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Placenta-Derived Mesenchymal Stem Cells in Chronic Kidney Disease via NADPH Oxidase

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Abstract

Introduction: Chronic kidney disease (CKD) is associated with gradual deterioration of renal structure and function, accompanied by persistent fibrosis and oxidative imbalance. Excessive generation of reactive oxygen species (ROS), particularly through NADPH oxidase pathways, contributes to inflammatory and profibrotic signaling during disease progression. This study investigated whether human placenta-derived mesenchymal stem cells (MSCs) could modulate oxidative stress and fibrotic responses in an experimental CKD model.

Methods: A subtotal nephrectomy model was used to establish CKD in rats. Following disease induction, placenta-derived MSCs were administered intravenously. Renal tissues were evaluated for markers associated with oxidative injury, including ROS, hydrogen peroxide (H_2O_2), and NADPH oxidase-4 (NOX4). Fibrosis-related molecules, including fibronectin, collagen IV, and α-smooth muscle actin (α-SMA), were also assessed and compared among study groups.

Results: MSC administration was associated with reductions in oxidative stress markers, including ROS, H_2O_2, and NOX4 expression. A trend toward reduced expression of fibrosis-related markers was also observed following MSC treatment; however, reductions in protein expression did not reach statistical significance for all comparisons.

Conclusion: Placenta-derived MSC treatment was associated with modulation of oxidative stress– and fibrosis-related pathways in experimental CKD. Although reductions in several molecular markers were observed following treatment, additional studies with larger sample sizes and longer follow-up periods are needed to confirm the therapeutic potential of MSCs and to further clarify their effects on renal fibrosis and disease progression.

Keywords: mesenchymal stem cells; chronic kidney disease; NADPH oxidase 4; oxidative stress; renal fibrosis.

Introduction

Mesenchymal stem cells (MSCs) have become an important focus of regenerative medicine because of their capacity to participate in tissue repair and restoration of cellular balance. These cells exhibit self-renewal properties and are capable of differentiating into multiple mesenchymal lineages under appropriate microenvironmental conditions. In addition to differentiation, MSCs exert biological effects through paracrine signaling, releasing growth factors, cytokines, and extracellular vesicles that contribute to regulation of inflammation, apoptosis, and tissue remodeling [1–3].

Among the available MSC sources, placental tissues have attracted considerable interest because they are easily obtainable, associated with minimal ethical concerns, and characterized by relatively low immunogenicity. Placenta-derived MSCs demonstrate high proliferative potential and may provide a rich source of progenitor cells suitable for regenerative applications. Experimental evidence suggests that these cells can influence tissue repair through immunomodulatory and antifibrotic actions. Previous investigations in renal injury models have further demonstrated that MSC-based interventions may reduce inflammation, improve renal morphology, and attenuate fibrotic progression in chronic kidney disease [4–9].

Chronic kidney disease (CKD) is a progressive disorder associated with gradual deterioration of renal structure and function. Persistent injury within the kidney promotes extracellular matrix accumulation, tubular

remodeling, and irreversible tissue damage. Fibrosis represents a major pathological process in CKD and contributes substantially to nephron loss and declining renal performance. As disease severity increases, structural alterations within renal tissue become increasingly resistant to endogenous repair mechanisms [10–11].

Oxidative stress is widely recognized as an important contributor to CKD progression. Excessive generation of ROS disrupts intracellular signaling pathways and enhances inflammatory activation. ROS accumulation may also accelerate cellular injury by promoting lipid peroxidation, mitochondrial dysfunction, and extracellular matrix deposition. Among enzymatic systems involved in ROS production, NADPH oxidases have been identified as major regulators of redox signaling within renal tissue [12–13].

NOX4 is the predominant NADPH oxidase isoform expressed in the kidney and has been linked to multiple forms of renal injury. Increased NOX4 activity has been associated with enhanced oxidative burden, activation of profibrotic pathways, and progression of tubulointerstitial damage. Experimental observations indicate that NOX4 contributes to extracellular matrix accumulation and myofibroblast activation, partly through interactions with transforming growth factor-beta–related signaling mechanisms [14–20]. Suppression of NOX4 activity has been reported to reduce oxidative injury and alleviate fibrotic remodeling in nephropathy models [21].

