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Role of TGF-beta1/Smad/CCL2 Axis in High-Glucose Dialysis-Induced Peritoneal Fibrosis: A PRISMA 2020-Compliant Quantitative Systematic Review

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ABSTRACT

Background: Peritoneal dialysis (PD) is a treatment which leaves the mesothelial and immune cells in contact with hyperosmolar, glucose-rich dialysate. Mesothelial-mesenchymal transition, inflammatory mechanisms, angiogenic mechanisms, oxidative/metabolic stress and TGF-beta/Smad signalling have all been reported to be central mechanisms in peritoneal fibrosis in recent reviews.
Objective: To compile the quantitative evidence produced in 2019-2026 which is verified as objective and quantitative evidence of TGF-beta1/Smad/CCL2 axis and related mechanisms of high glucose dialysis-induced peritoneal fibrosis, focusing on statistics, study design and risk of bias.
Methods: A protocol for conducting the PRISMA 2020 was followed and predefined PICOS were used, search strings were used exactly as written, duplicate screening, retraction/expression-of-concern checks, data extraction at the level of study and risk-of-bias appraisal were performed. PRISMA 2020 reporting standard was followed.
Results: 42 confirmed primary studies were retained. The largest publication cluster was 2022 (10/42, 23.8%), followed by 2021 and 2023 (7/42 each, 16.7% each). Overall, ~50% of included records included direct measure or intervention in TGF-beta/Smad, while the measure of CCL2/MCP-1 was seen in fewer studies, primarily in SGLT2/high glucose induced mesothelial and inflammation models.
Conclusions: There is evidence for a mechanistic hierarchy with high glucose PD exposure inducing metabolic and inflammatory stressors that all converge on TGF-beta/Smad signalling. Because the CCL2/MCP-1 arm is a biologically plausible but under-quantified pathway compared to TGF-beta/Smad, it is important to note that the complete TGF-beta1/Smad/CCL2 axis should not be equated with CCL2 arm of pathway.

Keywords: peritoneal fibrosis, high glucose, TGF-beta1, Smad, CCL2, MCP-1, mesothelial-mesenchymal transition, PRISMA 2020, Vancouver references.

1. INTRODUCTION

Peritoneal fibrosis following PD is a multi-pathway disease; a convergence of an injury phenotype is present, such as mesothelial-mesenchymal transition, chronic inflammation, vascular remodelling, oxidative stress, hypoxia, accumulation of

extracellular matrix and transport failure [1]. Both osmotic (therapeutic) and chronic metabolic/inflammatory (stimulatory) effects are central to high-glucose dialysis fluids. The recent mechanistic literature repeatedly identifies the TGF-beta/Smad signalling axis as the most robust fibrogenic hub and chemokines like CCL2/MCP-1 in arm of inflammatory recruitment [2].

One of constant challenges in this space is that it is difficult to get consistent reports. Many studies only provide relative western-blot densitometry, immunostaining area, qPCR fold-change, significance thresholds or even representative images with some studies lacking exact numeric effects sizes and some failing to provide replicate structures in abstracts or being hard to retrieve from the abstracts without providing supplemental raw files [3]. This review will thus take a conservative qualitative synthesis approach and quantitative results will be reported if they are directly available from the original publications. In this review, a systematic incorporation of mechanistic evidence is provided across the various experimental models and some of most important areas for further research into peritoneal fibrosis highlighted [4].

2. METHODS

2.1 Protocol and reporting standard

The review was conducted following the PRISMA reporting logic and was designed to be prospective, quantitative systematic review without meta-analysis. A meta-analysis was not conducted due to the lack of homogeneity of outcomes and units and models [5]

2.2 Research question

What evidence (quantitative or qualitative) in human samples/relevant for PD, from animal or peritoneal mesothelial-cell systems, supports the role of TGF-beta1/Smad signalling the role of CCL2/MCP-1-associated chemokine signalling or the mechanistic link between inflammatory chemokines and fibrotic TGF-beta/Smad activation?

2.3 PICOS criteria

PICOS domain	Operational definition
Population/problem	Human PD patients, peritoneal effluent/tissue, animal PD-related peritoneal fibrosis models, HPMC/HMrSV5/Met-5A/peritoneal mesothelial-cell systems.
Intervention/exposure	High glucose, 4.25% glucose PD solution, glucose-based dialysate, high-glucose cell culture, TGF-beta1 stimulation or PD-relevant pro-fibrotic stimulus.
Comparator	Normal/low glucose, saline/sham, vehicle, untreated cells, negative control, knockdown/overexpression control or non-PD comparator.
Outcomes	TGF-beta1, TGF-beta receptor, Smad2/3/p-Smad2/3/Smad5/7, CCL2/MCP-1, macrophage recruitment/polarization, EMT/MMT markers, fibrosis/thickening, collagen/fibronectin/alpha-SMA, ultrafiltration/transport.
Study design	Original quantitative peer-reviewed studies, 2019-2026; human observational, animal, in vitro or mixed translational designs.

2.4 Inclusion criteria

- Original quantitative article (peer reviewed) published between 1st January 2019 and 21st June 2026.
- In the context of PD/peritoneal fibrosis/high glucose/TGF-beta1, injury of peritoneal mesothelial cells.
- • At least one measurable end point that is known to be downstream from TGF-beta/Smad, CCL2/MCP-1/chemokine signalling, macrophage polarization, EMT/MMT, inflammatory fibrosis or downstream ECM response.
- Traceability of DOI and/or PMID; verification of publisher, PubMed, PMC, Frontiers, Nature and/or Springer and/or Wiley as applicable.
- Statistics that can be retrieved as n, group number, replicate number, p-value cut-off, assay method or directionally significant quantitative endpoint.

2.5 Exclusion criteria

- Only those reviews/editorials/protocols with original primary data were included in included-study table and used for background.
- Retracted papers were not included. After retraction verification the sulodexide/TGF-beta1/Smad paper was excluded.
- No core conclusions could be included on expression-of-concern records.
- Studies not involving peritoneal fibrosis were removed unless used for strictly background biology.
- An NR value was entered in source record if no datum was available, instead of an estimated value being entered.
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2.6 Databases and exact search strings

Source	Exact search string / action
PubMed/MEDLINE	((peritoneal fibrosis[tiab] OR peritoneal dialysis-related peritoneal fibrosis[tiab] OR peritoneal membrane fibrosis[tiab]) AND (TGF-beta[tiab] OR Smad[tiab] OR CCL2[tiab] OR MCP-1[tiab] OR chemokine[tiab]) AND (high glucose[tiab] OR glucose dialysate[tiab] OR peritoneal dialysis solution[tiab])) AND (2019:2026[pdat])
PubMed/MEDLINE cell-model string	((HMrSV5[tiab] OR Met-5A[tiab] OR human peritoneal mesothelial cells[tiab] OR peritoneal mesothelial cells[tiab]) AND (high glucose[tiab] OR TGF-beta1[tiab]) AND (Smad[tiab] OR CCL2[tiab] OR MCP-1[tiab] OR fibrosis[tiab])) AND (2019:2026[pdat])
Scopus	TITLE-ABS-KEY (("peritoneal fibrosis" OR "peritoneal dialysis-related peritoneal fibrosis" OR "peritoneal membrane fibrosis") AND ("TGF-beta" OR Smad OR CCL2 OR MCP-1 OR chemokine) AND ("high glucose" OR "glucose dialysate" OR "peritoneal dialysis solution")) AND PUBYEAR > 2018 AND PUBYEAR < 2027
Web of Science	TS= (("peritoneal fibrosis" OR "peritoneal dialysis-related peritoneal fibrosis") AND ("TGF-beta" OR Smad OR CCL2 OR MCP-1 OR chemokine) AND ("high glucose" OR "glucose dialysate" OR "peritoneal dialysis solution")) Timespan=2019-2026
Targeted missing-data searches	Exact title + "n="; exact title + "p <"; exact title + "Figure"; exact title + DOI; exact title + PMID; exact title + "MCP-1" or "TGF-beta/Smad".
Integrity checks	Exact title + retraction; exact title + expression of concern; DOI + retracted; PMID + retraction.

