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Review

Hepatic and Renal Responses to Mesenchymal Stromal Cell Therapy: Mechanisms and Biochemical Evidence

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Simple Summary

Mesenchymal stromal cells are being studied as a treatment for liver and kidney diseases because they can influence inflammation and help protect damaged tissue. Their proposed effects involve chemical messages released by the cells and responses from the patient's immune system, rather than the cells permanently becoming new liver or kidney cells. This review examines selected published studies using six blood measurements: two enzymes associated with liver-cell injury, bilirubin, total protein, urea, and creatinine. Animal studies often report improvements, but results depend on the disease, cell preparation, dose, route of administration, and timing of measurement. Human studies show less consistent benefits. One large kidney trial found no faster recovery after heart surgery, and a long-term liver study found no clear difference in bilirubin between treated and comparison groups. Evidence for changes in total protein is limited, while evidence for directly measured blood urea comes mainly from animal studies. These blood tests can also change because of hydration, nutrition, inflammation, or other processes unrelated to tissue repair. They therefore need to be considered alongside tissue findings and direct measurements of organ function. More rigorous clinical studies are needed before these cell treatments can be used routinely.

Abstract

Mesenchymal stromal cell (MSC) therapy is being investigated for hepatic and renal disorders, but biochemical changes do not necessarily establish organ regeneration or clinical benefit. This non-exhaustive narrative review evaluates direct MSC interventions and six blood analytes: alanine aminotransferase, aspartate aminotransferase, total bilirubin, total protein, urea, and creatinine. PubMed-indexed English-language studies published from 2000 through 11 October 2026 were considered when complete texts and relevant findings were accessible; reviews and methodological sources provide background. Evidence is

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Academic Editor: Tomas Majtan

Received: 16 October 2026
Revised: 10 November 2026
Accepted: 10 November 2026
Published: 18 November 2026

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interpreted by species, disease, specimen, cell product, comparison type, and follow-up. Proposed mechanisms include paracrine signaling, immunomodulation, and host responses to administered cells, with varying experimental support. Selected preclinical studies report biochemical improvements, whereas human findings are heterogeneous. Serum total-protein responses are limited and product-dependent, and direct serum-urea evidence is mainly preclinical. The ACT-AKI trial found no acceleration of creatinine-defined recovery, while a randomized cirrhosis follow-up showed a within-arm bilirubin decline without a significant between-group difference. Urea nitrogen, albumin, urinary protein, and filtration outcomes are distinguished from the specified concentrations. Findings are synthesized descriptively, with explicit source uncertainties. Standardized cell characterization and controlled trials combining biochemical, histological, and functional outcomes are needed to assess durable clinical benefit.

Keywords: mesenchymal stromal cells; liver injury; kidney injury; immunomodulation; alanine aminotransferase; aspartate aminotransferase; bilirubin; total protein; urea; creatinine

1. Introduction

This review aims to summarize and critically evaluate current evidence on the effects of mesenchymal stromal cell therapy on hepatic and renal function, with particular emphasis on the underlying cellular and molecular mechanisms and changes in biochemical markers, including alanine aminotransferase, aspartate aminotransferase, total bilirubin, total protein, urea, and creatinine.

Liver and kidney diseases constitute a major biomedical challenge because progressive injury to either organ may result in fibrosis, loss of functional parenchyma, systemic metabolic disturbances, and ultimately organ failure. Although the liver has a substantial regenerative capacity, persistent inflammation, oxidative stress, and extracellular matrix deposition can impair tissue repair and promote the development of fibrosis and cirrhosis. Similarly, renal recovery following acute or chronic injury is frequently limited by tubular cell death, microvascular dysfunction, maladaptive inflammation, and interstitial fibrosis. Current therapeutic approaches can slow disease progression and manage complications; however, they do not always restore damaged tissue. Consequently, regenerative strategies capable of simultaneously modulating inflammation and promoting tissue repair have attracted increasing attention. Mesenchymal stromal cells (MSCs), commonly referred to as mesenchymal stem cells, are multipotent cells that can be isolated from bone marrow, adipose tissue, umbilical cord, placental tissues, dental pulp, and several other sources. According to the minimal criteria proposed by the International Society for Cellular Therapy, cultured human MSCs should adhere to plastic, express CD73, CD90, and CD105, lack major hematopoietic and endothelial markers, and demonstrate osteogenic, adipogenic, and chondrogenic differentiation under appropriate in vitro conditions [1,2]. However, the International Society for Cell & Gene Therapy has subsequently emphasized that the term mesenchymal stem cell should be used cautiously unless stemness has been demonstrated using appropriate functional assays. The more conservative term mesenchymal stromal cell is therefore preferable for most culture-expanded cell populations [2].

The therapeutic interest in MSCs was initially based on their capacity for multilineage differentiation and tissue engraftment. Current evidence, however, indicates that their effects are mediated predominantly through paracrine and immunomodulatory mechanisms rather than through the stable replacement of damaged hepatocytes or renal epithelial cells. MSCs secrete cytokines, chemokines, growth factors, lipids, extracellular matrix components, and extracellular vesicles containing proteins, messenger RNAs, and microRNAs.

These bioactive products regulate innate and adaptive immune responses and may suppress excessive inflammation, inhibit apoptosis, reduce oxidative stress, stimulate angiogenesis, and support endogenous tissue repair. In particular, the therapeutic activity of MSCs involves a complex cytokine network that includes IL-6, IL-10, TGF-β, TNF-α, and IL-1β and contributes to the regulation of inflammatory responses and tissue regeneration [3,4].

In hepatic injury, MSC-based interventions have been associated with immunomodulatory, anti-apoptotic, and antifibrotic effects. Proposed mechanisms include suppression of pro-inflammatory cytokine signaling, modulation of macrophage and T-cell responses, inhibition of hepatic stellate cell activation, regulation of transforming growth factor-β/SMAD signaling, and promotion of extracellular matrix degradation. Differences in cell product, disease stage, and local microenvironment can modify the response, making treatment context essential when interpreting experimental findings [5,6]. This context-dependent behavior is an important consideration when interpreting apparently conflicting experimental findings.

Clinical evidence for liver disease remains promising but heterogeneous. In a randomized study involving patients with hepatitis B virus-related decompensated cirrhosis, repeated umbilical cord-derived MSC infusions were followed by a decline in total bilirubin from baseline within the MSC arm, without a significant between-group difference in total bilirubin during follow-up. The treated group also demonstrated improved long-term survival, although the study design, underlying disease, treatment protocol, and population characteristics limit the generalizability of these findings [7]. Systematic and pooled analyses have likewise suggested possible improvement in hepatic biochemical and clinical outcomes, while emphasizing uncertainty regarding the optimal cellular source, dose, administration route, treatment frequency, and patient-selection criteria [8].

MSC therapy has also been investigated in acute kidney injury, chronic kidney disease, diabetic nephropathy, and renal ischemia–reperfusion injury. The proposed renoprotective mechanisms include attenuation of tubular epithelial cell apoptosis, suppression of inflammatory cell infiltration, preservation of peritubular microcirculation, stimulation of angiogenesis, and reduction in interstitial fibrosis. A systematic review and network meta-analysis of 50 randomized animal studies found improvements in serum creatinine and renal histology following MSC administration. However, the authors identified limitations in study design, outcome measurement, and reporting, highlighting the need for more rigorous preclinical research before the results can be confidently translated into clinical practice [9].

Biochemical measurements provide a practical means of monitoring hepatic and renal responses to MSC-based interventions. Alanine aminotransferase (ALT) and aspartate aminotransferase (AST) are primarily interpreted as markers of hepatocellular injury rather than direct measurements of liver function. Total bilirubin reflects several processes, including bilirubin production, hepatic uptake, conjugation, and excretion. Total protein and albumin may provide information about hepatic synthetic activity, although their concentrations are also affected by nutritional status, systemic inflammation, immunoglobulin production, hydration, and renal or gastrointestinal protein loss. Consequently, changes in these variables should be interpreted together with histological, molecular, and additional functional findings rather than as isolated indicators of hepatic regeneration [10–12].

Serum creatinine and urea remain widely used indicators of renal function in experimental and clinical studies. Creatinine is frequently used to estimate glomerular filtration; however, its concentration is influenced by muscle mass, age, diet, tubular secretion, medication use, and the kinetics of kidney injury. Urea is similarly affected by protein intake, catabolic state, gastrointestinal bleeding, hydration, and hepatic urea synthesis. Both markers may therefore change independently of structural renal repair. Furthermore, crea-

tinine may rise relatively late after acute kidney injury, limiting its value as an early injury marker. Complementary measurements such as cystatin C, neutrophil gelatinase-associated lipocalin, kidney injury molecule-1, proteinuria, and histopathological assessment may provide a more comprehensive evaluation of the renal response [13,14].

These interpretive limitations are compounded by heterogeneity in MSC products and treatment protocols, which is examined in Sections 2.2 and 2.5.

Therefore, this review aims to summarize and critically evaluate current evidence on the effects of MSC therapy on hepatic and renal function, with particular emphasis on the underlying cellular and molecular mechanisms and changes in ALT, AST, total bilirubin, total protein, urea, and creatinine. Preclinical and clinical evidence will be examined separately to determine whether changes in these routinely measured biochemical parameters are supported by histological and molecular findings. The review will also assess the influence of MSC source, dose, administration route, treatment timing, and disease model and identify methodological limitations that must be addressed to facilitate the clinical translation of MSC-based therapies.

The organizing contribution is a joint hepatic–renal interpretation of six specific blood analytes, with explicit distinctions among specimens, cell products, and comparison types. This framework places favorable experimental observations beside null clinical findings and identifies where a laboratory change cannot establish organ recovery. It complements broader MSC syntheses by focusing on how the reported measurements constrain interpretation, without asserting a new treatment effect or exhaustive coverage.

Literature Search and Evidence Selection

This narrative review was informed by a structured literature search of PubMed for English-language publications from January 2000 through 11 October 2026. The search was designed to identify preclinical and clinical studies evaluating direct administration of mesenchymal stromal or stem cell products in liver or kidney diseases and reporting at least one of six prespecified circulating biochemical outcomes: ALT, AST, total bilirubin, total protein, urea, or creatinine.

The hepatic search block combined the terms ("mesenchymal stromal cell" OR "mesenchymal stem cell" OR MSC) with (liver OR hepatic OR cirrhosis OR fibrosis OR "liver failure") and with (ALT OR AST OR aminotransferase OR bilirubin OR "total protein" OR albumin). The renal search block combined the MSC terms with (kidney OR renal OR nephro* OR "acute kidney injury" OR "chronic kidney disease" OR "diabetic nephropathy" OR "ischemia–reperfusion") and with (urea OR "blood urea nitrogen" OR BUN OR creatinine OR eGFR OR "glomerular filtration rate"). Additional searches combined MSC-related terms with product and treatment variables, including tissue source, preconditioning, genetic modification, dose, administration route, timing, and cryopreservation.

Primary studies were considered eligible when they: (1) evaluated direct administration of an MSC or MSC-related cellular product in a hepatic or renal disease model or patient population; (2) reported at least one of the six prespecified circulating biochemical markers; (3) provided sufficient information to identify the cell product, disease context, and relevant outcome; and (4) were available as complete English-language articles that could be checked against the reported findings. Both clinical and animal studies were considered. Reviews, meta-analyses, consensus documents, and methodological articles were used to provide biological or interpretive background but were not counted as independent treatment comparisons.