Given the close relationship between oxidative stress, fibrosis, and CKD progression, therapeutic strategies targeting these mechanisms may offer meaningful clinical benefit. The present study was designed to investigate the effects of human placenta-derived mesenchymal stem cells on oxidative stress markers and fibrosis-related molecular pathways in a nephrectomy-induced CKD rat model, with particular emphasis on NOX4 expression and renal fibrogenesis.

Methods

Study Design and Experimental Animals

An experimental chronic kidney disease (CKD) model was established using 42 male Wistar rats weighing 250–300 g. Animals were obtained from the institutional Experimental Animal Research Unit and housed under standardized laboratory conditions (20–22°C, 12-h light/12-h dark cycle) with free access to standard pellet chow and tap water throughout the study.

All experimental procedures were conducted in accordance with institutional guidelines for the care and use of laboratory animals and complied with internationally accepted principles for animal research. The study protocol was approved by the Institutional Experimental Animal Ethics Committee (Approval No. 74; December 3, 2018).

The animals were assigned to six experimental groups (n = 7 per group): (1) Sham-operated control (SHAM), (2) nephrectomy (NEPH), (3) nephrectomy followed for 15 days (NEPH+15), (4) nephrectomy followed for 30 days (NEPH+30), (5) nephrectomy followed by MSC treatment and evaluated after 15 days (MSC+15), and (6) nephrectomy followed by MSC treatment and evaluated after 30 days (MSC+30).

Isolation and Culture of Human Placenta-Derived Mesenchymal Stem Cells

Human term placental tissues were obtained from the Department of Obstetrics and Gynecology of a university hospital following written informed consent. The amniotic membrane was carefully separated from the chorionic membrane under sterile conditions and repeatedly washed with physiological saline containing penicillin/streptomycin and amphotericin B to minimize microbial contamination.

The amniotic membrane was cut into approximately 3 × 3 cm fragments and incubated with dispase to facilitate epithelial cell removal. Tissue digestion was subsequently performed using collagenase and DNase in RPMI 1640 medium supplemented with fetal bovine serum (FBS) and L-glutamine. The resulting cell suspension was filtered through a 100-μm cell strainer and centrifuged to obtain the cellular pellet.

The recovered cells were cultured in mesenchymal stem cell growth medium and maintained at 37°C in a humidified atmosphere containing 5% CO_2. Culture medium was replaced at regular intervals, and adherent cells were expanded through serial passaging until sufficient cell numbers were obtained for transplantation.

Flow Cytometric Characterization

The immunophenotypic characteristics of the isolated cells were evaluated by flow cytometry. Cells exhibited positive expression of the mesenchymal stem cell markers CD44, CD73, CD90, and CD105, whereas hematopoietic markers (CD34, CD45, CD14, CD19, and HLA-DR) were not expressed. These findings confirmed the mesenchymal phenotype of the isolated cells and were consistent with the minimal criteria established by the International Society for Cellular Therapy (ISCT) for mesenchymal stem cells.

Induction of Chronic Kidney Disease and Experimental Groups

Chronic kidney disease was induced using a 5/6 subtotal nephrectomy model. Animals were assigned to six experimental groups as described above. Human placenta-derived mesenchymal stem cells (1×10^6 cells) suspended in 500 μL Dulbecco's Modified Eagle Medium (DMEM) were administered via tail vein injection to the treatment groups.

Because human-derived MSCs were transplanted into rats, cyclosporine A was administered subcutaneously at a dose of 1 mg/day beginning one day before cell transplantation and continued for seven days thereafter to minimize xenogeneic immune rejection.

Twenty-four-hour urine samples were collected using metabolic cages prior to sacrifice. At the end of each experimental period, animals were anesthetized with ketamine hydrochloride and 2% xylazine. Blood samples were collected from the abdominal artery, after which the animals were euthanized. Kidney tissues were harvested, immediately stored at −80°C for subsequent biochemical and molecular analyses, and serum samples were separated by centrifugation and stored at −20°C until analysis.

Western Blot Analysis

Renal tissue samples were homogenized in lysis buffer supplemented with protease inhibitor cocktail. Protein concentrations were determined prior to electrophoresis, and equal amounts of protein were separated by SDS–PAGE and transferred onto nitrocellulose membranes. Membranes were blocked with 5% non-fat dry milk in Tris-buffered saline containing 0.1% Tween-20 (TBS-T) and incubated overnight at 4°C with primary antibodies against NOX4, fibronectin, collagen IV, and α-smooth muscle actin (α-SMA). Following incubation with the appropriate horseradish peroxidase-conjugated secondary antibodies, protein bands were visualized using enhanced chemiluminescence. Densitometric analysis was

performed using Alpha DigiDoc 1000 software (Alpha Innotech Corporation, San Leandro, CA, USA), and protein expression levels were normalized to β-actin.

