RESEARCH ARTICLE OPEN ACCESS

hUC-MSCs Therapy with EVs Booster Improves Recovery in Stage 2 Chronic Kidney Disease with Hypercholesterolemia : a case report

Jutadi[1], Dian Respati Ayu[2]*, Dini Cahyani[3], Adzani Gaisani Arda[4], Naufal Sebastian Anggoro[4]

*Correspondence:
dianrespati@kmb.ac.id

[1]Graduate Student of Biomedical Sciences, Faculty of Medicine, Public Health, and Nursing, Universitas Gadjah Mada, Yogyakarta 55281 Indonesia
[2]Lecturer, Biomedical Science Undergraduate Program, Institut Karya Mulia Bangsa (IKMB), Semarang, 50223, Indonesia
3Lecturer, Biotechnology Undergraduate Program, Institut Karya Mulia Bangsa (IKMB), Semarang, 50223, Indonesia
[4]Research and Development, Stem Cell and Cancer Research (SCCR), Semarang, 50223, Indonesia

Submission September 29, 2025
Accepted October 09, 2025
Available online on October 11, 2025

ABSTRACT

Hypercholesterolemia is a common metabolic comorbidity that accelerates the progression of chronic kidney disease (CKD). Human umbilical cord-derived mesenchymal stem cells (hUC-MSCs) and their secretome, which consist of extracellular vesicles (EVs) and soluble bioactive molecules, have shown potential in modulating inflammation and metabolism. This case report describes significant improvement in serum lipid profile following hUC-MSC and secretome therapy in a patient with stage 2 CKD and hypercholesterolemia. A male patient with CKD stage 2 received two intravenous cycles of hUC-MSC and secretome therapy administered seven months apart. Serial evaluations demonstrated a progressive decline in total cholesterol from 294 mg/dL at baseline to 286 mg/dL after the first treatment and 225 mg/dL after the second. LDL cholesterol decreased from 188 mg/dL to 140 mg/dL, with a mild rebound to 175 mg/dL. HDL cholesterol, initially elevated at 214 mg/dL, showed a modest increase to 220 mg/dL after the first treatment, followed by normalization to 175 mg/dL. Triglyceride levels remained within the normal range (44–51 mg/dL) throughout the observation period. The marked improvement in lipid parameters suggests that hUC-MSC and secretome therapy may exert systemic metabolic regulation via anti-inflammatory, antioxidative, and hepatoprotective mechanisms. hUC-MSC and secretome administration demonstrated potential benefits in lipid homeostasis in a patient with CKD and hypercholesterolemia. These findings support the role of MSC-derived secretome as a promising adjunctive therapeutic approach. Larger controlled trials are warranted to confirm these outcomes and elucidate underlying mechanisms.

Keywords: Mesenchymal stem cells (MSCs), Secretome therapy, Hypercholesterolemia, Chronic kidney disease (CKD), Lipid metabolism.

INTRODUCTION

Chronic kidney disease (CKD) is a significant global health crisis, responsible for high rates of illness and death worldwide. The development and progression of CKD are driven by a variety of established risk factors. While diabetes and hypertension have long been recognized as the leading causes research has increasingly highlighted the critical role of lipid metabolism abnormalities[1]. Dyslipidemia, a disease characterized as abnormal serum levels of total cholesterol, triglycerides, low-density lipoprotein cholesterol (LDL-C), or high-density lipoprotein cholesterol (HDL-C), has been implicated in both cardiovascular complications and renal dysfunction[2]. Studies have shown that dyslipidemia can accelerate glomerulosclerosis, tubular injury, and loss of renal function[3]. Among its subtypes, hypercholesterolemia, a condition with elevated cholesterol levels (>200 mg/dL). Compared to people with normal cholesterol levels, those with high cholesterol levels are 1.5 times more likely to develop kidney dysfunction[4]. In murine models, hypercholesterolemia has been shown to promote early renal injury, further supporting its causal role in kidney disease[5].

Current management of dyslipidaemia in CKD primarily relies on statins and ezetimibe, which are recommended as cornerstone therapies in recent guidelines[6]. Although these agents are effective in lipid lowering and cardiovascular risk reduction, their capacity to halt CKD progression remains limited. Mesenchymal stem cells (MSCs) have emerged as a promising therapeutic approach. MSCs secrete microvesicles capable of transferring genetic material and protecting tubular epithelial cells from acute injury[7]. Moreover, MSC-derived secretome which contain extracellular vesicles (EVs), mRNA, miRNA, cytokines, and growth factors, have been shown to promote tubular regeneration, angiogenesis, and to reduce apoptosis, oxidative stress, inflammation, and fibrosis in both AKI and CKD models[8].