Extracellular-vesicle-only, exosome-only, and conditioned-medium interventions were excluded from the primary treatment synthesis. In vitro studies without an in vivo circulating biochemical outcome were also excluded. Albumin, urinary protein, tissue protein,

BUN, serum urea nitrogen, eGFR, and directly measured GFR were not relabeled as total protein, direct serum urea, or serum creatinine. These related outcomes were retained only when they provided complementary information and were identified explicitly.

Studies were prioritized according to their direct relevance to the prespecified markers, clarity of the intervention and comparator, availability of group-level biochemical results, ability to verify the analyte and specimen, and relevance to the comparison between preclinical and clinical evidence. Controlled and randomized studies were given greater interpretive weight than uncontrolled case series or small exploratory investigations. However, uncontrolled studies were retained when they provided relevant safety, feasibility, null, or descriptive findings and were identified as such.

Study selection was not based on the direction or statistical significance of the reported effect. Positive, negative, null, and inconclusive findings were retained where they were relevant and verifiable. When studies produced conflicting findings, the differences were not resolved by selecting a single preferred result. Instead, the studies were compared according to species, disease etiology and severity, MSC source and product modification, dose, administration route, treatment timing, comparator, follow-up duration, specimen, and endpoint definition. Reports based on overlapping populations or repeated analyses were identified and were not treated as fully independent confirmation.

Because the purpose of the review was critical narrative synthesis rather than exhaustive evidence enumeration, no PRISMA-compliant study-selection process or formal risk-of-bias assessment was performed. The use of a single database, restriction to English-language publications, dependence on full-text accessibility, and non-exhaustive screening may have resulted in the omission of relevant studies. The findings and publication counts should therefore be interpreted as a structured narrative representation of the accessible evidence rather than a complete systematic estimate of the literature.

2. Biological Characteristics of Mesenchymal Stromal Cells

2.1. Definition and Identification Criteria

Mesenchymal stromal cells are a heterogeneous population of non-hematopoietic, plastic-adherent cells with multilineage differentiation potential and extensive paracrine activity. Although the term ‘mesenchymal stem cells’ remains widely used, the International Society for Cell & Gene Therapy recommends the term mesenchymal stromal cells for culture-expanded populations unless their capacity for self-renewal and differentiation has been demonstrated using appropriate functional assays [2]. This distinction is important because many therapeutic MSC preparations satisfy phenotypic and functional laboratory criteria but have not been shown to behave as true stem cells after administration.

The minimal criteria proposed by the International Society for Cellular Therapy include plastic adherence under standard culture conditions; expression of CD73, CD90, and CD105; and the absence of CD11b or CD14, CD19 or CD79α, CD34, CD45, and HLA-DR. MSCs should also demonstrate osteogenic, adipogenic, and chondrogenic differentiation under appropriate in vitro conditions [1,2]. These criteria provide a standardized framework for identifying MSCs but do not establish the potency, homogeneity, or therapeutic efficacy of a particular cell product.

The conventional surface-marker profile is not exclusive to MSCs and may be shared by fibroblasts and other stromal populations. Furthermore, marker expression can change with tissue source, donor characteristics, culture medium, passage number, inflammatory priming, cryopreservation, and cellular senescence. Consequently, phenotypic characterization should be supplemented with assessments of cell viability, proliferative capacity, differentiation potential, secretory activity, and disease-relevant biological potency [5].

2.2. Tissue Sources and Functional Heterogeneity

MSCs can be isolated from numerous adult and perinatal tissues, including bone marrow, adipose tissue, umbilical cord, Wharton's jelly, placenta, dental pulp, synovial membrane, periosteum, and other connective tissues [1]. Bone marrow-derived MSCs are among the most extensively characterized populations and remain a common reference standard for comparative studies. However, bone marrow collection is invasive. Cultured bone marrow MSCs from elderly donors showed lower colony replication and differentiation and more senescence-associated features than young-donor cells, although harvest site and disease status also differed between groups [15]. These effects may depend on donor selection, isolation procedures, and culture conditions. Adipose tissue represents a comparatively abundant and accessible source of MSCs. Studies of adipose MSCs associate obesity with altered proliferation, senescence, differentiation, and immunophenotype, although these laboratory characteristics do not establish organ-specific treatment efficacy [16,17]. Anatomical origin also matters: MSCs isolated from subcutaneous and visceral fat showed different expression and functional profiles [18].

Umbilical cord- and Wharton's jelly-derived MSCs can be collected non-invasively after birth without donor-site morbidity. Compared with many adult tissue-derived populations, they frequently demonstrate rapid in vitro expansion, prolonged proliferative capacity, relatively low expression of immunogenic and costimulatory molecules, and substantial paracrine and immunomodulatory activity [19,20]. These properties make perinatal MSCs attractive candidates for allogeneic therapeutic applications. However, their biological characteristics remain dependent on tissue-processing methods, culture conditions, donor variability, and the specific umbilical cord compartment from which the cells are isolated. These source-related differences should be considered when interpreting therapeutic outcomes, because MSCs obtained from different tissues should not be regarded as biologically interchangeable products. The additional effects of donor characteristics, manufacturing conditions, cryopreservation, viability, and potency are discussed in Section 2.5.

2.3. Migration and Homing to Injured Tissues

MSC homing refers to the migration and retention of administered cells within injured or inflamed tissues. Tissue damage produces chemokines, cytokines, adhesion molecules, and extracellular matrix-remodeling enzymes that may attract circulating MSCs. The homing process involves several sequential stages: initial tethering and rolling along the vascular endothelium, chemokine-mediated activation, integrin-dependent adhesion, transendothelial migration, and movement through the extracellular matrix toward the injury-associated signaling gradient [2].

The stromal cell-derived factor-1/C-X-C chemokine receptor type 4 axis, also known as the CXCL12/CXCR4 axis, is one of the best-characterized signaling pathways involved in MSC recruitment. Injured tissues may increase CXCL12 production, thereby generating a chemotactic gradient for CXCR4-expressing cells [2,21]. Additional chemokine receptors, selectins, integrins, vascular cell adhesion molecule-1, intercellular adhesion molecule-1, and matrix metalloproteinases participate in MSC tethering, endothelial adhesion, transendothelial migration, and movement through the extracellular matrix [2,21]. However, CXCR4 and other homing-associated molecules may be expressed at relatively low levels or decline during prolonged ex vivo expansion, potentially reducing the migration capacity of culture-expanded MSCs [21,22].

Although MSCs demonstrate injury-directed migration under experimental conditions, systemic homing is generally inefficient. Only a small proportion of administered cells reach and persist within the liver, kidneys, or other target tissues following peripheral intravenous administration. The efficiency of MSC homing is influenced by cell size, viability,

passage number, culture conditions, administration route, inflammatory microenvironment, vascular integrity, recipient characteristics, and the timing of cell administration relative to tissue injury [2,21,22].

2.4. Biodistribution and the Pulmonary First-Pass Effect

Following intravenous administration, a substantial proportion of MSCs initially accumulates within the pulmonary microvasculature. This pulmonary first-pass effect is partly related to the relatively large size of culture-expanded cells and their interactions with endothelial adhesion molecules. Biodistribution studies indicate that some cellular material may subsequently be detected in the liver, spleen, and kidneys, although the persistence of viable MSCs in these organs is often limited and varies according to the tracking method [23].

The limited number of viable MSCs reaching the target organ challenges the assumption that therapeutic benefit depends primarily on long-term engraftment and differentiation. Instead, cells retained in the pulmonary circulation may exert systemic effects through soluble mediators, extracellular vesicles, and interactions with circulating or tissue-resident immune cells. Furthermore, intravenously administered MSCs can undergo apoptosis, after which they are engulfed by host phagocytes. This process, known as efferocytosis, may reprogram macrophage metabolic and inflammatory activity and contribute to the immunosuppressive effects of MSC therapy [24].

The route of administration strongly influences biodistribution. Intra-arterial delivery may partially bypass pulmonary entrapment and increase cell exposure within downstream organs, but it can also increase the risk of microvascular obstruction. Local or organ-directed administration may improve cellular delivery to the target tissue but is more invasive and may not be suitable for diffuse or systemic disease. These considerations are especially relevant when comparing hepatic and renal studies because differences in delivery route may influence both therapeutic efficacy and treatment-related risk.

2.5. Biological Potency and Therapeutic Identity

The therapeutic identity of MSCs is not determined by differentiation potential alone. Current evidence suggests that their biological activity depends mainly on their ability to sense the local environment and generate an adaptive secretory response. Exposure to hypoxia, oxidative stress, pathogen-associated molecules, and inflammatory cytokines may alter the production of immunoregulatory factors, growth factors, extracellular matrix components, and extracellular vesicles.

MSC viability and metabolic fitness are therefore important determinants of potency. However, viability immediately before administration may not fully predict in vivo activity because the host response to stressed, apoptotic, or fragmented MSCs may also contribute to therapeutic effects. Disease severity, immune status, age, comorbidities, and the inflammatory phenotype of the recipient can further modify treatment responses [25].

This biological complexity may contribute to cross-study variation in biochemical outcomes. Rigorous reporting of product and treatment characteristics is therefore essential for interpreting and comparing hepatic and renal responses.

To distinguish conventional MSC therapy from biologically distinct MSC-based interventions, the products included in this review were classified into four broad categories: (1) conventional unmodified MSC preparations; (2) genetically engineered or preconditioned MSC products; (3) selected, differentiated, or lineage-directed cell products, including mesenchymal precursor cells and MSC-derived hepatocyte-like cells; and (4) combination or delivery-assisted interventions in which MSCs were administered with biomaterials, gene-silencing systems, growth factors, physical stimulation, or other adjunctive strate-

gies. These categories were not considered biologically or therapeutically interchangeable, and findings obtained with modified, preconditioned, differentiated, precursor cells or combination products were identified as product- or protocol-specific evidence.

When a modified or preconditioned product was compared directly with unmodified MSCs, an additional effect was attributed to the specific modification only when supported by the between-product comparison. When no unmodified-MSC comparator was included, the observed response was attributed to the complete intervention rather than to conventional MSC therapy. Similarly, when biomaterials, physical stimulation, gene-silencing systems, growth factors, or other adjunctive treatments were used without an appropriate adjunct-only control, their contribution could not be separated from that of the administered cells.

Manufacturing conditions may alter functional activity even when a preparation retains conventional MSC markers. A comparison of freshly harvested and freeze-thawed MSCs found impaired immediate immunomodulatory responses and greater complement-associated injury after thawing; these product-level findings justify reporting cryopreservation and recovery conditions rather than assuming preparations are equivalent [26].

2.6. Levels of Mechanistic Evidence

Proposed mechanisms of MSC action should be interpreted according to the type and strength of the supporting experimental evidence. In this review, mechanistic findings are considered at three levels. First, direct functional evidence is provided when a pathway, cell population, or mediator is experimentally perturbed through cell depletion, receptor or pathway inhibition, neutralization, genetic modification, loss-of-function approaches, or rescue experiments, and the therapeutic effect is correspondingly reduced, abolished, or restored. Such studies provide the strongest support for a causal contribution within the specific experimental model.

Second, supportive mechanistic evidence includes concordant changes in cytokines, signaling proteins, gene expression, immune cell phenotypes, apoptosis, oxidative stress, vascular injury, or fibrosis that accompany biochemical or histological improvement. These findings strengthen biological plausibility and may identify pathways associated with the therapeutic response, but they do not independently establish that the measured pathway is necessary or sufficient for the observed benefit.