Quantitative Real-Time PCR Analysis

Total RNA was isolated from renal tissue using TRIzol reagent, and complementary DNA (cDNA) was synthesized from the extracted RNA. Quantitative real-time PCR was performed using SYBR Green chemistry on a QuantStudio™ 3 Real-Time PCR System (Applied Biosystems, Foster City, CA, USA). Gene expression levels of NOX4, fibronectin, collagen IV, and α-SMA were normalized to glyceraldehyde-3-phosphate dehydrogenase (GAPDH), and relative expression was calculated using the 2-ΔΔCt method. Melting curve analysis was performed to verify amplification specificity.

Assessment of Oxidative Stress Parameters

Hydrogen peroxide (H_2O_2) levels in renal tissue homogenates were determined using the Amplex Red Hydrogen Peroxide/Peroxidase Assay Kit (Thermo Fisher Scientific, Cat. No. A22188) according to the manufacturer's instructions. Reactive oxygen species (ROS) production was evaluated using the OxiSelect™ In Vitro ROS/RNS Assay Kit (Cell Biolabs, Inc., San Diego, CA, USA). Fluorescence measurements were obtained using a microplate reader, and values were normalized to tissue protein concentration.

Urinary Albumin-to-Creatinine Ratio

Urinary albumin-to-creatinine ratio (ACR) was determined using the Albumin-to-Creatinine Ratio Assay Kit (BioVision, Cat. No. K551-100) according to the manufacturer's instructions. Albumin and creatinine concentrations were measured separately, and the final ACR was expressed as mg/g creatinine.

Outcome Measures

The primary outcome measures were oxidative stress–related parameters, including NOX4 expression, reactive oxygen species (ROS), and hydrogen peroxide (H_2O_2) levels. Secondary outcome measures included fibrosis-related markers (fibronectin, collagen IV, and α-smooth muscle actin [α-SMA]) and urinary albumin-to-creatinine ratio (ACR).

Statistical Analysis

Statistical analyses were performed using GraphPad Prism software (GraphPad Software, San Diego, CA, USA). Data are presented as mean ± SEM. Comparisons among experimental