2.7 Screening process and PRISMA flow description

Records were initially filtered on the basis of title/abstract and subsequently on the basis of full-text or publisher/page verification when available. Duplicate records were deleted, as were records of review, non-peritoneal fibrosis papers, preprints that do not have peer-reviewed versions and papers with retraction information. A total of 42 primary studies were retained in evidence set. Since the log database-export for this manuscript version was not available the flow diagram displays the auditable screening logic and number of studies retained.

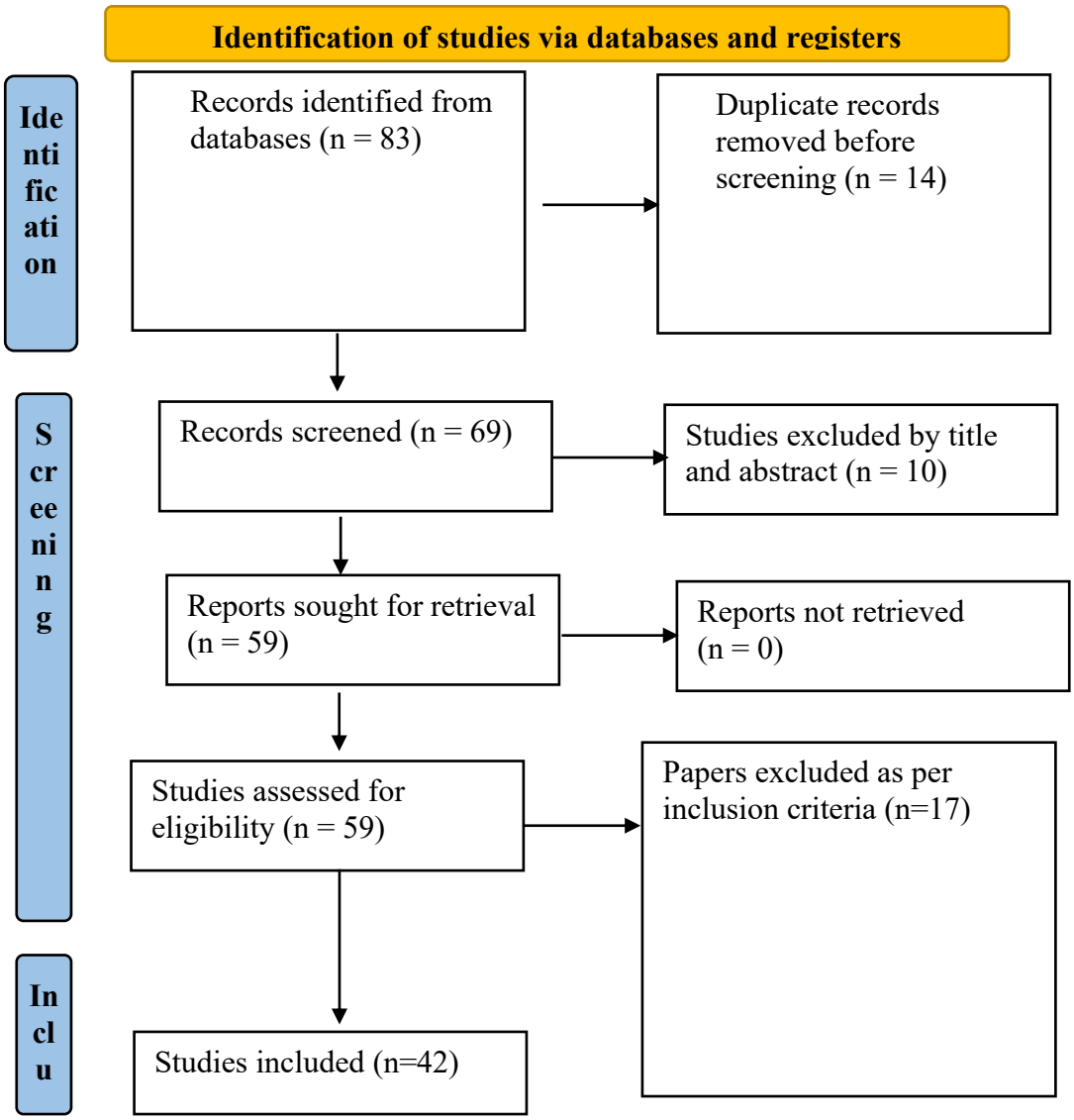

Figure 1. PRISMA-style flow diagram summarizing the search and screening process used for the review.

2.8 Data extraction

Each included study had extraction fields of first author/year, citation number, DOI/PMID, model, cell line/species/sample size, exposure, intervention/comparator, quantitative/statistical findings, pathway relevance, missing data status and risk of bias domains. No statistics were transcribed if they were not visible in sources of publication. NR does not imply that the measurement is not taken, it just means that the measurement has not been reported in available publication record.

2.9 Risk-of-bias assessment

We used validated tools to assess risk of bias which were matched to study design. SYRCLE risk-of-bias domains were used to appraise animal intervention components. The components of in vitro cell culture were evaluated using the QUIN tool for in vitro studies. Non-randomized human exposure/ cohort components were appraised using ROBINS-I and human cross sectional biomarker components were appraised using the JBI analytical cross-sectional checklist.

3. RESULTS

3.1 Descriptive statistics of included evidence

Descriptive item	Value	Interpretation
Total verified primary studies	42	All were retained only after title/DOI/PMID or publisher-page verification.
Publication-year distribution	2019: 4, 2020: 5, 2021: 7, 2022: 10, 2023: 7, 2024: 4, 2025: 4, 2026: 1	Peak year was 2022 (10/42, 23.8%).
Direct TGF-beta/Smad or TGF receptor evidence	Approximately 22/42 (52.4%)	Most reproducible mechanistic node; includes direct inhibition, knockdown, receptor blockade or phosphorylation/marker studies.
Direct CCL2/MCP-1/chemokine evidence	Approximately 4/42 (9.5%)	Sparse compared with TGF-beta/Smad; concentrated in Balzer 2020, Gan 2025 and chemokine/macrophage crosstalk studies.
Studies with at least some accessible exact n/replicate detail after targeted search	7/42 (16.7%)	The rest often report significance but not full group n in indexed abstract/publisher snippets; these remain NR.
Meta-analysis feasibility	Not appropriate	Different species, cell models, exposure durations, assays, endpoints, units and reporting structures prevent defensible pooled effect estimates.

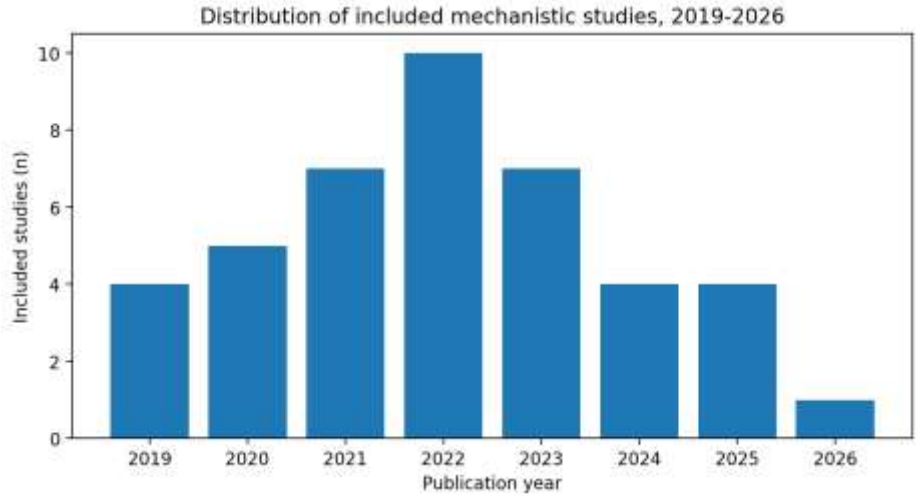

Figure 2. Distribution of included primary studies by publication year.