Third, proposed or context-dependent mechanisms are those inferred from established MSC biology, observational associations, or findings obtained in related disease models without direct functional testing in the study under discussion. These mechanisms may provide a reasonable explanation for biochemical changes but should not be presented as experimentally demonstrated effects in every organ, disease model, or MSC product.

This distinction is particularly important for macrophage-mediated effects. MSC administration may be accompanied by reduced pro-inflammatory cytokines, increased expression of macrophage polarization-associated markers, or changes in the relative abundance of macrophage subpopulations. However, such observations do not demonstrate that macrophages are responsible for the therapeutic effect. Stronger evidence is provided when macrophage depletion, inhibition of macrophage recruitment or function, or disruption of MSC–macrophage interactions attenuates the biochemical, histological, or functional benefit.

Host clearance of apoptotic MSCs represents a related but distinct mechanism. Experimental evidence indicates that apoptosis and subsequent phagocytic clearance of administered MSCs can contribute to their immunomodulatory activity [25]. Nevertheless, the importance of this process may depend on the MSC product, administration route, recipient

immune environment, and disease model. It should therefore not be assumed to explain every reported hepatic or renal response.

Accordingly, the terms "demonstrated", "supported", "associated", and "proposed" are used deliberately throughout this review. "Demonstrated" is reserved for mechanisms supported by direct functional intervention within the relevant model; "supported" or "associated" refers to concordant molecular or cellular findings without causal perturbation; and "proposed" identifies biologically plausible but incompletely tested explanations.

3. Biochemical Assessment of Hepatic and Renal Responses to MSC Therapy

Biochemical markers provide complementary but non-equivalent information about hepatocellular injury, hepatic handling and synthesis, nitrogen metabolism, and renal filtration. Their interpretation requires an appropriate comparator, consideration of the measurement time point, and integration with histological, molecular, and organ-specific functional outcomes, as discussed in Section 3.7.

Figure 1 summarizes the proposed links between MSC therapy, tissue responses, and the six biochemical markers [3,5,6,9,25].

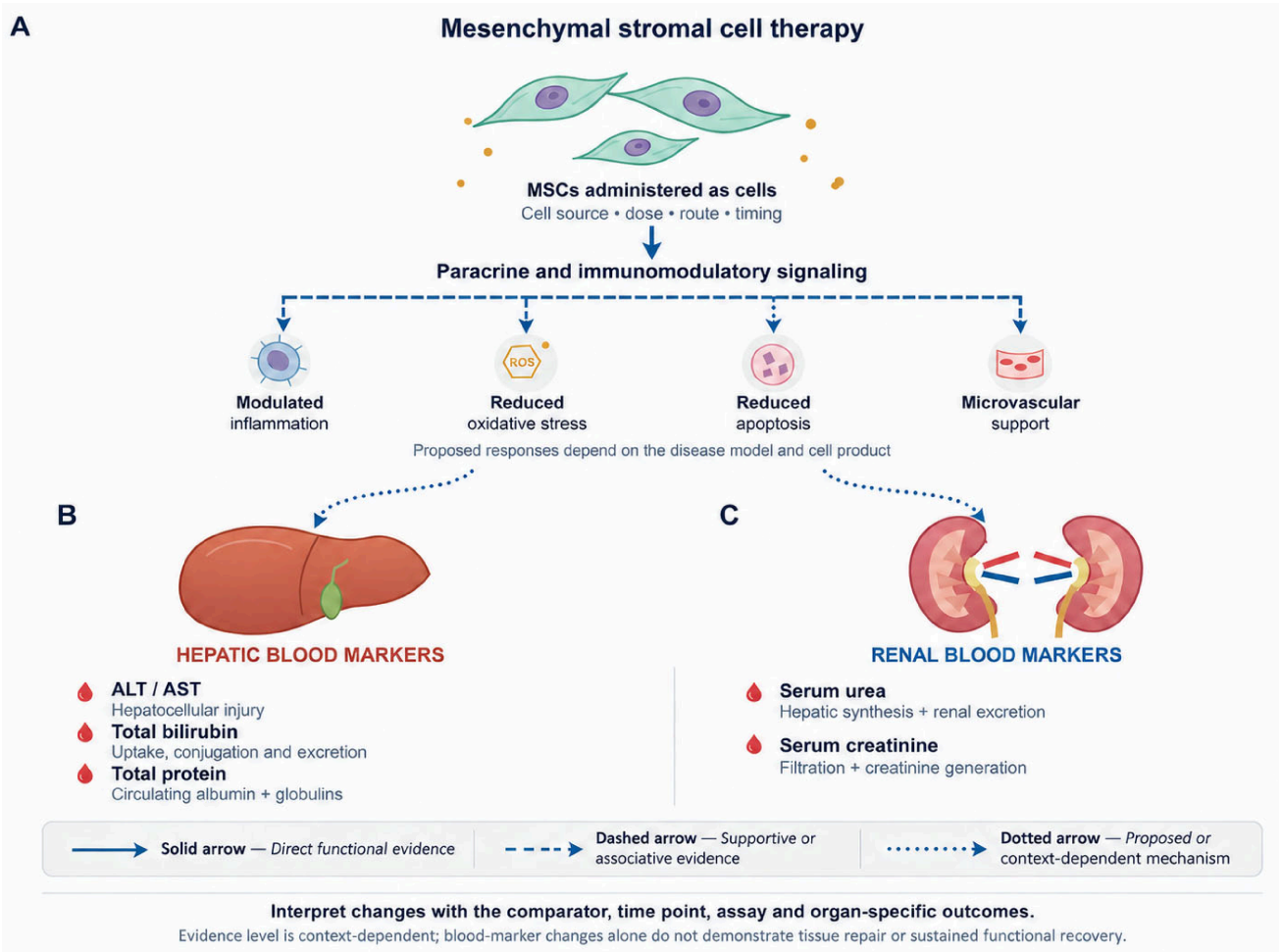


Figure 1. Conceptual framework linking mesenchymal stromal cell administration to hepatic and renal biochemical responses. (**A**) MSCs administered as cellular products may influence inflammation, oxidative stress, apoptosis, and microvascular function through paracrine and immunomodulatory signaling; the proposed responses depend on the cell source, dose, administration route, timing, disease model, and cell product. (**B**) Hepatic biochemical responses are evaluated using ALT, AST, total bilirubin, and total protein, which reflect hepatocellular injury, bilirubin handling, and circulating

protein concentrations. (**C**) Renal biochemical responses are evaluated using serum urea and creatinine, which are influenced by hepatic synthesis, renal excretion, filtration, and creatinine generation. Solid arrows indicate direct functional evidence, dashed arrows indicate supportive or associative evidence, and dotted arrows indicate proposed or context-dependent mechanisms. Biochemical improvement alone does not establish structural regeneration or sustained organ functional recovery.

3.1. Alanine Aminotransferase

Alanine aminotransferase is a cytosolic enzyme that catalyzes the reversible transfer of an amino group from alanine to α-ketoglutarate, producing pyruvate and glutamate. ALT is expressed predominantly in hepatocytes and is therefore commonly used as a biochemical indicator of hepatocellular injury. Damage to hepatocyte plasma membranes leads to the release of intracellular ALT into the circulation.

In experimental models of liver injury, increased serum ALT commonly reflects toxic, ischemic, inflammatory, metabolic, or fibrotic damage. A reduction in ALT following MSC administration may indicate stabilization of hepatocyte membranes, reduced necrosis or apoptosis, attenuation of oxidative stress, and suppression of inflammatory injury. Potential MSC-mediated mechanisms include reduced production of reactive oxygen species, inhibition of NF-κB-dependent inflammatory signaling, decreased expression of pro-apoptotic proteins, and secretion of hepatoprotective growth factors.

Nevertheless, normalization of ALT should not be interpreted as definitive evidence of restored liver function. ALT activity may decrease when active hepatocyte injury is reduced, but it may also be relatively low in advanced liver disease because of the loss of viable hepatocyte mass. ALT can additionally be affected by age, sex, body mass, metabolic status, medications, and laboratory methodology. Therefore, ALT results should be analyzed together with AST, bilirubin, albumin or total protein, histological findings, and markers of fibrosis [10–12].

The clinical and preclinical examples require separate interpretation. In an open-label controlled study of HBV-associated acute-on-chronic liver failure (24 UC-MSC recipients; 19 saline controls), ALT decreased following treatment [27]. In DEN-induced rat cirrhosis, UC-MSC-treated groups had lower ALT than injury controls [28]. A separate acute CCl4 liver-injury study reported lower ALT at day 3 in both the unmodified bone-marrow MSC arm and the hepatocyte-like differentiated-cell arm than in injured saline controls ($p < 0.05$); the differentiated cells represent a distinct treatment product [29].

Additional controlled animal studies broaden the injury settings. Bone marrow MSCs were tested in D-galactosamine/lipopolysaccharide acute liver failure, while viable placental MSCs were administered by different routes in miniature pigs; irradiated-cell arms and routes should remain separate [30,31]. Human UC-MSCs were also studied in acute-on-chronic rat injury, and adipose MSCs in CCl4-associated fibrosis, with different sampling schedules and molecular readouts [32,33]. These reports support model-specific observations rather than a common magnitude of ALT benefit.

Clinical ALT findings also depend on comparison design. A controlled liver-allograft-rejection pilot followed 14 MSC recipients and 13 controls receiving immunosuppression and reported lower ALT and AST over 12 weeks [34]. An HBV cohort measured transaminases after MSCs plus standard care without an untreated arm; its recipient-age analysis appears to reuse the same 123 treated participants and should not be counted as independent confirmation [35,36]. An HCV study combined MSCs with G-CSF, preventing attribution of the observed laboratory changes to MSCs alone [37].

Cell modification introduces another source of heterogeneity. An *HGF*-overexpression experiment compared engineered MSCs with ordinary BM-MSCs, and an HBV-related model combined MSCs with short-hairpin RNA; the extra effects of these products cannot be assigned to unmodified cells [38,39]. In murine liver fibrosis, glutathione or melatonin

preconditioning strengthened the biochemical response to adipose-derived MSCs, but the additional reduction in fibrotic area relative to unmodified MSCs was not statistically significant [40]. In S100-induced experimental autoimmune hepatitis, UC-MSC administration lowered serum ALT and AST and reduced histological activity alongside suppression of Th1 and Th17 responses [41].

Route and treatment timing further shape transaminase trajectories. In rat acute liver failure, intravenously administered BM-MSCs were associated with lower serum ALT and AST than disease controls at 120 and 168 h, illustrating the importance of sampling time [42]. A four-route rat study found lower ALT and AST seven days after endovascular BM-MSC delivery, while intraperitoneal administration showed no significant biochemical benefit [43]. In another rat acute liver failure experiment, tail vein BM-MSCs reduced ALT and AST at 24 and 72 h alongside lower HMGB1 expression, while the early 12-h transaminase contrast was not significant [44].

3.2. Aspartate Aminotransferase

Aspartate aminotransferase catalyzes the transfer of an amino group from aspartate to α-ketoglutarate. AST exists in cytosolic and mitochondrial forms and is found in the liver, skeletal muscle, myocardium, kidneys, brain, and erythrocytes. It is therefore less liver-specific than ALT.