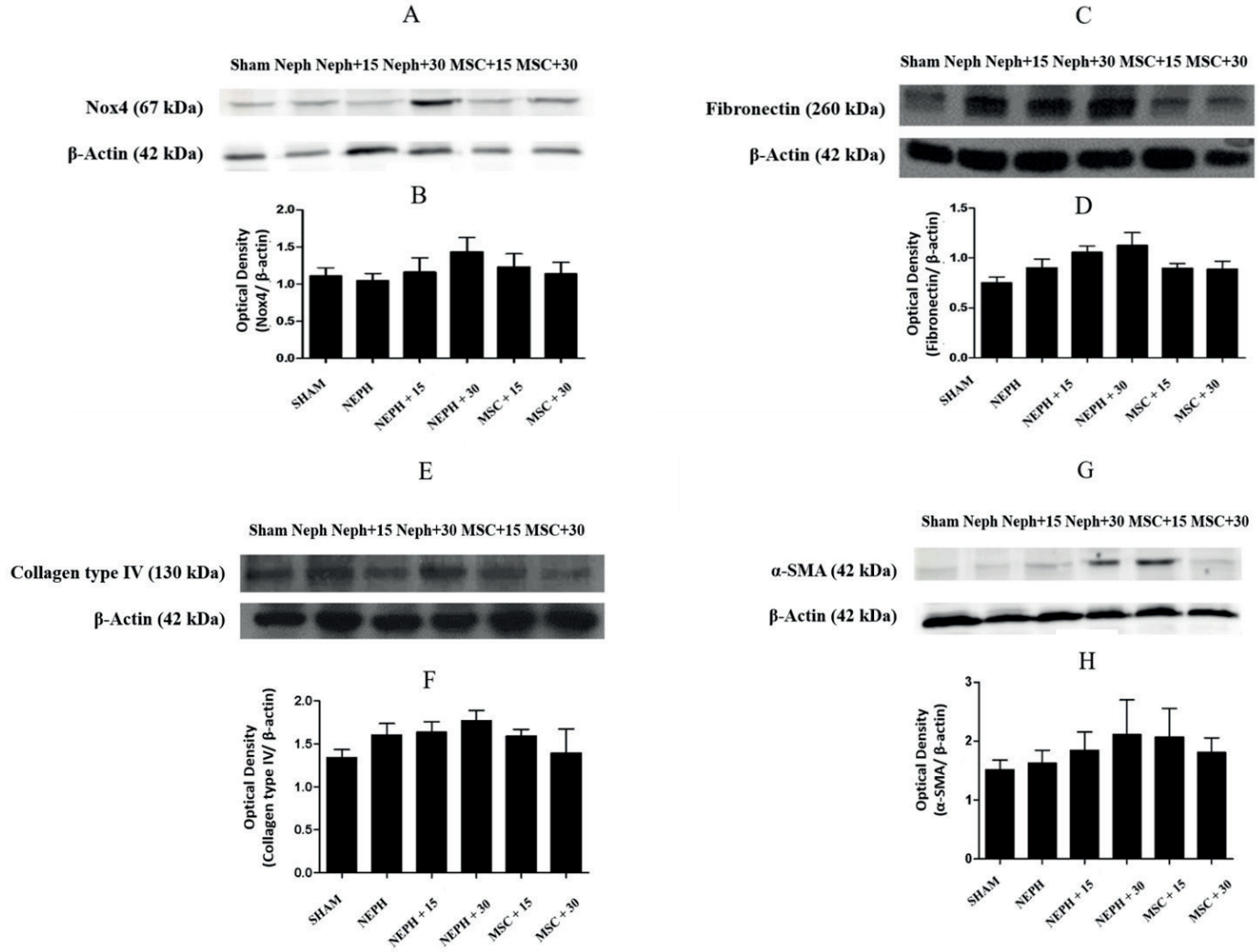

Figure 1 – Western blot analysis of oxidative stress– and fibrosis-related proteins in renal tissues from the experimental groups. Representative western blot images showing protein expression of (A) NOX4, (C) fibronectin, (E) collagen IV, and (G) α-SMA. Corresponding densitometric analyses normalized to β-actin are presented in (B), (D), (F), and (H), respectively.

Data are presented as mean ± SEM (n = 7 per group). Statistical analysis was performed using the Kruskal–Wallis test followed by Dunn's multiple comparisons test. Abbreviations: NOX4, NADPH oxidase 4; α-SMA, alpha-smooth muscle actin.

groups were performed using the Kruskal–Wallis test followed by Dunn's multiple comparisons test. Western blot densitometric analyses were performed using Alpha DigiDoc 1000 software (Alpha Innotech Corporation, San Leandro, CA, USA). A two-sided p value < 0.05 was considered statistically significant.

Results

Isolation and Characterization of Placenta-Derived Mesenchymal Stem Cells

Isolated human placenta-derived mesenchymal stem cells exhibited the characteristic spindle-shaped, fibroblast-like morphology and maintained stable growth throughout serial passaging. Flow cytometric analysis confirmed the mesenchymal immunophenotype of the cultured cells, demonstrating positive expression of CD44, CD73, CD90, and CD105, while hematopoietic markers (CD34, CD45, CD14, CD19, and HLA-DR) were not expressed. These findings confirmed that the isolated cells fulfilled the phenotypic characteristics of mesenchymal stem cells.

Protein Expression Analysis by Western Blot

Western blot analysis demonstrated increased expression of NOX4, fibronectin, collagen IV, and α-SMA in nephrectomy groups compared with the SHAM group, with the greatest increases generally observed in animals evaluated at the 30-day time point. Although MSC-treated groups showed lower protein expression levels than the corresponding nephrectomy groups, these reductions did not reach statistical significance for all comparisons. Representative western blot images and corresponding densitometric analyses are presented in Figure 1.

Gene Expression Analysis

Quantitative real-time PCR analysis demonstrated significant alterations in the expression of oxidative stress- and fibrosis-related genes among the experimental groups (Figure 2).