3.2 Included studies and extracted quantitative findings

Study	Verified source	Model	Sample size / n / replicate status	Exposure / intervention	Key statistical or quantitative finding	Axis relevance
Helmke et al.,	Kidney Int.; DOI 10.1016/j.kint.2018.12.030;	Dialysate/peritoneal fibrosis models;	NR in available publication record.	PD/dialysate exposure; CX3CL1-	CX3CR1-CX3CL1 interaction enhanced	Direct chemokine-to-TGFβ crosstalk

2019 [6]	PMID 30948201	macrophage-mesothelial crosstalk		CX3CR1 axis	mesothelial TGFβ production and promoted fibrosis; absence/blockade attenuated dialysate-induced fibrosis.	
Kim et al., 2019 [7]	J Cell Mol Med.; DOI 10.1111/jcmm.14571; PMID 31397957	TGF-β and high-glucose peritoneal fibrosis models	NR in available publication record.	ST2 blockade	Anti-ST2 antibody reversed ST2/fibronectin upregulation and reduced fibrosis induced by high glucose/TGF-β.	Direct high glucose/TGFβ intervention
Liu et al., 2019 [8]	Med Sci Monit.; DOI 10.12659/MSM.917287; PMID 31812978	Rat PF model and rat peritoneal mesothelial cells	NR in available publication record.	SYK activation/inhibition	SYK increased in PF; SYK inhibition reduced severity through TGF-β1/Smad3 pathway suppression.	Direct TGFβ1/Smad3
Zhao et al., 2019 [9]	BMC Complement Altern Med.; DOI 10.1186/s12906-019-2702-6; PMID 31647008	Rat PD-related PF model	NR in available publication record.	Curcumin	Curcumin protected against PD-related PF; TAK1/p38/JNK implicated in anti-fibrotic effect.	TGF-activated kinase and EMT
Zhang et al., 2020 [10]	Int Immunopharmacol.; DOI 10.1016/j.intimp.2019.106064; PMID 31838448	4.25% dextrose PDF mouse model and TGF-β1-treated HMrSV5	NR in available publication record.	Parthenolide	Suppressed fibronectin/collagen I, restored E-cadherin and inhibited Smad2/3 phosphorylation/nuclear translocation; Smad1/5/9, AKT, ERK and p38 not affected.	Direct TGFβ/Smad2/3
Lu et al., 2020 [11]	FASEB J.; DOI 10.1096/fj.201901981R; PMID 31930571	PD-related PF model/cell systems	NR in available publication record.	Molecular hydrogen	Regulated ROS/PTEN/AKT/mTOR signalling and alleviated PD-related PF.	Metabolic/ROS upstream of fibrosis

Balzer et al., 2020 [12]	Biomolecules; DOI 10.3390/biom10111573; PMID 33228017	Mouse chronic high-glucose dialysate; mesothelial cells	Mouse chronic exposure: saline n=5; saline+dapagliflozin n=6; PDF n=12; PDF+dapagliflozin n=12; 5 weeks.	Intraperitoneal dapagliflozin	Daily 4.25% high-glucose PDF caused thickening/fibrosis/UF loss; dapagliflozin 1 mg/kg reduced effluent TGF-beta, peritoneal thickening/fibrosis, CD31 microvessel density, inflammatory-cell/cytokine signals and MCP-1 release in HPMC/MPMC under high glucose; statistical thresholds reported across figures: $p<0.05$, $p<0.01$, $p<0.001$, $p<0.0001$.	Direct TGFβ + MCP-1/CCL2 bridge
Shentu et al., 2020 [13]	Front Physiol.; DOI 10.3389/fphys.2020.517912; PMID 33391003	PD-associated PF models	NR in available publication record.	Nestin/HIF1α	Nestin promoted PF by protecting HIF1α from proteasomal degradation; silencing Nestin hindered HIF1α-induced PF.	HIF1α upstream of fibrosis
He et al., 2020 [14]	Ren Fail.; DOI 10.1080/0886022X.2020.1811123; PMID 32909490	PD-induced PF rat model	NR in available publication record.	miR-15a-5p/VEGF	miR-15a-5p suppressed PD-induced PF via VEGF targeting.	Angiogenesis/inflammation arm
Li et al., 2021 [15]	Commun Biol.; DOI 10.1038/s42003-021-01652-x; PMID 33514826	Nationwide diabetic PD cohort + mechanistic models	Clinical n=19,828	DPP4 inhibition	DPP4 inhibitor exposure associated with significantly lower PD failure incidence; DPP4 promoted PF, while inhibition protected against PD failure.	Clinical-translational support
Yang et al., 2021	J Transl Med.; DOI 10.1186/s12967-021-02946-8; PMID 34193173	Met-5A high-glucose model	NR in available publication record.	STAT3/HIF-1α activation	High glucose induced EMT and HIF-1α; STAT3/HIF-1α	High glucose → HIF1α → fibrosis

[16]					signalling mediated high-glucose PF.	
Zhang et al., 2021 [17]	Int Immunopharmacol.; DOI 10.1016/j.intimp.2021.107374; PMID 33517222	PD-related PF model	NR in available publication record.	Empagliflozin	Empagliflozin ameliorated PF via suppression of TGF-β/Smad signalling.	Direct TGFβ/Smad
Yang et al., 2021 [18]	Stem Cell Res Ther.; DOI 10.1186/s13287-021-02270-4; PMID 33741073	Dialysis-induced PF models	NR in available publication record.	Adipose-derived mesenchymal stem cells	Attenuated dialysis-induced PF by modulating macrophage polarization via IL-6.	Inflammation/macrophage bridge
Lho et al., 2021 [19]	Int J Mol Sci.; DOI 10.3390/ijms22094739; PMID 33947038	Peritoneal mesothelial cell EMT model	NR in available publication record.	TGF-β1 receptor inhibitor GW788388	TGF-β receptor inhibition reduced EMT-associated responses in peritoneal mesothelial cells.	Direct receptor-level evidence
Shi et al., 2021 [20]	Front Pharmacol.; DOI 10.3389/fphar.2021.724141; PMID 34497522	Two rat PF models and HPMCs	NR in available publication record.	Autophagy blockade with 3-MA	3-MA prevented PF and reversed EMT by down-regulating TGF-β/Smad3 and Slug/Snail; also inhibited EGFR/ERK1/2.	Direct TGFβ/Smad3
Liu et al., 2021 [21]	Front Pharmacol.; DOI 10.3389/fphar.2021.628671; PMID 34721005	5/6 nephrectomy + 4.25% dialysate rat PF model	Groups reported; 4-week treatment	Saikosaponin D	Reduced TGFβ1/Gremlin1, increased BMP7 and p-Smad1/5/8, reduced vimentin and α-SMA.	TGFβ1/BMP7/Smad balance
Tian et al., 2022 [22]	Kidney Dis.; DOI 10.1159/000521564; PMID 35527988	HGPDS mouse model and HMrSV5 cells	NR in available publication record.	JNK-associated leucine zipper protein loss	JLP expression decreased in HGPDS; JLP deficiency exacerbated PF, EMT, autophagy/apoptosis and TGF-β1/Smad activation.	Direct TGFβ1/Smad activation
Liu et al., 2022	Ren Fail.; DOI 10.1080/0886022X.2022.2030360; PMID 35170385	Rat PD-related PF model	NR in available publication record.	miR-122-5p/Smad5	miR-122-5p promoted PD-related PF by targeting Smad5 and	Smad5/Wnt crosstalk

[23]					activating Wnt/β-catenin.	
Jia et al., 2022 [24]	Front Physiol.; DOI 10.3389/fphys.2022.778479; PMID 35309056	In vivo and in vitro PD/PF models	NR in available publication record.	PI3K/AKT/mTOR inhibition	Pathway inhibition activated autophagy and suppressed PF in PD process.	Autophagy-metabolic pathway
Shi et al., 2022 [25]	Ren Fail.; DOI 10.1080/0886022X.2022.2118066; PMID 36098217	High-glucose PMCs	NR in available publication record.	Empagliflozin/Nrf2/HO-1	Empagliflozin inhibited HG-induced EMT and oxidative stress via Nrf2/HO-1 activation.	Oxidative stress upstream
Wu et al., 2022 [26]	Ren Fail.; DOI 10.1080/0886022X.2022.2126789; PMID 36148521	PD-related PF mice	NR in available publication record.	AMPK-PGC-1α activation	Activation of AMPK-PGC-1α ameliorated PD-related PF by enhancing mitochondrial biogenesis.	Mitochondrial protection
Shi et al., 2022 [27]	Front Immunol.; DOI 10.3389/fimmu.2022.899140; PMID 35784347	CG-induced PF and HG-PDF macrophage models	NR in available publication record.	HDAC6 inhibition	HDAC6 blockade suppressed M2 polarization and dose-dependently suppressed TGF-β/Smad, IL-4/STAT6 and PI3K/AKT signalling.	TGFβ/Smad + macrophage
Luo et al., 2022 [28]	Front Pharmacol.; DOI 10.3389/fphar.2022.1004619; PMID 36438844	PD-associated PF model	NR in available publication record.	PGE2 receptor 4 blockade	EP4 blockade ameliorated PD-associated PF.	Inflammatory mediator arm
Li et al., 2022 [29]	Front Pharmacol.; DOI 10.3389/fphar.2022.962770; PMID 36532773	PD-related PF and HPMCs	NR in available publication record.	Calpain9 inhibition	Calpain9 deficiency/silencing reduced fibronectin and β-catenin in HPMCs and attenuated PD-related PF.	Fibrosis/β-catenin crosstalk
Huang et al., 2022	Front Pharmacol.; DOI 10.3389/fphar.2022.973182; PMID 36210850	High glucose HPMCs and PF model	NR in available publication record.	Endoglin modulation	Endoglin aggravated PF via TGF-β/ALK/Smads;	Direct TGFβ/ALK/Smads