Elevated AST in liver injury may indicate hepatocyte membrane damage and, when mitochondrial AST is released, more severe cellular or mitochondrial injury. A decrease in AST following MSC therapy may reflect reduced hepatic necrosis, improved mitochondrial stability, lower oxidative stress, and attenuation of inflammatory damage. However, changes in AST can also result from muscle injury, hemolysis, cardiac damage, or alterations in other tissues.

For AST, the selected evidence is primarily preclinical. Lower AST was reported after UC-MSC administration in DEN-induced rat cirrhosis [28] and at day 3 after either bone-marrow MSCs or hepatocyte-like cells in acute CCl4 injury ($p < 0.05$ versus injured controls) [29]. These observations should be read with the accompanying ALT results, disease model, comparator, and histological findings rather than generalized to a clinical treatment effect.

The AST-to-ALT ratio is sensitive to disease context, sampling time, enzyme clearance, and assay conditions; muscle injury and sample hemolysis can raise AST independently of hepatic injury. Consequently, the ratio supplies context rather than a specific measure of MSC-induced liver regeneration [10].

Further fibrosis experiments illustrate different AST sampling windows. In CCl4-induced rat cirrhosis, portal and tail vein BM-MSC transplantation produced similar biochemical responses: ALT declined by two weeks, whereas significant AST differences emerged at six weeks [45]. In a CCl4 mouse model, BM-MSC infusion through either the tail or portal vein reduced circulating transaminases at 21 days; the bilirubin outcome was direct bilirubin and should not be grouped with total bilirubin [46]. In a CCl4 rat fibrosis study, repeated intravenous BM-MSC administration was associated with lower ALT and AST than the fibrosis control and herbal comparator groups [47].

3.3. Total Bilirubin

Bilirubin is produced mainly through the degradation of heme. Unconjugated bilirubin is transported to the liver bound to albumin, taken up by hepatocytes, conjugated by UDP-glucuronosyltransferase, and subsequently excreted into bile. Serum bilirubin therefore reflects the combined influence of bilirubin production, hepatic uptake, conjugation, biliary transport, and excretion. A reduction in total bilirubin following MSC therapy may

indicate improvement in hepatocyte function, bile transport, or intrahepatic cholestasis. Such changes may result from reduced inflammation, preservation of hepatocyte viability, improved microcirculation, and attenuation of fibrosis. Clinical studies of MSC therapy in decompensated cirrhosis have reported improvements in total bilirubin together with albumin and other indicators of liver function, although the magnitude and durability of the response vary among studies.

Total bilirubin should preferably be accompanied by direct and indirect bilirubin measurements. A decrease in total bilirubin cannot automatically be attributed to hepatic regeneration because bilirubin is also influenced by hemolysis, erythrocyte turnover, biliary obstruction, genetic variation in conjugating enzymes, and medications. In MSC studies, bilirubin should therefore be evaluated together with aminotransferases, alkaline phosphatase, γ-glutamyl transferase, albumin, coagulation indices, and liver histology.

Human bilirubin findings differ by study setting and comparison. The open-label acute-on-chronic liver-failure study reported lower total bilirubin after UC-MSC transfusions, with between-group differences reported at weeks 36 and 48 [27]. In the separate long-term randomized cirrhosis follow-up, total bilirubin declined from baseline in the MSC arm, but the between-group difference was not significant [7]. Preclinical DEN-cirrhosis and acute CCl4-injury studies also reported lower bilirubin in treated groups than in injury controls [28,29]. A within-group decline and a controlled treatment contrast therefore cannot be treated as equivalent evidence.

Total-bilirubin findings extend to different injury mechanisms. In CCl4-induced rat acute liver failure, human UC-MSC delivery through the tail vein or directly into the liver lowered total bilirubin compared with disease controls, with no significant difference between routes [48]. In miniature pigs with acute liver failure, immediate intraportal menstrual blood-derived MSC infusion attenuated later ALT, AST, and total bilirubin increases and prolonged survival, although this early-treatment design differs from clinical rescue therapy [49]. In DDC-induced chronic cholestasis, menstrual blood-derived MSCs lowered total bilirubin and transaminases relative to vehicle controls, extending biochemical evidence to a cholestatic rather than solely hepatotoxic model [50]. These controlled animal results should be considered alongside the non-significant between-arm bilirubin contrast in the randomized human cirrhosis follow-up, rather than extrapolated to clinical efficacy.

3.4. Total Protein and Albumin

Serum total protein consists primarily of albumin and globulins. Albumin is synthesized by hepatocytes, whereas the globulin fraction includes immunoglobulins and numerous transport, inflammatory, and complement proteins. Thus, total protein is not a liver-specific marker and does not directly measure the regenerative activity of MSCs.

An increase in total protein after MSC administration may suggest improved hepatic protein synthesis, reduced protein loss, improvement in nutritional status, or changes in inflammatory protein production. However, total protein may remain within the reference range despite reduced albumin if the globulin fraction is increased. Conversely, dehydration can increase total protein without improving hepatic synthesis.

Albumin should therefore be reported separately whenever possible. Because albumin has a relatively long circulating half-life, it may respond more slowly than ALT or AST. Short-term experimental studies may consequently demonstrate reductions in aminotransferases without a measurable increase in albumin or total protein. Albumin concentrations are also affected by inflammation, malnutrition, renal protein loss, gastrointestinal loss, and fluid balance.

For MSC studies, the most informative approach is to report total protein, albumin, and, where possible, the albumin-to-globulin ratio. Interpretation should also account for the duration of follow-up and the presence of systemic inflammation.

Direct serum total-protein evidence is less consistent than the aminotransferase findings. In the human acute-on-chronic liver-failure article, the total-protein figure illustrates one patient and cannot establish a cohort treatment effect [27]. In DEN-induced rat cirrhosis, total protein was 57.33 ± 1.33 g/L in injury controls and 57.59–64.50 g/L across UC-MSC arms, without a marked significant treatment contrast [28]. In a CCl4-cirrhosis study ($n = 6$/group), day-21 total protein (mean ± SD) was similar in injury controls and unmodified MSC recipients (43.8 ± 6.4 versus 44.9 ± 6.3), while a higher value (63.6 ± 5.3) occurred in the *Smad7*-engineered MSC arm [6]. The source table labels these total-protein values as g/dL; the intended unit remains unresolved, and the values have not been converted. The latter finding belongs to a modified cell product and should not be attributed to ordinary MSC therapy. The unit reported for total protein in the original study by Su et al. could not be independently verified and appears physiologically inconsistent. Therefore, the numerical values are retained only as a descriptive account of the original report and are not used as key quantitative evidence of therapeutic efficacy. Importantly, the marked increase was observed in the *Smad7*-engineered MSC group, whereas the total-protein value in the unmodified MSC group remained similar to that in the injury-control group. The finding should therefore be interpreted as product-specific evidence related to genetically modified MSCs rather than as evidence of an effect of conventional unmodified MSC therapy.

Specimen identity also matters: urinary total-protein outcomes in a diabetic-nephropathy rat study [51] are not serum total protein, and urinary albumin in another rat study [52] is not a measure of circulating total protein. These outcomes provide complementary renal information but do not fill the serum total-protein evidence gap.

Additional total-protein measurements do not close the clinical effect gap. A rat fibrosis study using surgically implanted adipose-cell-bearing discs reported serum total protein, but the plotted data do not provide a readily transcribed estimate with uncertainty for this synthesis [53]. A diabetic-monkey ischemia experiment measured total protein separately from albumin in only two MSC-treated animals and reported no significant total-protein difference; figure-panel labels also conflict between the caption and text [54]. In children with resistant nephrotic syndrome, the visible serum-total-protein comparison describes baseline responders versus nonresponders, rather than a controlled MSC effect [55].

3.5. Urea and Blood Urea Nitrogen

Urea is the principal nitrogen-containing end product of amino acid catabolism. It is synthesized in the liver through the urea cycle and eliminated predominantly by the kidneys. Depending on laboratory practice, studies may report either serum urea or blood urea nitrogen.

These measurements are related but are not numerically interchangeable; therefore, the reported units and conversion method must be stated.

In renal injury models, increased urea or blood urea nitrogen may reflect reduced glomerular filtration and impaired renal excretion. A reduction following MSC therapy may indicate preservation of renal perfusion, attenuation of tubular damage, suppression of inflammation, or improved filtration. However, urea is not determined exclusively by kidney function. Its concentration is affected by protein intake, catabolic activity, gastrointestinal bleeding, hydration, hepatic urea synthesis, corticosteroid exposure, and urinary flow.

This dual dependence on hepatic synthesis and renal excretion is especially important in a review examining both organs. Reduced urea in severe liver injury may indicate impaired hepatic synthesis rather than improved kidney function. Therefore, urea should always be

interpreted together with creatinine, hepatic biochemical markers, and the experimental or clinical context.

Direct serum-urea findings in the accessible evidence are preclinical. In diabetic-nephropathy rats, one intravenous dose of 1×10^6 bone-marrow MSCs was followed by lower serum urea and creatinine than in untreated diabetic rats after four weeks ($p = 0.001$) [52]. In a canine 5/6-nephrectomy model ($n = 3$/group), week-12 serum urea (nine weeks after the first cell injection; mean ± SE) was 26.6 ± 1.76 mg/dL in treated dogs, and 71 ± 3.78 mg/dL in CKD controls [56]. The small veterinary study has limited applicability to human CKD. No direct human serum or plasma urea result was documented in the current accessible-source set.

Blood urea nitrogen (BUN) in the UC-MSC diabetic-nephropathy study [51] is reported separately and is not relabeled as serum urea. Consequently, the selected studies do not support pooling nitrogen measurements without accounting for the measured analyte, units, and conversion method.

Direct-urea reports should be classified by analyte and specimen. A mouse folic-acid injury study measured serum urea after adipose-cell administration, with small and variable group sizes [57]. A cisplatin rat study measured serum urea and creatinine in ordinary BM-MSC and electric-field-directed arms, which represent distinct interventions [58]. A cyclophosphamide experiment separately reported blood urea and BUN: mean ± SD blood urea was 51.6 ± 7.3 mg/dL in injury controls ($n = 6$) and 50.9 ± 5.5 mg/dL after MSC treatment ($n = 5$); the overall three-group Kruskal–Wallis comparison was not significant ($p = 0.8$), and its precise specimen label remains unresolved [59]. The short-hairpin-RNA liver study's urea-production measurement was in culture medium, not serum [39].

3.6. Creatinine

Creatinine is generated from creatine and phosphocreatine, primarily in skeletal muscle, and is eliminated mainly through glomerular filtration. Serum creatinine is the most commonly reported biochemical marker of renal function in MSC studies. An increase generally indicates reduced filtration, whereas a decline after treatment may suggest recovery of kidney function.

Experimental studies frequently report lower creatinine concentrations after MSC administration in models of ischemia–reperfusion injury, drug-induced nephrotoxicity, sepsis-associated acute kidney injury, and chronic renal fibrosis. Proposed explanations include preservation of tubular epithelial cells, improved renal microcirculation, reduced inflammatory infiltration, inhibition of apoptosis, and attenuation of oxidative and fibrotic damage.

However, creatinine is an insensitive early marker of acute kidney injury. Its concentration may not rise until substantial functional impairment has occurred, and changes can be delayed relative to the initial tissue injury. Creatinine is additionally influenced by muscle mass, age, sex, nutritional status, hydration, tubular secretion, and certain medications. In small-animal experiments, low baseline concentrations and differences in analytical methods may further affect measurement reliability [13,14].

