alleviate joint pain in OA patients.

4. Conclusions and Future Perspectives

The collective evidence positions incretin receptor agonists as a unique class of drugs with multi-organ anti-fibrotic potential, now extending to fibro-inflammatory diseases like osteoarthritis. Their ability to target both direct (TGF-β inhibition) and indirect (metabolic, inflammatory) drivers of fibrosis may provide a powerful, synergistic therapeutic approach. However, key knowledge gaps remain. The relative contributions of the direct effects of incretin receptor agonists on fibrosis versus the secondary effects of weight loss and systemic reductions in inflammation remain to be delineated. It is also unclear if specific incretin receptor agonists, for example selective GIP receptor and GLP-1 receptor agonists will possess different efficacies across tissue types.

A critical challenge for future clinical studies will be the robust assessment of treatment effects on in situ fibrosis. Across organ systems, this will require incorporation of validated imaging modalities and circulating or tissue-based biomarkers of fibrogenesis and matrix turnover. In liver disease, non-invasive approaches such as transient elastography, magnetic resonance elastography (MRE), and serum fibrosis panels (e.g., ELF score, Pro-C3) can be readily applied in incretin-based trials. In cardiovascular disease, emerging cardiac MRI techniques, including T1 mapping and extracellular volume fraction, offer quantitative assessment of myocardial fibrosis, while circulating collagen turnover markers may provide complementary information. In chronic kidney disease, urinary and plasma biomarkers of fibrosis, together with functional MRI approaches, represent promising tools, although further validation is required. In pulmonary fibrosis, high-resolution CT combined with quantitative imaging analysis and circulating markers of epithelial injury and matrix remodelling may enable the detection of fibrotic change. In OA, contrast-enhanced MRI, ultrasound-based assessment of synovitis, and synovial fluid or serum biomarkers of fibrosis and inflammation could be leveraged to directly assess changes in synovial fibro-inflammatory pathology. Integration of such modalities into future trials will be essential to distinguish true anti-fibrotic effects from indirect improvements driven by weight loss or systemic metabolic changes.

Future research should focus on designing clinical trials that use fibrosis regression or synovitis reduction as primary endpoints in diseases like osteoarthritis, employing advanced imaging or histological techniques. Additional priorities include evaluating incretin receptor agonists in fibrotic diseases where diabetes is not a major comorbidity, such as idiopathic pulmonary fibrosis or in osteoarthritis; exploring combination therapies with other anti-fibrotic or specific disease-modifying drugs; and deepening mechanistic investigations to clarify direct mechanisms of incretin receptor signalling in fibroblasts and immune cells across different tissue types.

In conclusion, preclinical and emerging clinical evidence are changing the paradigm, viewing incretin receptor agonists solely as metabolic-based therapeutics for treating obesity and diabetes to recognising them as multifaceted agents with significant disease-modifying potential for inflammatory fibrotic disorders across different organ systems. By exerting direct effects that modulate key pro-fibrotic pathways and reduce drivers of inflammation, incretin receptor agonists offer a promising approach for treating a broad spectrum of fibrotic and fibro-inflammatory disorders.

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