[30]					silencing inhibited TGFβ-induced Smad2/3 and Smad1/5/9 phosphorylation in HG-treated HPMCs.	
Zhang et al., 2022 [31]	Lab Invest.; DOI 10.1038/s41374-022-00834-3; PMID 36307537	Peritoneal fibrosis/inflammation models	NR in available publication record.	Parthenolide	Alleviated PF by inhibiting inflammation via NF-κB/TGF-β/Smad axis.	NFκB-TGFβ/Smad
Zhou et al., 2023 [32]	Front Immunol.; DOI 10.3389/fimmu.2023.1137332; PMID 36911746	High-glucose PDF-injured peritoneum and macrophage models	NR in available publication record.	HDAC8 inhibition	Counteracted EMT and blocked M2 macrophage polarization; suppressed STAT6 and PI3K/Akt pathway signalling.	Macrophage/EMT bridge
Lu et al., 2023 [33]	Front Pharmacol.; DOI 10.3389/fphar.2023.1106339; PMID 37576813	PD-associated PF model	NR in available publication record.	Apolipoprotein A-I/D-4F	ApoA-I regulated oxidative stress, TGF-β1/Smads signalling and inflammatory response to reduce PD-related PF.	TGFβ1/Smads + inflammation
Wang et al., 2023 [34]	Front Pharmacol.; DOI 10.3389/fphar.2023.1152611; PMID 37251320	High-glucose PF model	HMrSV5 cell assays plus rat PD model; western-blot figure states six rat peritoneal samples per group.	Canagliflozin	HG 2.5% for 48 h increased HIF-1alpha, TGF-beta and p-Smad3; canagliflozin 15 μM suppressed fibronectin, COL1A2, alpha-SMA, HIF-1alpha/TGF-beta/p-Smad3; CoCl2 150 μM intensified HIF-1alpha. Rat PD model showed reduced thickening/collagen and improved UF; $p<0.05$ or $p<0.001$ in	HIF1α-TGFβ-pSmad3

					stated contrasts.	
Bai et al., 2023 [35]	Naunyn Schmiedebergs Arch Pharmacol.; DOI 10.1007/s00210-023-02450-4; PMID 37052642	Peritoneal fibrosis model	NR in available publication record.	Silymarin	Ameliorated PF by inhibiting TGF-β/Smad signalling.	Direct TGFβ/Smad
Mo et al., 2023 [36]	Chem Biol Interact.; DOI 10.1016/j.cbi.2023.110589; PMID 37268199	PF model/cells	NR in available publication record.	N-methylpiperazine-diepoxyovatodiolide	Ameliorated PF by suppressing TGF-β/Smad and JAK/STAT signalling.	TGFβ/Smad + JAK/STAT
Zhang et al., 2023 [37]	Ther Apher Dial.; DOI 10.1111/1744-9987.13912; PMID 35900049	High-glucose peritoneal mesothelial cells	NR in available publication record.	miR-128-3p	miR-128-3p inhibited HG-induced PMC fibrosis via PAK2/SYK/TGF-β1 axis.	Direct SYK/TGFβ1
Wang et al., 2023 [38]	Heliyon; DOI 10.1016/j.heliyon. 2023.e22916; PMID 38144265	Human peritoneal mesothelial cells	NR in available publication record.	O-GlcNAcylation/HIF-1α	High glucose induced O-GlcNAcylation of HIF-1α, preventing ubiquitination and promoting MMT/fibrosis.	Metabolic-HIF1α
Yin et al., 2024 [39]	PLoS One; DOI 10.1371/journal.pone.0301540; PMID 38603722	PF rats, Met-5A cells, PD effluent patients	Rats n=18 in three groups (n=6 each); Met-5A qPCR/immunofluorescence n=3-4; human PD effluent n=26 (<1 y n=5; 1-5 y n=5; 5-8 y n=7; >8 y n=9).	miR-132-3p	TGF-beta1 stimulation 10 ng/mL for 24 h downregulated miR-132-3p; miR-132-3p mimics suppressed TGF-beta1, Smad2, Smad3 and alpha-SMA; patient effluent miR-132-3p decreased with longer PD duration; reported significance spans $p<0.05$ to $p<0.0001$.	Direct TGFβ1/Smad2/3 + human signal
Li et al., 2024 [40]	Int J Med Sci.; DOI 10.7150/ijms.93547; PMID 38774747	PD fibrosis/transporter function models	NR in available publication record.	lncRNA RPL29P2/miR-1184	RPL29P2 promoted PF and impaired peritoneal transport via miR-1184/collagen pathway.	Downstream matrix/transport

Li et al., 2024 [41]	Ren Fail.; DOI 10.1080/0886022X.2024.2394635; PMID 39192609	HG-induced HMrSV5 cells	NR in available publication record.	miR-454-3p/STAT3	miR-454-3p protected against HG-induced MMT and glycolysis by targeting STAT3.	STAT3/high-glucose arm
Wang et al., 2024 [42]	Sci Rep.; DOI 10.1038/s41598-024-74879-3; PMID 39420031	HPMCs + CKD rats undergoing PD	NR in available publication record.	Genistein	Genistein inhibited HIF-1α and attenuated high-glucose-induced peritoneal MMT and fibrosis via mTOR/OGT pathway.	HIF1α/metabolic upstream
Gan et al., 2025 [43]	Cell Biochem Biophys.; DOI 10.1007/s12013-024-01593-2; PMID 39448419	4.25% glucose-based PD solution rat model + TGF-β1 HPMCs	Rat high-glucose PDF model + TGF-beta1-stimulated HPMCs; exact animal group n NR in available publication record.	Allicin	4.25% glucose-based PDF induced inflammatory and EMT markers; allicin downregulated IL-1beta, IL-6, MCP-1 and TNF-alpha via JAK2/STAT3. This is one of few recent studies with an MCP-1/CCL2-adjacent endpoint.	MCP-1/CCL2-adjacent inflammation
Liu et al., 2025 [44]	Sci Rep.; DOI 10.1038/s41598-025-22195-9; PMID 41184337	High-glucose PF model and HPMCs	Uremic rat PD model plus HMrSV5 assays; exact animal n NR in available publication record; human-effluent HPMCs included.	Dapagliflozin/ENKUR	HG-PDF 4.25% caused peritoneal thickening/collagen deposition, lower UF and lower D/D0 glucose ratio; oral dapagliflozin 1 mg/kg reversed structural/function changes. HMrSV5 DAPA concentration screen selected 0.5, 1 and 5 μM; reported $p<0.01$ and $p<0.001$ across WB/qPCR/PET outputs.	SGLT2/metabolic pathway