Whenever possible, serum creatinine should be combined with measured or estimated glomerular filtration, urine output, proteinuria, cystatin C, neutrophil gelatinase-associated lipocalin, kidney injury molecule-1, and renal histology. This combined approach provides a more reliable assessment of whether MSC therapy improves renal filtration, limits structural injury, or produces both effects.

A rat diabetic-nephropathy study reported serum creatinine of 113.77 ± 8.46 μmol/L after UC-MSC treatment versus 148.82 ± 12.22 μmol/L in disease controls (mean ± SEM; $p < 0.05$; Figure 1 reports $n = 4$–5, but creatinine-specific counts for each arm are not stated) [51]. A separate bone-marrow MSC study in diabetic-nephropathy rats also reported

lower serum creatinine than in untreated diabetic rats after four weeks ($p = 0.001$) [52]. These are controlled preclinical observations; they do not by themselves establish improved renal outcomes in patients.

Additional kidney models report creatinine with different delivery routes and specimen labels. A folic-acid mouse study measured serum creatinine but serum urea nitrogen, not direct urea [60]. In rat ischemia–reperfusion injury, separate intra-aortic and local-delivery comparisons reported lower day-1 serum creatinine than vehicle [61]. Another rat experiment reported lower creatinine at 24 h, although "serum" in its abstract and "plasma" in Methods leave the specimen label unresolved [62]. An aristolochic-acid nephropathy study combined MSCs with an omental delivery strategy and ultrasound enhancement, which should remain explicit when interpreting the result [63].

Immune interactions and product state may modify experimental renoprotection. In murine ischemic AKI, intravenous BM-MSCs lowered serum creatinine at 24 and 72 h; attenuation after regulatory T-cell depletion and loss of benefit after splenectomy implicated systemic immune interactions in this model [64]. BM-MSCs reduced serum creatinine and tubular injury after glycerol-induced rhabdomyolysis in mice, with macrophage-depletion experiments supporting an immune contribution to the observed renoprotection [65]. In rat ischemia–reperfusion AKI, both untreated and erythropoietin-pretreated BM-MSCs reduced serum creatinine, with the pretreated product showing an additional day-5 benefit over untreated cells [66].

Local delivery of BM-MSC-loaded gelatin microcryogels with an omental flap reduced serum creatinine and fibrosis in nephrectomized rats, although implantation during model induction and the lack of an acellular comparator limit attribution and therapeutic extrapolation [67]. A mouse ischemia–reperfusion study found greater creatinine reduction with poly(I:C)-preconditioned BM-MSCs than with untreated MSCs, whereas LPS-preconditioned cells lacked similar protection, highlighting product-state dependence [68]. In cisplatin-treated rats, human UC-MSC administration lowered serum creatinine and tubular injury by day 5 relative to untreated injury, but its biochemical effects were not significantly different from those of cord-blood mononuclear cells [69]. The poly(I:C) report labels the assay serum creatinine despite heparinized collection; this specimen ambiguity limits precise comparison with other concentration measurements.

The clinical studies distinguish serum-creatinine concentration from estimated glomerular filtration rate (eGFR) and directly measured glomerular filtration rate (GFR). A creatinine-based estimate, an iohexol-measured filtration endpoint, and a change in filtration over time answer related but different questions; NEPHSTROM reports both estimated and measured outcomes [70]. These endpoints should remain separate from a concentration effect.

Controlled human renal findings are more limited. In the multicentre ACT-AKI trial, intra-aortic allogeneic MSCs did not accelerate creatinine-defined recovery after cardiac surgery (median 15 versus 12 days with placebo; $p = 0.32$), illustrating the gap between experimental renoprotection and clinical efficacy [71]. A 30-patient randomized study of rexlemestrocel-L, an allogeneic STRO-3-selected bone-marrow mesenchymal precursor cell (MPC) product, in diabetic nephropathy reported exploratory renal-function signals, but measured GFR differences were not significant and serum creatinine changes were small; these findings require confirmation in larger trials [72]. Single doses were 150×10^6 or 300×10^6 cells, with ten recipients per dose and ten pooled placebo recipients [72].

In the first NEPHSTROM cohort, ORBCEL-M was associated with slower decline in creatinine-based eGFR over 18 months, whereas iohexol-measured GFR did not differ significantly from placebo; the small cohort supports further investigation rather than definitive efficacy [70]. In a matched, nonrandomized renovascular-disease study, renal-

artery adipose MSC administration increased cortical perfusion and preserved single-kidney GFR, while a small transient serum creatinine rise resolved during follow-up [73].

Small uncontrolled reports and veterinary trials add useful null or descriptive findings. In a six-patient phase I ADPKD study, autologous BM-MSC infusion produced no significant reduction in serum creatinine at 12 months (2.5 mg/dL at baseline and follow-up), and the uncontrolled design limits conclusions about disease modification [74]. An uncontrolled six-patient CKD pilot reported reduced proteinuria after autologous adipose MSC infusion, but plasma-creatinine-based eGFR and its pre/post-treatment slopes did not show significant improvement [75]. A seven-recipient renal-transplant feasibility study reported serum creatinine without an untreated concentration comparator [76]. A two-patient chronic antibody-mediated rejection series showed later creatinine increases without a control group, while a blinded randomized feline CKD study found no significant creatinine change [77,78]. These studies cannot establish a general treatment effect.

3.7. Integrated Interpretation of Biochemical Outcomes

The biochemical response to MSC therapy should be evaluated as a coordinated pattern rather than as isolated changes. A decrease in ALT and AST accompanied by lower bilirubin and increased albumin provides stronger evidence of hepatic improvement than aminotransferase reduction alone. Similarly, concurrent reductions in creatinine and urea, improvement in urine output, and attenuation of tubular or glomerular damage provide more convincing evidence of renal protection.

To facilitate evidence integration, therapeutic responses may be interpreted across four complementary levels. The first level comprises biochemical markers of cellular injury or metabolic handling, including ALT, AST, bilirubin, total protein, urea, and creatinine. The second level includes organ-specific functional outcomes, such as hepatic synthetic function, urine output, creatinine-based eGFR, and directly measured GFR. The third level includes structural and mechanistic evidence, such as histological injury, fibrosis severity, inflammatory responses, oxidative stress, apoptosis, and microvascular changes. The fourth level comprises long-term outcomes, including sustained organ function, disease progression, hospitalization, need for organ-replacement therapy, transplantation, and survival. Evidence of therapeutic benefit becomes more convincing when improvements are consistent across several levels rather than being limited to a short-term change in a single biochemical marker.

Within this framework, biochemical improvement was defined as a favorable change in one or more circulating markers without sufficient evidence of structural or durable functional recovery. Tissue protection was considered more strongly supported when biochemical changes were accompanied by reduced histological injury, inflammation, apoptosis, oxidative stress, microvascular damage, or fibrosis. Functional recovery required sustained improvement in organ-specific function, whereas functional regeneration required evidence of durable restoration of specialized tissue structure and function. Regeneration was therefore not inferred from transient normalization of a single biochemical marker.

The timing of sample collection is equally important. Enzymes released during acute cellular injury may change within hours or days, whereas total protein and albumin may require longer observation periods. Creatinine and urea may lag behind molecular and histological evidence of kidney injury. Therefore, studies with a single biochemical measurement may fail to capture the complete therapeutic response.

The selected studies differ in disease, time point, cell source, cell modification, and specimen. Their findings are therefore presented descriptively rather than pooled.

Mechanistic evidence also varies in strength. Proposed pathways and associated molecular changes can explain a biochemical observation without isolating its cause. Regulatory

T-cell depletion and splenectomy [64], and macrophage interventions [65], test specific immune links in their respective injury models. Host responses to administered MSCs likewise have experimental support in particular settings [25]. These findings should be distinguished from proposed pathways and not treated as a common mechanism established for every hepatic or renal intervention.

The amount and consistency of evidence differ substantially among the six biochemical markers. ALT, AST, and creatinine have been evaluated relatively frequently, particularly in preclinical studies, whereas direct evidence for total protein and serum urea remains limited. Moreover, the availability of studies should not be equated with evidence of efficacy, because many reports involve small samples, uncontrolled designs, modified MSC products, surrogate endpoints, or uncertain analyte definitions. Table 1 therefore provides a qualitative, marker-specific summary of the clinical and preclinical evidence discussed in this review, together with the principal methodological limitations. This summary is descriptive and does not represent a formal systematic evidence grade. Selected human and preclinical study characteristics and biochemical findings are summarized in Tables 2 and 3, respectively.

Table 1. Qualitative evidence profile for biochemical markers evaluated in the reviewed MSC studies.

Biochemical Marker	Clinical Evidence in the Reviewed Studies	Preclinical Evidence in the Reviewed Studies	Overall Direction of Findings	Major Limitations	Qualitative Evidence Profile
ALT	Several clinical reports, including controlled and uncontrolled studies	Relatively extensive animal evidence	Frequently decreased after MSC administration, particularly in experimental liver injury	Heterogeneous liver diseases, treatment timing, cell products, and comparators; reduction does not demonstrate hepatic regeneration	Moderate but heterogeneous
AST	Several clinical reports	Relatively extensive animal evidence	Frequently decreased, often together with ALT	Lower liver specificity than ALT; variable sampling times and study designs	Moderate but heterogeneous
Total bilirubin	Limited clinical evidence	Moderate preclinical evidence	Decreases reported in some studies, but controlled clinical effects are inconsistent	Disease-dependent kinetics; within-group changes may not correspond to between-group benefit	Limited to moderate
Total protein	Very limited direct clinical evidence	Limited preclinical evidence	Inconsistent or product-specific findings	Frequently confused with albumin, urinary protein, or tissue protein; unresolved units in one study	Very limited
Urea	Very limited direct clinical evidence	Mainly preclinical evidence	Frequently decreased in some animal renal-injury models	Often reported as BUN or serum urea nitrogen rather than direct serum urea; influenced by hepatic synthesis and protein metabolism	Limited and predominantly preclinical
Creatinine	Limited and inconsistent clinical evidence	Relatively extensive preclinical evidence	Frequently decreased in animal studies; clinical benefit remains inconsistent	Influenced by muscle mass and volume status; creatinine concentration, eGFR, and measured GFR are non-equivalent endpoints	Moderate preclinical but limited clinical evidence

Note: This qualitative profile summarizes the studies included and discussed in the present narrative review. It should not be interpreted as a formal systematic evidence grade. The terms "very limited", "limited", "moderate", and "relatively extensive" describe the relative amount and consistency of the reviewed evidence rather than certainty ratings derived from a formal risk-of-bias or GRADE assessment. BUN, blood urea nitrogen; eGFR, estimated glomerular filtration rate; GFR, glomerular filtration rate.

Table 2. Selected clinical studies of MSC-based interventions reporting hepatic or renal biochemical outcomes.