NOX4: NOX4 mRNA expression was significantly increased following nephrectomy, with the highest expression observed in the NEPH+30 group compared with the SHAM group. MSC treatment was associated with lower NOX4 mRNA expression at both 15- and 30-day evaluation time points. Significant differences were identified for selected pairwise

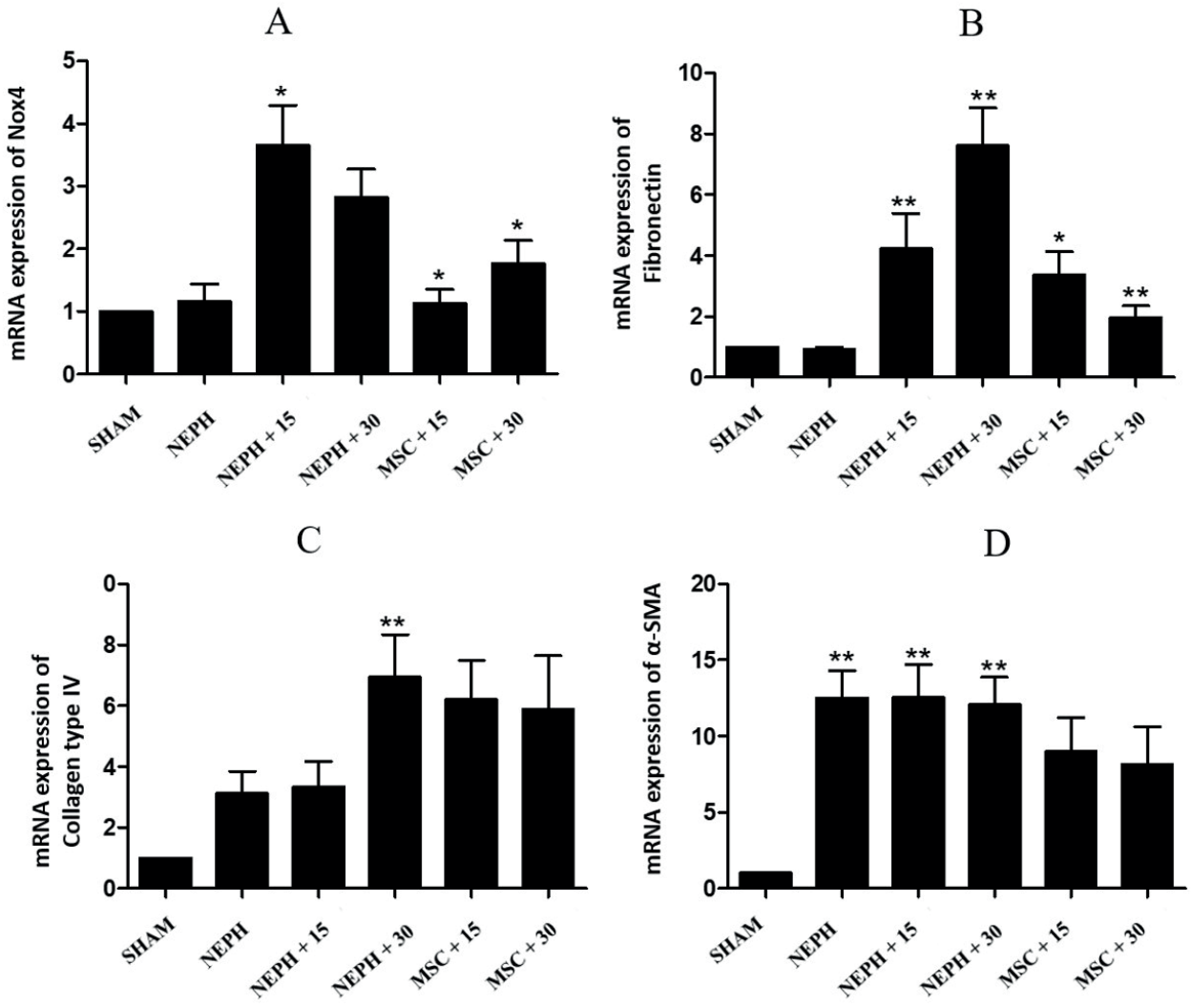

Figure 2 – Relative mRNA expression levels of oxidative stress– and fibrosis-related genes determined by quantitative real-time PCR. (A) Relative NOX4 mRNA expression, (B) fibronectin mRNA expression, (C) collagen IV mRNA expression, and (D) α-SMA mRNA expression.