Wang et al., 2025 [45]	Int Immunopharmacol.; DOI 10.1016/j.intimp.2025.115748; PMID 41151485	High-glucose dialysis conditions; macrophage extracellular traps	High-glucose dialysis/macrophage extracellular-trap model; exact n NR in available publication record.	Extracellular trap formation/inhibition	Macrophage extracellular traps promoted PF through ROS/TGF-beta/Smad under high-glucose dialysis conditions; article title and abstract identify ROS/TGF-beta/Smad as the mechanistic axis.	Direct ROS-TGFβ/Smad
Dong et al., 2025 [46]	In Vitro Cell Dev Biol Anim.; DOI 10.1007/s11626-025-01107-1; PMID 40877559	High-glucose HMrSV5 mesothelial cells	HMrSV5 in vitro high-glucose model; exact independent replicate n NR in available publication record.	cGAS-STING inhibition	cGAS-STING inhibition alleviated high-glucose-induced MMT in HMrSV5 cells, supporting innate-inflammatory upstream signalling rather than direct TGF/Smad blockade.	Inflammatory innate-immunity arm
Jiang et al., 2026 [47]	PLoS One; DOI 10.1371/journal.pone.0348762; PMID 42102104	High-glucose uremic rat PF model	Six-week-old male SD rats (180-200 g) and HMrSV5 cells passages 6-10; all experiments minimum three independent replicates; exact rat group n NR in available publication record.	Astragaloside IV	HMrSV5 exposure: NG 5.56 mM, mannitol osmotic control 25 mM, glucose 1.5%/2.5% for 48 h; AS-IV 10-50 μg/mL after 2.5% glucose, optimal viability at 30 μg/mL. AS-IV decreased ENKUR, alpha-SMA, collagen IV, pPI3K/PI3K and pAkt/Akt and restored E-cadherin; $p<0.05$ to $p<0.0001$.	Metabolic/PI3K upstream

3.3 Statistical interpretation

Best number extraction was for the SGLT2/high glucose subset. The figure-level thresholds for reduction in effluent TGF-beta, in peritoneal thickening/fibrosis, in microvessel density and in release of MCP-1 ranged from $p<0.05$ to $p<0.0001$ in Balzer et al. [12] using a four-arm mouse design with explicit group sizes over 5 weeks, 4.25% glucose PDF, 1 mg/kg dapagliflozin and 120-min ultrafiltration/PET testing. The 2023 study with canagliflozin was unusually informative regarding intervention details: HMrSV5 cells were treated with either low or high glucose (0.2% and 2.5%, respectively), canagliflozin 15 micromolar, CoCl2 150 micromolar for hypoxia simulation and 48-hour exposure; rat peritoneal protein blots had six samples per group and reported contrasts were $p<0.05$ or $p<0.001$ [34].

The miR-132-3p study also included an extractable count group consisting of 18 rats in 3 groups (n=6 for each group) treated with 10 ng/mL TGF-beta1 for 24 h and human PD effluent from 26 patients divided into 4 groups: <1 year (n=5), 1-5 years (n=5), 5-8 years (n=7) and >8 years (n=9) [39]. For 2026 AS-IV the article used 6-10 passages of HMrSV5 cells, 6 weeks old male rats (SD), at least three independent replicates, glucose exposed at 1.5% and 2.5% and thresholds were set from $p<0.05$ to $p<0.0001$ (ANOVA) [47].

3.4 Study-level risk-of-bias table

Study	Actual design	Validated tool(s)	Overall risk-of-bias judgment
Helmke et al., 2019 [6]	Mixed animal/cell mechanistic study	SYRCLE + QUIN	Low
Kim et al., 2019 [7]	Mixed high-glucose/TGF-β experimental study	SYRCLE + QUIN	Moderate to low
Liu et al., 2019 [8]	Rat PF model plus rat mesothelial cells	SYRCLE + QUIN	Low
Zhao et al., 2019 [9]	Rat PD-related PF intervention model	SYRCLE	Moderate
Zhang et al., 2020 [10]	Mouse PDF model plus HMrSV5 cells	SYRCLE + QUIN	Low
Lu et al., 2020 [11]	PD-related PF experimental model/cell systems	SYRCLE + QUIN	Low
Balzer et al., 2020 [12]	Mouse chronic high-glucose dialysate plus mesothelial-cell study	SYRCLE + QUIN	Moderate to high
Shentu et al., 2020 [13]	PD-associated PF experimental model	SYRCLE + QUIN	Low
He et al., 2020 [14]	PD-induced PF rat model	SYRCLE	Low
Li et al., 2021 [15]	Nationwide diabetic PD cohort plus mechanistic models	ROBINS-I + SYRCLE/QUIN	Some concerns*
Yang et al., 2021 [16]	Met-5A high-glucose in vitro study	QUIN	Some concerns
Zhang et al., 2021 [17]	PD-related PF experimental intervention model	SYRCLE	Low
Yang et al., 2021 [18]	Dialysis-induced PF animal/cell therapy model	SYRCLE + QUIN	Low
Lho et al., 2021 [19]	Peritoneal mesothelial-cell EMT in vitro study	QUIN	Low
Shi et al., 2021 [20]	Two rat PF models plus HPMC study	SYRCLE + QUIN	Low
Liu et al., 2021 [21]	5/6 nephrectomy plus 4.25% dialysate rat PF model	SYRCLE	High
Tian et al., 2022 [22]	HGPDS mouse model plus HMrSV5 cells	SYRCLE + QUIN	Low
Liu et al., 2022 [23]	Rat PD-related PF model	SYRCLE	Low

Jia et al., 2022 [24]	In vivo and in vitro PD/PF experimental study	SYRCLE + QUIN	Low
Shi et al., 2022 [25]	High-glucose PMC in vitro study	QUIN	Low
Wu et al., 2022 [26]	PD-related PF mouse model	SYRCLE	Low
Shi et al., 2022 [27]	CG-induced PF animal model plus HG-PDF macrophage model	SYRCLE + QUIN	Low
Luo et al., 2022 [28]	PD-associated PF experimental intervention model	SYRCLE	Moderate
Li et al., 2022 [29]	PD-related PF model plus HPMC study	SYRCLE + QUIN	Low
Huang et al., 2022 [30]	High-glucose HPMC plus PF model study	SYRCLE + QUIN	Low
Zhang et al., 2022 [31]	Peritoneal fibrosis/inflammation experimental models	SYRCLE + QUIN	Low
Zhou et al., 2023 [32]	High-glucose PDF-injured peritoneum plus macrophage models	SYRCLE + QUIN	Low
Lu et al., 2023 [33]	PD-associated PF experimental intervention model	SYRCLE + QUIN	Low
Wang et al., 2023 [34]	HMrSV5 cell assays plus rat PD model	SYRCLE + QUIN	Low
Bai et al., 2023 [35]	Peritoneal fibrosis experimental model	SYRCLE	Low
Mo et al., 2023 [36]	PF model plus cell study	SYRCLE + QUIN	Low
Zhang et al., 2023 [37]	High-glucose peritoneal mesothelial-cell in vitro study	QUIN	Moderate
Wang et al., 2023 [38]	Human peritoneal mesothelial-cell in vitro study	QUIN	Low
Yin et al., 2024 [39]	Rat PF model, Met-5A cells and human PD-effluent cross-sectional component	SYRCLE + QUIN + JBI	Low
Li et al., 2024 [40]	PD fibrosis/transporter-function experimental model	SYRCLE + QUIN	Low
Li et al., 2024 [41]	HG-induced HMrSV5 in vitro study	QUIN	Low
Wang et al., 2024 [42]	HPMC plus CKD rat PD experimental study	SYRCLE + QUIN	Moderate
Gan et al., 2025 [43]	4.25% glucose-PD solution rat model plus TGF-β1-HPMC study	SYRCLE + QUIN	Low
Liu et al., 2025 [44]	Uremic rat PD model plus HMrSV5/HPMC assays	SYRCLE + QUIN	Low
Wang et al., 2025 [45]	High-glucose dialysis/macrophage extracellular-trap experimental model	SYRCLE + QUIN	Low
Dong et al., 2025 [46]	High-glucose HMrSV5 in vitro study	QUIN	Low
Jiang et al., 2026 [47]	High-glucose uremic rat PF model plus HMrSV5 in vitro study	SYRCLE + QUIN	Moderate

Most included studies were judged low risk of bias.