Study and Population	MSC Source and Product	Dose and Treatment Schedule	Administration Route and Treatment Timing	Follow-Up	Relevant Biochemical and Functional Outcomes	Principal Limitations
Shi et al. [27]; HBV-associated ACLF; $n = 43$	Human UC-MSCs; conventional unmodified product	NR in the current evidence extract	MSC transfusion; timing relative to disease course NR	Up to 48 weeks	ALT and total bilirubin decreased after treatment; between-group bilirubin differences reported at weeks 36 and 48	Open-label study; small sample; total protein illustrated for one patient only and does not establish a cohort-level effect
Shi et al. [7]; HBV-associated decompensated cirrhosis; 250 randomized, 219 analyzed	Human UC-MSCs; conventional unmodified product	Repeated treatment; exact cell dose and interval NR in the current evidence extract	Route NR; administered in addition to standard care	Long-term follow-up	Total bilirubin declined from baseline in the MSC group; no significant overall between-group bilirubin difference	Withdrawals and loss to follow-up; visit-specific denominators unclear; within-group improvement does not establish a between-group treatment effect; albumin is not total protein
Shi et al. [34]; acute liver-allograft rejection; $n = 27$	MSC product; tissue source not reliably specified in the current evidence extract	Treatment schedule varied; one recipient received three infusions	Route and exact timing NR; MSCs administered with immunosuppressive therapy	12 weeks	Lower ALT, AST, and total bilirubin reported during follow-up	Small controlled pilot; concomitant immunosuppression; plotted values require extraction; variable infusion schedule
Jia et al. [35]; HBV-related liver failure and cirrhosis; $n = 123$ treated	Human UC-MSCs; conventional unmodified product	Repeated treatment; exact dose NR	Route NR; MSCs administered with standard care	Treatment-duration analysis; exact maximum follow-up NR	ALT, AST, and bilirubin trajectories reported after treatment	No untreated comparator; treatment effect cannot be separated fully from standard care or natural disease course
Zhang et al. [36]; recipient-age analysis of HBV-related liver failure and cirrhosis	Human UC-MSCs; same or apparently overlapping treated cohort as Jia et al.	As reported in the parent treatment cohort	Route NR; treatment timing as in the parent cohort	NR	ALT, AST, and bilirubin trajectories assessed according to recipient age	Apparent overlap with Jia et al.; subgroup analysis should not be counted as independent confirmation
Swaminathan et al. [71]; postoperative AKI; $n = 156$ randomized, 135 dosed	Allogeneic MSC product	Single administration; exact dose NR in the current evidence extract	Intra-aortic administration after cardiac surgery	Time to creatinine-defined renal recovery and clinical follow-up	Median time to renal recovery: 15 days with MSCs versus 12 days with placebo; $p = 0.32$	Randomized placebo-controlled trial stopped for futility; no acceleration of creatinine-defined recovery
Packham et al. [72]; diabetic nephropathy; $n = 30$	Rexlemestrocel-L; allogeneic STRO-3-selected, culture-expanded bone-marrow mesenchymal precursor cell product	Single dose of 150×10^6 or 300×10^6 cells; $n = 10$ per dose; pooled placebo $n = 10$	Administration route NR in the current evidence extract; treatment in established diabetic nephropathy	NR in the current evidence extract	Small serum-creatinine changes and exploratory filtration signals; measured GFR difference not significant	Small dose-escalation trial; underpowered for efficacy; selected precursor cell product is not equivalent to conventional unmodified MSCs

Table 2. *Cont.*

Study and Population	MSC Source and Product	Dose and Treatment Schedule	Administration Route and Treatment Timing	Follow-Up	Relevant Biochemical and Functional Outcomes	Principal Limitations
Perico et al. [70]; NEPHSTROM diabetic kidney disease cohort; $n = 16$ men	ORBCEL-M allogeneic stromal cell product	Single administration; exact dose NR in the current evidence extract	Route NR; treatment in established diabetic kidney disease	18 months	Median annual CKD-EPI eGFR slope: −2.6 versus −8.7 mL/min/1.73 m^2/year; $p = 0.034$; iohexol-measured GFR difference not significant	Very small placebo group ($n = 4$); discrepancy between estimated and directly measured GFR; preliminary efficacy evidence
Makhlough et al. [74]; ADPKD; $n = 6$	Autologous BM-MSCs	Single infusion; exact dose NR in the current evidence extract	Infusion route NR; treatment in established ADPKD	12 months	Serum creatinine was 2.5 mg/dL at baseline and 12 months; $p = 0.96$	Uncontrolled phase I study; no significant creatinine reduction; no untreated comparator; designed primarily for safety and tolerability
Saad et al. [73]; renovascular disease; MSC $n = 14$, matched control $n = 14$	Autologous adipose-derived MSCs	Single treatment; exact dose NR in the current evidence extract	Renal-artery administration in established renovascular disease	3 months	Treated-cohort creatinine: 1.52 mg/dL at baseline, 1.72 mg/dL the next day, and 1.53 mg/dL at 3 months; increased cortical perfusion and preserved single-kidney GFR	Matched nonrandomized design; transient creatinine increase; perfusion and single-kidney GFR findings do not establish a reduction in serum creatinine
Villanueva et al. [75]; CKD; $n = 6$	Autologous adipose-derived MSCs	Single infusion; exact dose NR in the current evidence extract	Route NR; treatment in established CKD	NR in the current evidence extract	Proteinuria decreased; plasma-creatinine-based eGFR and pre/post-treatment slopes did not improve significantly	Uncontrolled pilot; very small sample; proteinuria is complementary but does not establish a creatinine or filtration treatment effect
Lee et al. [76]; living-donor kidney transplantation; $n = 7$	Donor-derived MSCs; tissue source NR in the current evidence extract	Treatment schedule NR	Intra-osseous administration into bone marrow in the transplantation setting	NR	Descriptive serum-creatinine trajectory reported	Feasibility study; no untreated concentration comparator; transplantation and concomitant immunosuppression complicate attribution
Ban et al. [77]; chronic active antibody-mediated rejection; $n = 2$	Allogeneic MSC product	Treatment schedule NR	Route and timing NR; administered after failure of rituximab and intravenous immunoglobulin	NR	Later serum-creatinine increases; no sustained functional improvement established	Two-patient uncontrolled series; refractory population; concomitant and previous therapies; no comparator
Morello et al. [55]; pediatric multidrug-resistant nephrotic syndrome	Cord-blood-derived MSCs	Dose and treatment schedule NR in the current evidence extract	Route and timing NR	NR	Serum total protein reported separately from albumin	Baseline responder versus nonresponder comparison; does not establish an MSC-induced total-protein treatment effect

Table 3. Selected preclinical studies of MSC-based interventions reporting hepatic or renal biochemical outcomes.

Study and Disease Model	MSC Source and Product	Dose and Treatment Schedule	Administration Route and Timing Relative to Injury	Follow-Up or Assessment Time	Biochemical, Functional, and Histological Outcomes	Principal Limitations
Hong et al. [28]; DEN-induced rat cirrhosis	Human UC-MSCs; conventional unmodified product	Five dose or treatment-schedule groups; exact doses NR in the current evidence extract	Infusion route and timing NR	NR	ALT, AST, and bilirubin were lower; total protein: 57.33 ± 1.33 g/L in injury controls and 57.59–64.50 g/L across MSC groups	No significant total-protein contrast was clearly marked; several dose and schedule groups complicate a single treatment estimate
Li et al. [29]; acute CCl_4-induced rat liver injury	Unmodified BM-MSCs and MSC-derived hepatocyte-like cells	Dose NR	Route and timing NR	Day 3	ALT, AST, and bilirubin were lower in both cell-treatment groups than in injured saline controls; $p < 0.05$	Hepatocyte-like differentiated cells represent a distinct product and should not be interpreted as conventional MSCs
Su et al. [6]; CCl_4-induced rat cirrhosis; $n = 6$ per group	Unmodified BM-MSCs and *Smad7*-engineered BM-MSCs	Dose NR	Route and timing NR	Day 21	Total protein was similar in the injury-control and unmodified-MSC groups but higher in the Smad7-engineered group	Original total-protein unit could not be verified; numerical values should not be used as key evidence; higher value was product-specific
Abdel Aziz et al. [52]; rat diabetic nephropathy	BM-MSCs; conventional unmodified product	One dose of 1×10^6 cells	Intravenous administration; exact timing relative to model induction NR	Week 4	Serum urea and creatinine were lower than in diabetic controls; $p = 0.001$	Urinary albumin was measured separately and is not serum total protein; timing and other product characteristics require verification
El Miniawy et al. [56]; canine 5/6-nephrectomy CKD; $n = 3$ per group	Camel Wharton's-jelly-derived MSCs	Two cell administrations; exact cell dose NR	Ultrasound-guided renal-cortex injections; first injection timing relative to nephrectomy NR	Week 12; 9 weeks after the first cell injection	Serum urea: 26.6 ± 1.76 mg/dL in the MSC group versus 71 ± 3.78 mg/dL in untreated CKD controls	Very small veterinary model; local renal delivery; limited generalizability to human CKD
Chen et al. [51]; rat diabetic nephropathy	Human UC-MSCs; conventional unmodified product	Dose and schedule NR	Route and timing NR	NR	Serum creatinine: 113.77 ± 8.46 versus 148.82 ± 12.22 μmol/L in diabetic-nephropathy controls; $p < 0.05$	Figure-specific sample size appears to be 4–5; arm- and analyte-specific denominators unresolved; BUN is not serum urea; urinary protein is not serum total protein
Sun et al. [43]; rat acute liver failure	BM-MSCs; conventional unmodified product	Dose NR; four delivery-route groups	Four administration routes, including endovascular and intraperitoneal delivery; exact timing NR	Day 7	ALT and AST were lower after endovascular delivery	Intraperitoneal effect was not significant; figure caption appears to reverse marker labels; route groups should be interpreted separately

Table 3. *Cont.*

Study and Disease Model	MSC Source and Product	Dose and Treatment Schedule	Administration Route and Timing Relative to Injury	Follow-Up or Assessment Time	Biochemical, Functional, and Histological Outcomes	Principal Limitations
Song et al. [45]; CCl_4-induced rat cirrhosis	BM-MSCs; conventional unmodified product	Dose and schedule NR	Portal-vein or tail-vein administration; timing relative to established cirrhosis NR	ALT assessed at week 2; AST difference at week 6	ALT and AST responses differed according to assessment time	Different marker kinetics; route-specific effects require separate interpretation; albumin is not total protein
Zheng et al. [48]; CCl_4-induced rat acute liver failure	Human UC-MSCs; conventional unmodified product	Dose NR	Tail-vein or direct intraliver administration; exact treatment timing NR	48 h	Total bilirubin: 2.2 ± 1.0 μmol/L after tail-vein delivery, 3.0 ± 1.2 μmol/L after intraliver delivery, and 7.6 ± 1.3 μmol/L in controls	Route difference was not significant; findings apply to an acute experimental model
Cen et al. [49]; pig acute liver failure	Menstrual-blood-derived MSCs	Dose and schedule NR	Immediate intraportal administration at model induction	Later time points; exact schedule NR	Subsequent increases in ALT, AST, and total bilirubin were attenuated; survival was prolonged	Administration at injury induction evaluates prevention or immediate protection rather than clinically realistic rescue therapy
Yang et al. [50]; DDC-induced mouse cholestasis	Human menstrual-blood-derived MSCs	Dose and schedule NR	Route and timing NR	NR	Total bilirubin and transaminases were lower than in vehicle controls	Cholestatic model; cannot be generalized to all hepatic diseases; intervention characteristics incompletely represented in the current extract
Nomura et al. [53]; experimentally induced rat hepatic fibrosis	Human adipose-derived cell-bearing discs; biomaterial-assisted intervention	Cell dose and implantation schedule NR	Surgical implantation of cell-bearing discs; timing relative to fibrosis induction NR	NR	Serum total protein was measured; additional fibrosis outcomes reported in the original study	Exact serum-total-protein values and uncertainty were not readily extractable; biomaterial-assisted product lacks equivalence to conventional MSC infusion
Lee et al. [54]; renal ischemia–reperfusion in diabetic monkeys	Human BM-MSCs; conventional product	Dose and schedule NR; two MSC-treated animals	Route and timing NR	NR	Total protein was measured separately from albumin; no significant total-protein difference reported	Only two MSC-treated monkeys; figure-panel labels conflict between caption and text; insufficient evidence for a total-protein effect
Abdelrahman et al. [58]; cisplatin-induced rat nephrotoxicity	Conventional BM-MSCs and electric-field-directed BM-MSC intervention	Dose and schedule NR	Route and timing NR	NR	Serum urea and creatinine were assessed in separate MSC-intervention groups	Electric-field-directed intervention represents an enhanced treatment protocol; effects cannot be attributed directly to conventional MSCs without an appropriate comparison