*Gene expression levels were normalized to GAPDH and calculated using the 2^−ΔΔCt method. Data are presented as mean ± SEM (n = 7 per group). Statistical analysis was performed using the Kruskal–Wallis test followed by Dunn's multiple comparisons test. Asterisks indicate statistically significant differences compared with the SHAM group (*p < 0.05, **p < 0.001). Abbreviations: NOX4, NADPH oxidase 4; α-SMA, alpha-smooth muscle actin.*

comparisons, whereas differences between MSC-treated and the corresponding nephrectomy groups were not statistically significant in all comparisons (Figure 2A).

Fibronectin: Fibronectin mRNA expression was elevated in nephrectomized animals relative to SHAM controls. MSC-treated groups exhibited lower fibronectin expression than the corresponding nephrectomy groups, with the greatest reduction observed in the MSC+30 group. However, statistically significant differences were observed only in selected pairwise comparisons (Figure 2B).

Collagen IV: Collagen IV mRNA expression increased following nephrectomy, particularly in the NEPH+30 group. Although MSC treatment was associated with lower collagen IV expression, statistically significant differences were limited to specific pairwise comparisons (Figure 2C).

α-SMA: α-SMA mRNA expression was significantly increased in nephrectomy groups compared with the SHAM group. Lower α-SMA expression was observed following MSC treatment at both evaluation time points; however, these reductions did not reach statistical significance for all pairwise comparisons (Figure 2D).

Oxidative Stress Parameters

Renal H_2O_2 levels were significantly increased in nephrectomized animals compared with the SHAM group. MSC treatment was associated with lower H_2O_2 levels, with a statistically significant reduction observed in the MSC+30 group relative to the SHAM group (Figure 3A).

ROS production showed a similar overall pattern. Nephrectomy was associated with increased oxidative stress, whereas MSC-treated animals exhibited lower ROS levels than the corresponding nephrectomy groups. However, these differences did not reach statistical significance in all pairwise comparisons (Figure 3B).

Urinary Albumin-to-Creatinine Ratio

Urinary ACR was significantly increased in nephrectomized animals compared with the SHAM group, indicating impaired renal function. MSC-treated groups demonstrated lower ACR values than the corresponding nephrectomy groups at both evaluation time points. A statistically significant reduction in urinary ACR was observed following MSC treatment, suggesting partial preservation of renal function (Figure 3C).