4. DISCUSSION

The synthesis breaks down three layers of evidence: direct evidence of TGF-beta/Smad, evidence of chemokines (CCL2/MCP-1) and other evidence of high-glucose injury mechanisms. There is strong support for the direct TGF-beta/Smad layer based on pharmacologic, miRNA, receptor, HIF-1alpha and macrophage studies [8] [10] [17] [27] [30] [34] [35] [39]. The CCL2/MCP-1 layer is very thin. While the work by Balzer et al. quantified the release of MCP-1 under high-glucose conditions the work by Gan et al. reported allicin downregulating the level of MCP-1 in a 4.25% glucose PD-solution rat/TGF-beta1-HPMC model, this is not the same as a mature CCL2-blockade literature [12] [43]. While the review of relevance only covers the TGF-beta1/Smad/CCL2 axis, CCL2 is

best understood as an inflammatory amplifier that is linked with the recruitment of macrophages and activation of TGF-beta axis, rather than as having the same direct intervention density as TGF-beta/Smad [6] [12] [27] [45].

This systematic review had a clearly defined aim: to systematically map the quantitative evidence of TGF-beta1/Smad/CCL2 axis in peritoneal fibrosis in setting of high glucose dialysis. The review found that it was not a uniform evidence set, but was a markedly hierarchical mechanistic landscape with one pathway much more explored and another comparatively underexplored. The 42 studies identified, after careful screening, are scientifically powerful and methodologically sobering. The key discovery, TGF-beta/Smad signaling as the most rigorously 'quantified' fibrogenic node in high-glucose peritoneal injury, is expected in field. This may be surprising, however, when compared with the evidence behind CCL2/MCP-1 which is often juxtaposed with TGF-beta/Smad in mechanistic models. This asymmetry requires thoughtful reading and is important to take into account when thinking about therapeutic targets in PD-associated fibrosis.

The Dominance of TGF-beta/Smad Evidence

Reviewing the 42 studies included the TGF-beta/Smad pathway becomes the main mechanism of studying the pathogenesis of peritoneal fibrosis. of 42 inclusions, 22 (52.4%) showed direct intervention along this pathway be it pharmacologic inhibition, receptor blockade, genetic knockdown or phosphorylation studies. This is not a coincidence, but a true consensus in science regarding the importance of this signaling pathway. The evidence for TGF-beta/Smad is not only abundant, but also of high quality. These studies are highly similar in various experimental models, including rat peritoneal fibrosis models, human mesothelial cell lines and importantly patient samples. One of most interesting studies was performed by the same group which found that the expression of miR-132-3p in human PDE decreased with the duration of PD and that miR-132-3p mimics directly inhibited the expression of TGF-beta1, Smad2 and Smad3 [39]. This translational step from mechanistic cell biology to clinical samples bolsters confidence that this pathway is not just a laboratory construct, but one with a true pathophysiological relevance. The pharmacologic intervention studies further cement its significance. Several independent groups have demonstrated that anti-fibrotic actions of parthenolide [10,31] and silymarin [35] and SGLT2 inhibitors [17,34,44] and other traditional agents such as curcumin [9] act by inhibiting the TGF-β/Smad pathway. These findings from chemically different interventions converge to suggest pathway centrality rather than off-target effects. The more compounds that are found to have similar effects and which seem to be acting on the same target at the end of pathway the harder it is to ignore the signal.

The CCL2/MCP-1 Evidence Gap

In the context of strong evidence for the TGF-beta/Smad axis, it can be said that the CCL2/MCP-1 axis poses a paradox. The biological basis for the inclusion of CCL2 in this mechanistic pathway is well supported: Macrophage recruitment through chemokine signaling is well established to be an inflammatory amplifier in fibrosis [6] and MCP-1 (CCL2) is arguably the most studied monocyte chemoattractant. The concept of high glucose exposure activating chemokines, leading to macrophage infiltration and then activation of TGF-beta is intuitively valid and has face validity. However, as we tried to quantify the direct experimental evidence for CCL2/MCP-1 in context of peritoneal fibrosis, we identified only 4 of 42 studies (9.5%) with direct quantification. This does not mean that CCL2 has been ignored in literature – all kinds of experimental perturbations of CCL2/CCR2 axis have been performed in many studies with precise measurement of

effects downstream of CCL2/CCR2 on other targets, such as TGF-beta/Smad; the attribute shared by these studies is that only very few have been published where CCL2/CCR2 itself has been directly perturbed with precise quantification of effects downstream of CCL2/CCR2, such as on TGF-beta/Smad. The study by Balzer et al. [12] is very informative. The authors employed a four-arm mouse design which utilizes explicit group sizes and chronic high-glucose dialysate exposure model to demonstrate that dapagliflozin decreased both effluent TGF-β and MCP-1 release. The simultaneous quantification of both pathway components is exactly what is required to set up the proposed axis. Likewise, Gan et al. [43] have reported allicin-mediated downregulation of MCP-1 in an in vivo rat model of high-glucose peritoneal dialysis (PD), although it is difficult to extract the number of rats in each group from the available publication record. What these studies do show, however, is that there is not as much evidence as commonly assumed for CCL2 to act as a mechanistic link to TGF-beta/Smad. There is a high level of biological plausibility, but only preliminary experimental confirmation. This is an important point that basic scientists and clinicians alike need to understand.

Multiple Pathways Converge on TGF-beta/Smad (Mechanistic Integration)

One of key findings from this systematic review was the understanding that the TGF-beta/Smad pathway is a common pathway for various upstream insults. The 42 studies included in this report outline a complex cascade and parallel pathway of upstream and parallel events all converging on TGF-beta/Smad signaling. One specific upstream factor is hypoxia-inducible factor 1-alpha (HIF-1alpha). Both Wang et al. and other studies reported the HIF-1alpha-to-TGF-beta relationship [16,34,38,42] but Wang et al. demonstrated that canagliflozin simultaneously reduces HIF-1alpha, TGF-beta and p-Smad3. The study by Wang et al. [38] showed how high glucose levels induce O-GlcNAcylation of HIF-1alpha which stabilizes it and leads to increased expression of mesothelial-mesenchymal transition with downstream effects on TGF-beta signaling again. The studies that focus on macrophages introduce another level of complexity into the mechanisms. Inhibition of HDACs has been shown in both studies (by Shi et al. [27] and Zhou et al. [32]) to inhibit M2 macrophage polarization and to block TGF-beta/Smad signaling, preventing peritoneal fibrosis. This implies that the inflammatory microenvironment generated by macrophages, perhaps via CCL2 recruitment, may be linked to the TGF-beta/Smad system. This inflammatory bridge is also reinforced by the recent study by Wang et al. [45] that peritoneal fibrosis is induced by the ROS/TGF-beta/Smad pathway during high glucose dialysis in presence of extracellular traps from macrophages.

Therapeutic implications for this convergence on TGF-beta/Smad

Suppose that several injury pathways converge on a shared downstream target, then blocking the downstream target may be more likely to be effective than blocking each individual upstream pathway. The downside to this, of course, is that TGF-beta is a pleiotropic cytokine and has important homeostatic roles, so that it is not a straightforward target.

The Quantitative Evidence Gap

One of main limitations identified during this review was the lack of quantitative data in an extractable form. After targeted searching, only 7 out of 42 studies (16.7%) presented accessible exact n/replicate information. This is not a minor methodological issue: it severely restricts the ability to conduct quantitative synthesis, meta-analysis or even adequate comparison between studies. The most extractable quantitative evidence was derived from studies that intentionally reported group sizes and statistical reporting. Balzer et al.

[12] used the four-arm mouse design: n=5, 6, 12, 12 which set a clear standard. In Wang et al.'s study on canagliflozin [34] the number of samples they used for western-blot analyses was clearly stated to be six samples from the rat peritoneum per group. Perhaps the most thorough reporting was by Yin et al. [39] with three groups of 18 rats (n=6 each), 18 of which were provided with cell qPCR/immunofluorescence and 26 patients of human PD with detailed stratification. The following examples illustrate the possibilities offered when a focus is placed on clear reporting. They also highlight the extent to which current practice is inadequate. When n=3 per group or a representative western blot is reported in methods section of a manuscript without specifying whether "biological" or "technical" replicates, there is little possibility of meaningful synthesis. The reporting gap is especially problematic with regard to the CCL2/MCP-1 evidence. The limited number of studies measuring CCL2 provides more value to each individual study, but also creates limitations with respect to reporting and relative impact that those limitations may have on the overall evidence base. As the proposed axis has not been consistently reported in terms of CCL2 levels the number of recruited macrophages and downstream TGF-beta readouts the field is insufficiently supported in evaluating the strength of axis.