Table 3. *Cont.*

Study and Disease Model	MSC Source and Product	Dose and Treatment Schedule	Administration Route and Timing Relative to Injury	Follow-Up or Assessment Time	Biochemical, Functional, and Histological Outcomes	Principal Limitations
Çaydere et al. [59]; cyclophosphamide-induced rat nephrotoxicity	MSC product; source not reliably specified in the current evidence extract	MSC group $n = 5$; dose and schedule NR	Route and timing NR	NR	Blood urea: 51.6 ± 7.3 mg/dL in injury controls versus 50.9 ± 5.5 mg/dL in MSC-treated animals; three-group Kruskal–Wallis $p = 0.8$	Specimen designation unresolved; blood urea and BUN reported separately; reported p value is not a pairwise MSC-versus-injury comparison
Hu et al. [64]; mouse ischemic AKI	BM-MSCs; conventional product with regulatory T-cell depletion and splenectomy experiments	Dose and schedule NR	Intravenous administration; timing relative to ischemia–reperfusion NR	Serum creatinine assessed at 24 and 72 h	Lower serum creatinine; attenuation after regulatory T-cell depletion and loss of benefit after splenectomy supported immune involvement	Mechanistic evidence is model-specific; depletion and splenectomy may have broader physiological effects
Geng et al. [65]; mouse rhabdomyolysis-induced AKI	BM-MSCs; conventional product with macrophage-depletion experiments	Dose and schedule NR	Route and timing relative to glycerol-induced injury NR	NR	Lower serum creatinine and tubular injury; macrophage intervention supported an immune contribution	Mechanistic evidence is specific to the rhabdomyolysis model; exact treatment characteristics require verification
Geng et al. [67]; nephrectomized rats	BM-MSC-loaded gelatin microcryogels with an omental flap	Dose and implantation schedule NR	Local implantation during model induction	Weeks 4, 8, and 12	Lower creatinine and reduced fibrosis	Combined biomaterial and omental-flap intervention; no acellular microcryogel comparator; implantation at model induction limits therapeutic extrapolation
Chen et al. [68]; mouse renal ischemia–reperfusion injury	Unmodified, poly(I:C)-preconditioned, and LPS-preconditioned BM-MSCs	Dose and schedule NR	Route and timing NR	NR	Poly(I:C)-preconditioned MSCs produced greater creatinine reduction; LPS-preconditioned MSCs did not provide similar protection	Preconditioned products are biologically distinct; heparinized collection conflicts with the serum-creatinine label
Quimby et al. [78]; feline CKD; $n = 8$	Allogeneic adipose-derived MSCs	MSC $n = 4$ and placebo $n = 4$; dose and schedule NR in the current evidence extract	Intravenous administration; timing in established feline CKD	NR	No significant change in serum creatinine	Very small veterinary trial; crossover observations are not independent randomized evidence; limited power

Note: MSC products, doses, treatment schedules, administration routes, treatment timing, and follow-up periods are reported as described in the accessible evidence. NR indicates information that was not reported or could not be reliably verified from the available full text or current evidence extract. Modified, preconditioned, selected, differentiated, biomaterial-assisted, and combination products should not be considered therapeutically interchangeable with conventional unmodified MSCs. BUN, blood urea nitrogen; eGFR, estimated glomerular filtration rate; GFR, glomerular filtration rate; BM-MSC, bone-marrow-derived mesenchymal stromal cell; UC-MSC, umbilical-cord-derived mesenchymal stromal cell.

Quantitative findings were treated cautiously when the original reports contained unresolved units, inconsistent specimen labels, conflicting figure annotations, unclear analyte-specific sample sizes, or values available only in graphical form. Such findings were retained, where relevant, as descriptive observations but were not used as key quantitative evidence of therapeutic efficacy or for direct numerical comparison across studies.

3.8. Comparative Hepatic and Renal Responses and Liver–Kidney Interactions

MSC-based interventions may influence liver and kidney injury through several shared biological pathways, including modulation of innate and adaptive immune responses, regulation of macrophage phenotypes, attenuation of oxidative stress and apoptosis, secretion of trophic and angiogenic mediators, support of microvascular integrity, and suppression of profibrotic signaling [3,5,24,25]. However, the cellular targets, inflammatory environments, injury kinetics, and functional consequences of these pathways differ between the two organs. Similar directions of biochemical change should therefore not be assumed to reflect identical mechanisms or equivalent degrees of tissue recovery. The shared pathways, organ-specific cellular targets, and strength of the corresponding mechanistic evidence are summarized in Table 4.

Table 4. Shared and organ-specific mechanisms of hepatic and renal responses to MSC-based interventions and the strength of mechanistic support.

Comparative Domain	Shared MSC-Associated Pathways	Hepatic Context	Renal Context	Evidence Status and Interpretive Limitation
Inflammatory modulation	Reduced inflammatory signaling and altered cytokine profiles	Effects may involve Kupffer cells, recruited monocytes, hepatocytes, and hepatic stellate cells	Effects may involve infiltrating immune cells, tubular epithelial cells, glomerular cells, and the renal interstitium	Cytokine and gene-expression changes provide supportive evidence but do not establish that inflammatory modulation is necessary for therapeutic benefit
Macrophage regulation	Changes in macrophage abundance, activation state, cytokine production, and polarization-associated markers	Kupffer cells and recruited hepatic macrophages may influence hepatocyte injury and stellate cell activation	Renal macrophages may influence tubular injury, interstitial inflammation, microvascular dysfunction, and fibrosis	Marker changes are associative. Loss of benefit after macrophage depletion provides stronger functional evidence within the specific experimental model [65]
Host immune cell interactions	MSCs may interact with T cells, splenic immune cells, monocytes, and tissue-resident phagocytes	May modify hepatic inflammatory and fibrotic responses	May influence renal inflammation and recovery after acute injury	T-cell depletion and splenectomy experiments provide direct functional support for immune cell involvement in the examined renal model, but not for a universal mechanism [64]
Apoptotic MSC clearance	Apoptotic MSCs may be engulfed by host phagocytes and alter their immunoregulatory activity	May contribute to systemic or hepatic immune modulation after administration	May contribute to systemic or renal immune modulation after administration	Experimental evidence supports a functional role for MSC apoptosis and phagocytic clearance in specific settings, but its importance across liver and kidney models remains context-dependent [25]

Table 4. *Cont.*

Comparative Domain	Shared MSC-Associated Pathways	Hepatic Context	Renal Context	Evidence Status and Interpretive Limitation
Paracrine and trophic signaling	Secretion of cytokines, growth factors, extracellular-matrix regulators, lipids, and extracellular vesicles	May support hepatocyte survival, sinusoidal integrity, angiogenesis, and endogenous repair	May support tubular cell survival, peritubular microcirculation, endothelial integrity, and endogenous repair	Changes in secreted mediators and downstream signaling usually provide supportive evidence. Causality requires mediator neutralization, receptor blockade, loss-of-function, or rescue experiments
Oxidative stress and apoptosis	Reduced oxidative injury and expression of apoptosis-associated markers	May reduce hepatocyte injury and cell death	May reduce tubular epithelial cell injury and apoptosis	Reduced oxidative-stress or apoptosis markers are biologically supportive but do not independently demonstrate that these pathways caused biochemical improvement
Microvascular protection	Support of endothelial integrity, perfusion, and angiogenic responses	Hepatic sinusoidal endothelial function and intrahepatic microcirculation	Glomerular and peritubular endothelial function, cortical perfusion, and renal microcirculation	Perfusion measurements provide functional support, whereas angiogenic-marker changes alone remain associative
Fibrotic remodeling	Modulation of TGF-β-related signaling, fibroblast activation, and extracellular-matrix deposition	Hepatic stellate cell activation and hepatic collagen deposition	Interstitial fibroblast activation, glomerulosclerosis, and tubulointerstitial fibrosis	Reduced fibrosis on histological or morphometric assessment provides structural evidence; changes in profibrotic gene expression alone provide supportive evidence
Biochemical response	Reduced circulating markers associated with injury, metabolism, or organ function	ALT, AST, bilirubin, total protein, and albumin	Urea, creatinine, eGFR, measured GFR, proteinuria, and albuminuria	Biochemical improvement demonstrates neither mechanism nor regeneration. Interpretation requires concordance with functional and structural outcomes
Evidence of tissue protection	Concordant biochemical, functional, inflammatory, and histological improvement	Lower hepatocellular injury together with improved bilirubin handling, synthetic function, histology, and fibrosis	Improved filtration or urine findings together with reduced tubular or glomerular injury and fibrosis	Concordant outcomes support tissue protection more strongly than a single biochemical marker, but do not necessarily demonstrate regeneration
Evidence of functional regeneration	Sustained restoration of specialized tissue structure and function	Durable recovery of hepatic architecture, synthetic and excretory function, and clinically relevant outcomes	Durable recovery of renal filtration, nephron-related structure, urinary function, and clinically relevant outcomes	Regeneration requires long-term structural and functional evidence and should not be inferred from transient biochemical improvement

Note: Mechanistic evidence was categorized as direct functional, supportive or associative, or proposed and context-dependent. Direct functional evidence requires experimental perturbation of the proposed mediator, pathway, or cell population, followed by attenuation, abolition, or restoration of the therapeutic effect. Changes in cytokines, gene expression, signaling proteins, histological markers, or immune cell phenotypes without functional perturbation were considered supportive or associative. Evidence obtained in one organ, disease model, or MSC product should not be generalized automatically to other experimental or clinical contexts. ALT, alanine aminotransferase; AST, aspartate aminotransferase; eGFR, estimated glomerular filtration rate; GFR, glomerular filtration rate; MSC, mesenchymal stromal cell; TGF-β, transforming growth factor beta.

In the liver, the principal cellular targets include injured hepatocytes, resident Kupffer cells, recruited monocyte-derived macrophages, hepatic stellate cells, and sinusoidal

endothelial cells. Reduced inflammatory signaling and hepatocyte injury may lower circulating ALT and AST, whereas changes in bilirubin additionally depend on hepatic uptake, conjugation, canalicular transport, and biliary excretion. Effects on hepatic stellate cell activation and extracellular-matrix deposition are more directly relevant to fibrosis than aminotransferase normalization. Similarly, improvement in albumin or other measures of hepatic synthetic function may occur on a different timescale from reductions in hepatocellular injury markers.

In the kidney, relevant targets include tubular epithelial cells, glomerular and peritubular endothelial cells, podocytes, infiltrating immune cells, interstitial fibroblasts, and the renal microvasculature. MSC-associated reductions in inflammation, tubular apoptosis, and microvascular injury may contribute to lower creatinine or urea in experimental models. However, these circulating markers are influenced by filtration, generation, distribution, hydration, protein metabolism, and treatment timing. Renal protection should therefore be evaluated using filtration measurements, urine output, urinary biomarkers, proteinuria or albuminuria, renal histology, fibrosis, and longer-term functional recovery.