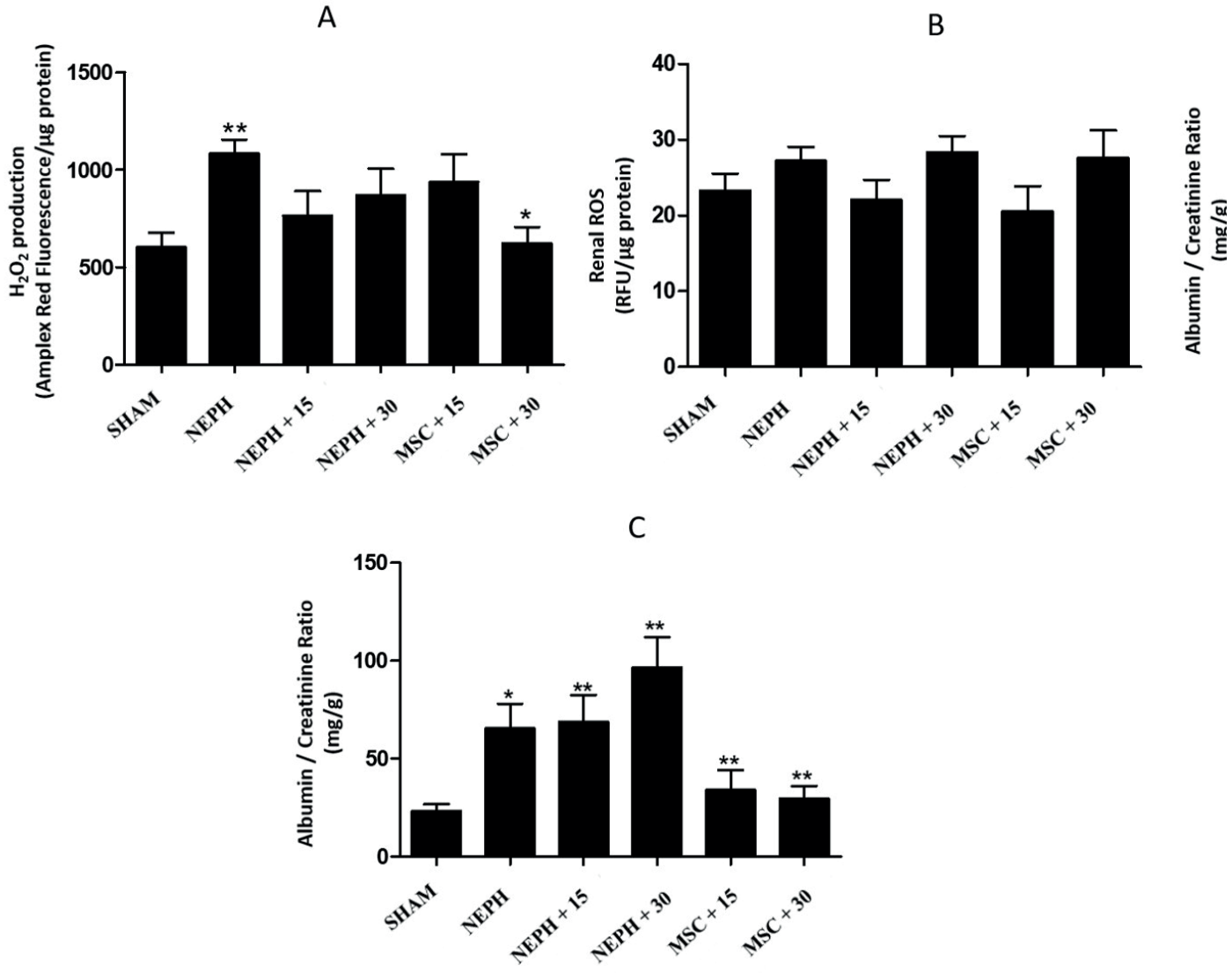

Figure 3 – Oxidative stress parameters and urinary albumin-to-creatinine ratio in the experimental groups. (A) Renal hydrogen peroxide (H_2O_2) levels determined using the Amplex Red assay. (B) Renal reactive oxygen species (ROS) levels. (C) Urinary albumin-to-creatinine ratio (ACR). Data are presented as mean ± SEM (n = 7 per group).

*Statistical analysis was performed using the Kruskal–Wallis test followed by Dunn's multiple comparisons test. Asterisks indicate statistically significant differences compared with the SHAM group (*p < 0.05, **p < 0.001). Abbreviations: NOX4, NADPH oxidase 4; α-SMA, alpha-smooth muscle actin.*

Discussion

The present study investigated the effects of human placenta-derived mesenchymal stem cells on oxidative stress and fibrosis in a nephrectomy-induced chronic kidney disease model. The findings demonstrated that MSC administration was associated with reduced oxidative stress, reflected by lower ROS and H_2O_2 levels together with modulation of NOX4 expression. In addition, MSC treatment was associated with trends toward reduced expression of fibrosis-related markers, although corresponding protein-level changes did not reach statistical significance in all comparisons. Furthermore, lower urinary albumin-to-creatinine ratios observed in MSC-treated animals suggested partial preservation of renal function.

Chronic kidney disease is characterized by progressive structural and functional deterioration of renal tissue. Persistent oxidative stress, inflammatory signaling, and extracellular matrix accumulation contribute to ongoing renal injury and fibrotic remodeling. These mechanisms interact throughout disease progression, ultimately leading to nephron loss and irreversible decline in kidney function [10–13].

Mesenchymal stem cells have been increasingly investigated as regenerative candidates because of their immunomodulatory and reparative properties. Although their differentiation potential remains important, accumulating evidence indicates that many therapeutic effects of MSCs are mediated through paracrine mechanisms rather than direct tissue replacement. Secreted cytokines, growth factors, and extracellular vesicles contribute to suppression of inflammation, regulation of fibrosis, and promotion of endogenous repair pathways [1–3].

Placenta-derived MSCs represent an attractive source for experimental and translational applications because placental tissue is abundant, readily accessible, and associated with fewer ethical concerns than many alternative stem cell sources. In addition, placenta-derived MSCs exhibit low immunogenicity and high proliferative capacity, supporting their potential use in regenerative strategies targeting chronic organ injury [4–6].

One of the principal findings of the present study was the modulation of NOX4 expression following MSC treatment. NOX4 is highly expressed in renal tissue and plays a central role in reactive oxygen species generation. Increased NOX4 activity has been associated with oxidative injury, mitochondrial dysfunction, and activation of profibrotic signaling pathways in chronic kidney disease [12–15]. In the present study, nephrectomy was associated with increased NOX4 expression, whereas MSC treatment was accompanied by lower NOX4 expression, supporting a potential role for MSCs in the regulation of renal redox homeostasis.