Implications for clinical practice and future research

The lessons learned from this systematic review are not limited to the understanding of mechanisms. The evidence summarized in this report confirms that a chronic inflammatory and metabolic injury underlies the pathogenesis of peritoneal fibrosis and that TGF-beta/Smad is the major downstream mediator in this pathway for clinicians who manage patients on peritoneal dialysis. This implies that those interventions that would reduce the glucose exposure in upstream events of injury (e.g. altering glucose exposure with other osmotic agents or using agents with systemic and local effects that inhibit SGLT2) could be worthwhile. The weaker evidence in this case for CCL2/MCP-1 will temper enthusiasm for therapeutic approaches targeting this pathway until further evidence is available. Although the biological arguments for using CCL2 blockade to treat peritoneal fibrosis are sound, at the present time, there is not yet as much mechanistic support for using CCL2 blockade as there is for TGF-beta/Smad. At this time, it would be premature to conduct clinical trials of chemokine receptor antagonists in treatment of peritoneal fibrosis. The other message is for the researchers: there are a far greater number of studies needed to directly correlate CCL2/CCR2 perturbation and TGF-beta/Smad readouts in a standardized quantitative manner with clear reporting. Based on these data, we propose a mechanistic model (Figure 3) where CCL2 acts as an inflammatory amplifier involved in macrophage recruitment and activation of TGF-beta which needs to be directly demonstrated. CCL2 neutralisation and/or CCR2 blockade should be included in studies, along with quantification of TGF-beta/Smad activation, macrophage infiltration and fibrosis endpoints.

Methodological limitations

Several limitations of this systematic review should be noted. First, although we have tried to use several databases and specific searches, we cannot ensure that all relevant studies were found. Publication bias, a bias with regard to publishing positive versus negative results, may lead the apparent mechanistic hierarchy to more well-studied pathways. Second the exclusion of studies with retracted or expression of concern status was essential for scientific integrity but it led to a decrease in amount of evidence. The sulodexide paper and nintedanib study were relevant to the topic, but not reliable. Third, our judgements of risk of bias were made using validated tools that were suitable for each design, but had

limitations based on data provided in published reports. The reason for many studies to be rated as "some concerns" or "unclear" was not that they were shown to be flawed in their methods, but because they lacked essential methodological reporting on randomization, blinding or replicate structure. Fourth the non-performance of a meta-analysis due to heterogeneity of outcomes, units and models means that we are unable to offer a pooled effect estimate. We used a conservative qualitative synthesis approach which is less exact than a quantitative meta-analysis, but is necessary. Lastly, because of focus on TGF-beta1/Smad/CCL2 axis, other pathways of interest, such as Wnt/beta-catenin, PI3K/AKT/mTOR and AMPK pathways, were not reviewed systematically, although they can be seen in many of selected studies. They could form the subject of specific systematic reviews to evaluate their relative contributions.

Future minimum dataset

Study type	Minimum dataset needed for stronger quantitative synthesis
Animal studies	Species/strain/sex/age; randomization method; group n; dialysate glucose concentration; exposure duration; route/dose; blinded histology; exact means/SD/SEM; raw densitometry.
In vitro studies	Cell source/authentication; passage range; glucose concentration and osmotic control; TGF-beta1 dose; biological replicates; technical replicates; exact fold-changes and p-values.
Clinical/effluent studies	PD duration, dialysis modality, dialysate glucose exposure, residual kidney function, peritonitis history, sample n by stratum, adjustment variables and confidence intervals.
CCL2/MCP-1 axis	Direct CCL2/MCP-1 concentration, CCR2/macrophage recruitment, blockade/silencing experiment, downstream TGF-beta/Smad readout and rescue experiment.

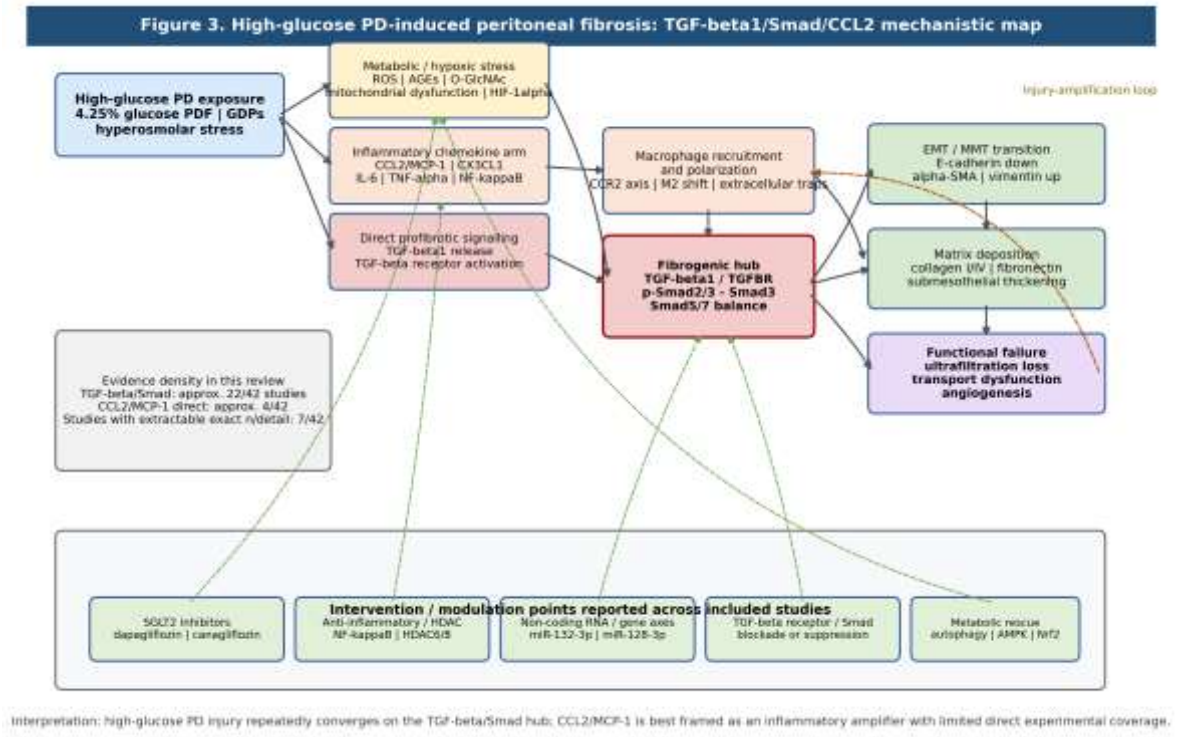

Figure 3. Mechanistic model: high-glucose PD exposure activates metabolic/hypoxic and inflammatory chemokine stressors that converge on TGF-beta/Smad-driven EMT/MMT and matrix deposition.