Macrophage regulation represents a potentially shared pathway but occurs in organ-specific cellular contexts. In the liver, MSC-mediated effects may involve Kupffer cells and recruited hepatic macrophages that influence hepatocyte injury and stellate cell activation. In the kidney, macrophage responses may affect tubular injury, interstitial inflammation, vascular dysfunction, and fibrotic remodeling. Changes in macrophage markers or inflammatory cytokines support an association with treatment response but do not, without functional perturbation experiments, demonstrate that macrophages are necessary mediators of therapeutic benefit. As shown in Table 4, changes in macrophage markers and inflammatory cytokines were classified as supportive or associative evidence, whereas depletion or other functional perturbation experiments were considered stronger evidence of mechanistic involvement.

Liver–kidney interactions further complicate interpretation. Urea is synthesized in the liver and excreted by the kidneys, while creatinine-based assessment of renal function may be affected by reduced muscle mass in advanced liver disease. Total protein is influenced by hepatic synthesis, immunoglobulins, inflammation, nutrition, protein loss, and hydration. Consequently, an isolated change in urea, creatinine, or total protein cannot always be attributed to recovery of a single organ. Concordant biochemical, functional, histological, and clinical findings are required to distinguish common systemic effects from organ-specific tissue protection.

4. Discussion

The evidence supports a cautious, marker-specific interpretation of MSC therapy. Preclinical studies report lower ALT, AST, bilirubin, urea, or creatinine in several injury models, but results vary with disease, timing, route, and cell product. Human liver studies provide signals for some outcomes, yet controlled effects are not uniform: the long-term cirrhosis follow-up did not demonstrate a between-group total-bilirubin difference [7]. Human renal studies now include a multicentre randomized postoperative-AKI trial and smaller CKD, diabetic nephropathy, renovascular, and transplant reports; their controlled and uncontrolled findings require separate interpretation.

The discrepancy between preclinical and clinical findings may be explained by several translational factors. Experimental animal models commonly involve standardized, synchronized, and relatively homogeneous injuries, whereas patients present with heterogeneous disease etiologies, durations, stages, comorbidities, concomitant treatments, and degrees of irreversible structural damage. In many animal studies, MSCs are administered shortly before, during, or soon after injury induction, when inflammatory and tissue-repair

responses may still be modifiable. In clinical practice, treatment is often initiated later, after fibrosis, vascular injury, or loss of functional tissue has already developed. Differences in cell dose relative to body weight, administration route, cell viability, biodistribution, immune microenvironment, and therapeutic window may further modify treatment responses. In addition, short-term reductions in ALT, AST, urea, or creatinine in experimental models may not correspond to sustained recovery of organ function in patients.

Clinical endpoint selection represents an additional source of discrepancy. Serum creatinine concentration, creatinine-based estimated glomerular filtration rate, and directly measured glomerular filtration rate are related but non-equivalent outcomes. The ACT-AKI trial did not demonstrate accelerated creatinine-defined renal recovery after MSC administration, whereas the NEPHSTROM study reported a slower decline in creatinine-based eGFR without a statistically significant difference in iohexol-measured GFR [70,71]. These findings illustrate that improvement in a surrogate biochemical or estimated endpoint should not be interpreted automatically as evidence of directly measured or durable organ functional recovery. Similarly, within-group improvement from baseline does not establish a treatment effect when the corresponding between-group difference is not significant.

Total protein and serum urea are important evidence gaps. Total protein must be distinguished from albumin, urinary protein, and tissue protein; the available human total-protein example is an individual patient, while animal findings include null or product-specific results [6,27,28]. Direct serum urea must likewise be distinguished from BUN and serum urea nitrogen. Although serum urea and BUN are physiologically related, they are not numerically interchangeable unless the units and conversion method are explicitly stated. Many renal studies report one of the latter, and these values should not be relabeled as serum urea. The current evidence therefore supports a descriptive, marker-specific synthesis rather than a pooled treatment estimate across biologically and methodologically heterogeneous conditions.

The interpretive weight of the included evidence was considered according to six study-level domains: study design and comparator, sample size and statistical precision, disease definition and severity, cell-product and treatment characterization, endpoint validity, and duration and completeness of follow-up. This qualitative appraisal was not intended to replace a formal risk-of-bias assessment. Randomized controlled trials with clearly defined comparators and prespecified functional endpoints were given greater interpretive weight than uncontrolled studies, case series, or within-group pre–post comparisons. Nevertheless, randomized design alone does not eliminate limitations related to small sample size, incomplete follow-up, exploratory endpoints, or insufficient cell-product characterization.

Controlled nonrandomized studies may provide informative comparative evidence, but their findings remain susceptible to baseline differences, treatment-selection bias, concomitant interventions, and residual confounding. Uncontrolled studies and small case series were considered primarily informative for safety, feasibility, and descriptive biochemical trajectories. They were not treated as sufficient evidence of therapeutic efficacy or disease modification. Similarly, statistically significant within-group improvement was not considered equivalent to a demonstrated between-group treatment effect.

Preclinical studies were interpreted according to the relevance of the disease model, timing of treatment relative to injury induction, presence of appropriate disease and intervention controls, group size, follow-up duration, cell-product characterization, and concordance among biochemical, functional, and histological outcomes. Studies in which MSCs were administered before, during, or immediately after injury induction may evaluate prevention or early tissue protection rather than clinically realistic rescue therapy. Evidence from such animal studies should not be considered equivalent to evidence from controlled clinical trials, even when the reported biochemical effect is large or statistically significant.

The reviewed studies differ substantially in species, disease etiology and severity, baseline injury, MSC source, product modification, dose, administration route, treatment timing, follow-up duration, assay, specimen, comparator, and outcome definition. Some studies report only within-arm changes, values available exclusively in graphical form, unclear analyte-specific sample sizes, or very small experimental groups. These reporting limitations reduce the reliability of precise cross-study comparisons. Table 1 provides a qualitative marker-specific evidence profile, whereas Tables 2 and 3 present selected clinical and preclinical examples, respectively. These tables should not be interpreted as a complete census of the available literature.

The publication count does not measure the number of independent populations or successful interventions. The two HBV cohort reports are related analyses, and multiple outcomes within one experiment share the same animals. A systematic review of diabetic kidney disease pools creatinine and BUN across heterogeneous MSC models, but its BUN estimate is not a pooled direct-urea estimate, and the review adds no independent primary treatment comparison [79]. The negative ACT-AKI result and the difference between estimated and measured GFR in NEPHSTROM further limit extrapolation from animal biochemical signals to clinical benefit [70,71].

The present review also has methodological limitations. The literature search and full-text screening were not exhaustive; only PubMed-indexed English-language publications were considered, and full-text accessibility influenced study inclusion. No PRISMA-compliant selection process or formal study-level risk-of-bias assessment was performed. Relevant publications may therefore have been omitted, and the qualitative evidence profiles should not be interpreted as formal certainty ratings. Nevertheless, positive, negative, null, and inconclusive findings were retained where they were directly relevant and could be verified, and controlled and uncontrolled evidence was interpreted separately.

Product heterogeneity further limits cross-study comparison. As defined in Section 2.5, findings obtained with genetically engineered, preconditioned, differentiated, selected, or delivery-assisted products were interpreted as product-specific evidence and were not attributed directly to conventional unmodified MSC therapy.

5. Conclusions

MSC-based interventions have been associated with changes in hepatic and renal biochemical markers, particularly in preclinical models. However, reductions in ALT, AST, urea, or creatinine do not independently demonstrate hepatic regeneration, structural renal recovery, or a clinically meaningful treatment effect. The evidence differs substantially among the six evaluated markers. Direct evidence for total protein remains very limited, while direct serum-urea findings are predominantly preclinical and should be distinguished from BUN or serum urea nitrogen. Clinical findings for creatinine and renal filtration remain inconsistent, and results obtained with modified, preconditioned, differentiated, or combination MSC products should not be attributed directly to conventional unmodified MSC therapy.

Future research should prioritize standardized characterization of MSC products, including tissue source, donor characteristics, culture conditions, passage number, cryopreservation and post-thaw recovery, viability, dose, route of administration, and disease-relevant potency assays. Dose-ranging studies and comparisons of administration routes and treatment timing are needed to define appropriate therapeutic windows for specific liver and kidney diseases. Clinical trials should stratify participants according to disease etiology, stage, severity, inflammatory phenotype, comorbidities, and the presence of potentially irreversible fibrosis or functional tissue loss. Patient-selection criteria, concomitant treatments, and comparator interventions should be clearly defined. Longer follow-up is required to

determine whether early biochemical responses are transient or translate into sustained organ protection. Future trials should therefore integrate biochemical markers with hepatic synthetic function, urine output, proteinuria or albuminuria, directly measured or appropriately estimated GFR, histological injury, fibrosis, inflammatory and oxidative-stress markers, need for organ-replacement therapy, hospitalization, transplantation, survival, and other disease-relevant clinical outcomes. This approach will help distinguish short-term laboratory changes from durable recovery of organ function.

Author Contributions: Conceptualization, B.B.K., N.Z.A. and B.K.M.; data curation, N.Z.A., A.O.S., T.T.Y., A.I.G., A.K.Z. and B.M.A.; formal analysis, N.Z.A., A.O.S., A.I.G., A.K.Z. and B.M.A.; writing—original draft preparation, T.T.Y., D.S.T., A.Z.Z., A.A.A. and A.M.G.; writing—review and editing, S.M., T.S.B., E.K.C., B.B.K., A.O.S., A.K.M., A.K.Z., A.M.G. and B.K.M. All authors have read and agreed to the published version of the manuscript.

Funding: This research was funded by the Committee of Science of the Ministry of Science and Higher Education of the Republic of Kazakhstan (grant number IRN BR28713159, "Innovative Approaches to the Development of a Cell-Based Product for the Treatment of Chronic and Socially Significant Diseases", 2025–2027).

Institutional Review Board Statement: Not applicable.

Informed Consent Statement: Not applicable.

Data Availability Statement: A qualitative evidence profile and selected clinical and preclinical study characteristics are presented in Tables 1–3.

Acknowledgments: During the preparation of this manuscript, the authors used ChatGPT (OpenAI, San Francisco, CA, USA; GPT-6 family) for English-language editing and improvement of clarity in author-drafted text.

Conflicts of Interest: The authors declare no conflicts of interest.

Abbreviations

ACLF	Acute-on-chronic liver failure
ADPKD	Autosomal dominant polycystic kidney disease
AKI	Acute kidney injury
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
BM-MSC	Bone-marrow-derived mesenchymal stromal cell
BUN	Blood urea nitrogen
CKD	Chronic kidney disease
DEN	Diethylnitrosamine
eGFR	Estimated glomerular filtration rate
GFR	Glomerular filtration rate
HBV	Hepatitis B virus
HGF	Hepatocyte growth factor
IL	Interleukin
IV	Intravenous
LPS	Lipopolysaccharide
MPC	Mesenchymal precursor cell
MSC	Mesenchymal stromal cell
PBS	Phosphate-buffered saline
SD	Standard deviation
SE	Standard error
SEM	Standard error of the mean
TGF	Transforming growth factor
TNF	Tumor necrosis factor
UC-MSC	Umbilical-cord-derived mesenchymal stromal cell

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