Excessive ROS generation promotes inflammatory activation and extracellular matrix accumulation within damaged renal tissue. Consistent with previous reports, nephrectomy-induced CKD was associated with elevated ROS and H_2O_2 levels. MSC treatment was associated with lower oxidative stress parameters, suggesting that MSCs may contribute to restoration of redox balance within injured renal tissue [22–24].

Fibrosis-related pathways were also influenced by MSC treatment. Elevated expression of fibronectin, collagen IV, and α-SMA in nephrectomy groups reflected extracellular matrix accumulation and myofibroblast activation characteristic of progressive renal fibrosis. Although lower expression of these markers was observed following MSC administration, corresponding protein-level changes did not reach statistical significance in all comparisons. This apparent discrepancy between gene and protein expression may reflect differences in post-transcriptional regulation, protein turnover, translational efficiency, and the temporal dynamics of mRNA and protein expression. Therefore, the present findings should be interpreted as evidence of partial modulation of profibrotic pathways rather than definitive suppression of renal fibrosis.

The interaction between NOX4 activity and transforming growth factor-β (TGF-β)-associated signaling has been highlighted in previous experimental studies. Increased NOX4 signaling amplifies fibrotic responses by promoting extracellular matrix protein synthesis and myofibroblast activation [16–20]. Furthermore, NOX4-dependent redox signaling contributes to extracellular matrix deposition and progressive renal scarring [24–26]. The lower NOX4 expression observed following MSC treatment therefore supports the hypothesis that MSCs may interfere with oxidative stress-related profibrotic signaling during CKD progression.

In addition to the molecular findings, lower urinary albumin-to-creatinine ratios were observed in MSC-treated animals. Albuminuria is a well-established marker of glomerular injury and an important predictor of CKD progression. The reduction in urinary ACR observed following MSC treatment suggests partial preservation of renal function and supports the biological relevance of the molecular findings.

Several limitations of the present study should be acknowledged. First, the relatively small sample size may have limited the statistical power to detect significant differences for some outcome measures. Second, only selected oxidative stress and fibrosis-related markers were evaluated. Future studies incorporating inflammatory mediators, mitochondrial function, and long-term tracking of transplanted cells would provide a more comprehensive understanding of the underlying mechanisms. In addition, only a single MSC dose and a relatively short observation period were investigated.

Because human placenta-derived MSCs were transplanted into rats, low-dose cyclosporine A was administered to minimize xenogeneic immune rejection. However, a nephrectomy plus cyclosporine A control group was not included; therefore, the independent contribution of cyclosporine A to the observed findings cannot be completely excluded. Furthermore, detailed maternal and pregnancy-related donor characteristics of the placental tissues, including maternal age, gestational age, and pregnancy-related clinical information, were not available. Since donor characteristics may influence the biological properties of placenta-derived MSCs, future studies should include more comprehensive donor characterization.

Despite these limitations, the present findings suggest that placenta-derived MSCs may modulate oxidative stress–related pathways in experimental CKD and may partially influence fibrosis-associated molecular responses. Although reductions in fibrosis-related protein expression did not reach statistical significance in all comparisons, the overall molecular findings, together with the reduction in urinary albumin-to-creatinine ratio, support further investigation of MSC-based therapies in chronic kidney disease. Additional experimental and translational studies involving larger cohorts and longer follow-up periods are warranted to further clarify the therapeutic potential and clinical applicability of this approach.

Conclusion

The findings of the present study suggest that human placenta-derived mesenchymal stem cells may modulate oxidative stress– and fibrosis-related pathways in experimental chronic kidney disease. MSC treatment was associated with

lower oxidative stress parameters, modulation of NOX4 expression, and trends toward reduced expression of fibrosis-related markers. Although reductions in fibrosis-related protein expression did not reach statistical significance in all comparisons, the overall findings suggest that MSC therapy may partially influence molecular pathways involved in CKD progression.

The observed reduction in urinary albumin-to-creatinine ratio further supports a potential beneficial effect of MSC treatment on renal injury in nephrectomy-induced CKD. Nevertheless, additional studies involving larger experimental cohorts, longer follow-up periods, broader mechanistic investigations, and well-controlled experimental designs are required to confirm these findings and to further clarify the therapeutic potential and translational applicability of MSC-based interventions in chronic kidney disease.

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