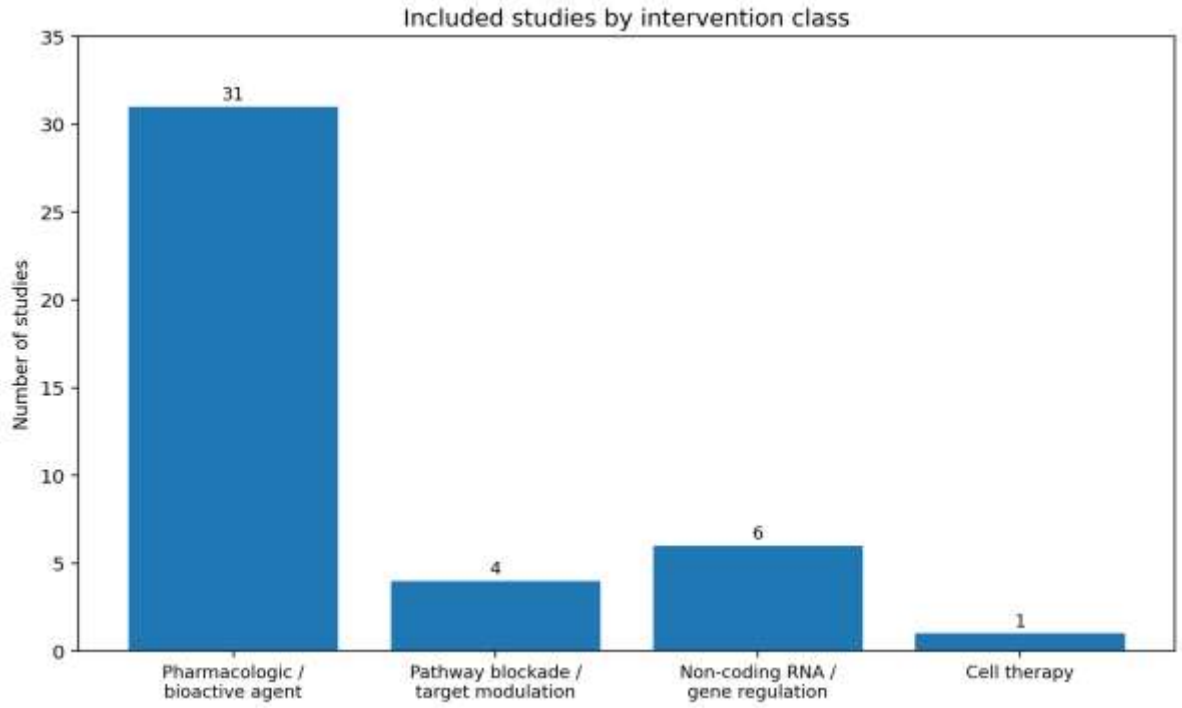

Figure 4. Distribution of included studies by intervention class.

Pharmacologic and bioactive agents dominated the evidence base with smaller contributions from pathway blockade studies, non-coding RNA/gene-regulation studies and one cell-therapy study.

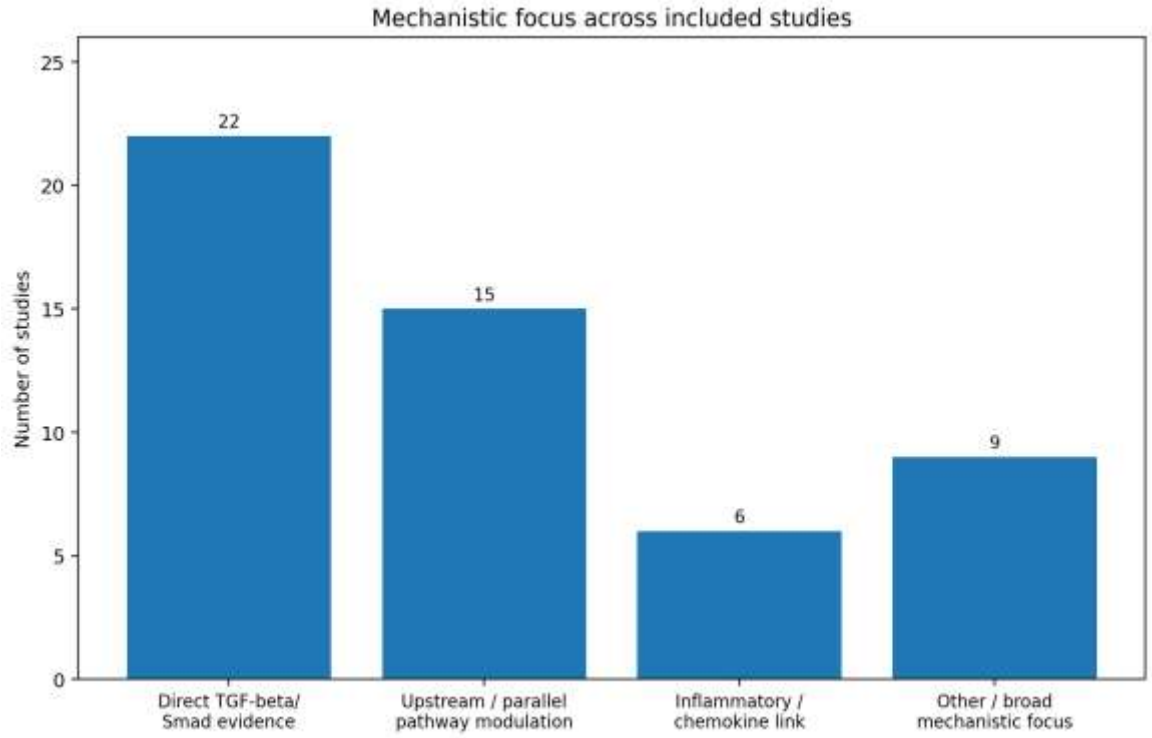

Figure 5. Mechanistic focus across included studies (categories are not mutually exclusive).

Direct TGF-beta/Smad evidence was the most frequent mechanistic category, followed by upstream or parallel pathway modulation; explicit inflammatory/chemokine linkage was less common.

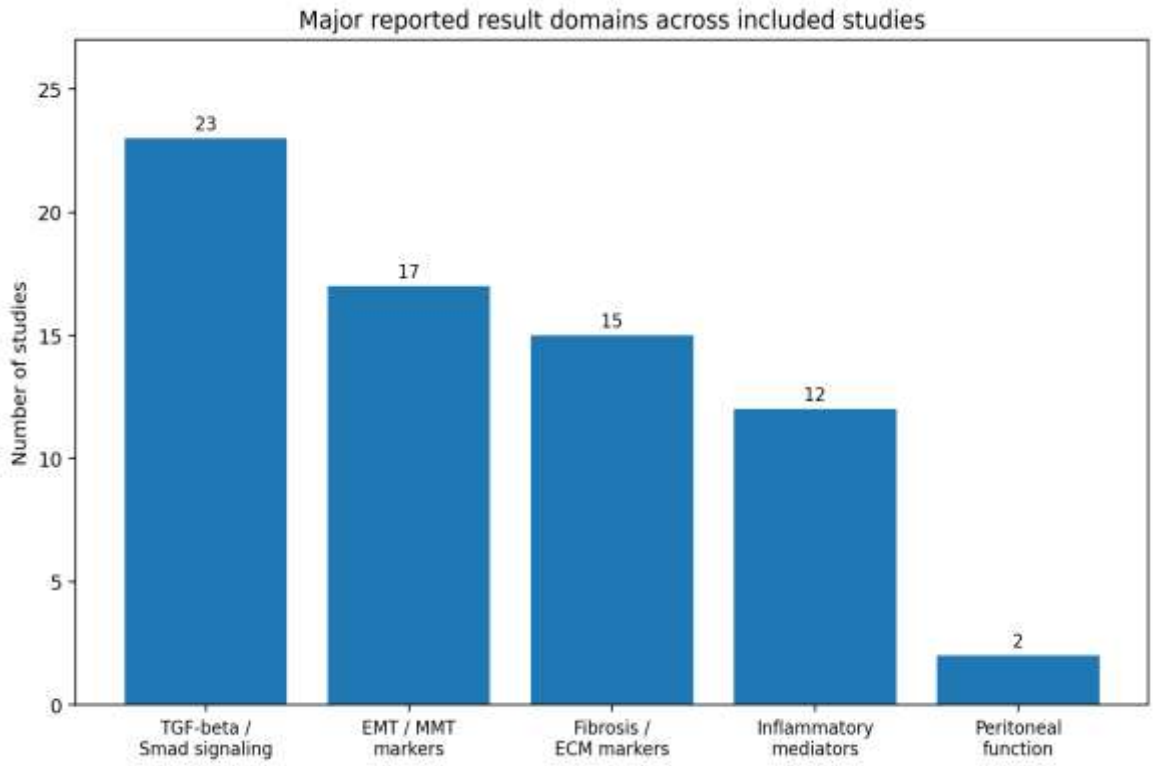

Figure 6. Major reported result domains across included studies (categories are not mutually exclusive).

Most studies reported TGF-beta/Smad signaling readouts, followed by EMT/MMT and fibrosis/ECM markers; fewer directly reported inflammatory mediators or peritoneal-function outcomes.

5. CONCLUSION

The review confirms that TGF-beta/Smad is the main and repeatedly quantified fibrogenic axis in high-glucose PD associated peritoneal injury. CCL2/MCP-1 is also part of evidence base, however, its direct experimental coverage is smaller and should not be interpreted as being as well-established a therapeutic target. The best future studies will include high glucose PD models and direct CCL2/CCR2 perturbation, quantification of macrophage recruitment and downstream readout of TGF-beta/Smad signals, reporting n, mean/SD, p value and confidence intervals.

Declaration by Authors

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