CASE PRESENTATION

A 55-year-old male presented with a history of severe headache localized in the occipital region, accompanied by intermittent nausea without vomiting. The patient reported abnormal and foamy urination, right leg swelling that had persisted for one week, and occasional lower back pain. Physical examination revealed a body weight of 65 kg, height of 160 cm, blood pressure of 130/80 mmHg, body temperature of 36°C, pulse rate of 80 bpm, respiratory rate of 20 breaths per minute, and oxygen saturation (SpO_2) of 98%. Initial laboratory investigations indicated impaired renal function consistent with stage 2 chronic kidney disease (CKD), as evidenced by an estimated glomerular filtration rate (eGFR) of 73 mL/min and serum creatinine level of 1.13 mg/dL. Additional laboratory findings included elevated eosinophil count (8.2%), total cholesterol (294 mg/dL), direct LDL cholesterol (214 mg/dL), and uric acid (8.5 mg/dL), while other biochemical parameters remained within normal limits.

Based on the initial anamnesis, the patient had a history of hypercholesterolemia diagnosed one year prior and was found to have decreased renal function during routine annual medical check-ups. The patient also had a history of alcohol consumption (alcoholism) and had occasionally complained of shortness of breath accompanied by back pain. The patient was on pharmacological therapy consisting of simvastatin 10 mg once daily (0-0-1) for cholesterol control and vitamin D supplementation once daily (1-0-0). The patient received an intravenous infusion of UC-MSCs at a dose of 98×10^6 cells, followed by Secretome therapy consisting of seven intramuscular injections at a dose of 1.5 cc each, with the first injection administered on the same day as the MSC infusion. The patient also committed to adopting a healthy lifestyle, supported by a renal-friendly dietary plan and the use of an herbal antioxidant supplement (Centella curma), while reducing alcohol consumption.

One day after the initial treatment, the patient continued with daily intramuscular Secretome injections (1.5 cc) for the next two consecutive days, followed by weekly extracellular vesicle (EV) doses for four consecutive weeks. The patient reported feeling more energetic and no longer experienced fatigue or nausea following the treatment.

Six months after the first UC-MSC treatment, laboratory evaluations revealed improvements in several biochemical parameters, including serum creatinine 1.05 mg/dL, estimated glomerular filtration rate (eGFR) 80 mL/min, eosinophil count 6.8%, and total cholesterol 286 mg/dL. Clinically, the patient reported significant symptomatic improvement, including resolution of nausea, normalization of urination frequency, and a marked reduction in the frequency of headaches. The patient subsequently received a second course of therapy (UC-MSC II) followed by a secretome treatment program consisting of seven intramuscular injections of 1.5 mL each, administered in a schedule of three injections every three days and four injections weekly thereafter. Laboratory evaluation three months after the second UC-MSC treatment showed further improvement in multiple markers: serum creatinine 0.95 mg/dL, eGFR 90 mL/min, eosinophil count 5.9%, total cholesterol 286 mg/dL, direct LDL cholesterol 161 mg/dL, and uric acid 7.0 mg/dL. These biochemical findings were supported by continued clinical improvement, as the patient reported diminished headache episodes, normalized urination frequency without foamy urine, and complete resolution of right leg edema.

DISCUSSION

Creatinine is a waste product of muscle metabolism formed from the breakdown of creatine phosphate, a high-energy compound used by muscle cells. Because muscle activity occurs daily, creatinine is produced constantly in relatively stable amounts[9]. The primary pathway for creatinine excretion is through the kidneys, specifically through glomerular filtration. Under normal physiological conditions, the kidneys filter creatinine efficiently, keeping blood levels stable. However, when kidney function declines, for example due to a decrease in the glomerular filtration rate (eGFR), a normal value of ≥90 mL/min, creatinine excretion is impaired. As a result, creatinine accumulates in the bloodstream, increasing its levels[10]. Decreased eGFR is usually associated with structural kidney damage, such as glomerulosclerosis, interstitial fibrosis, or tubulointerstitial damage due to chronic inflammation [11].

Mesenchymal stem cell (MSC)-based therapy has shown significant potential in improving kidney function in various preclinical models. Generally, two main mechanisms underlie the repair effects of MSCs on the kidney: homing and paracrine effects. In the homing mechanism, some MSCs migrate to the site of kidney injury guided by chemical signals such as SDF-1, PDGF, IGF, and IL-8. MSCs interact with the vascular endothelium through integrins, penetrate the blood vessel membrane with the aid of enzymes, and then migrate to the injured tissue[12]. In the paracrine mechanism, MSCs release a secretome containing over 1,500 bioactive molecules, including proteins, peptides, mRNA, miRNA, and lipids. These molecules can exist in soluble form or packaged in extracellular vesicles (EVs), particularly exosomes measuring 50–150 nm, which provide therapeutic effects without the MSCs having to directly integrate with the tissue[13].

Several studies have shown that EVs derived from MSCs have a protective effect against kidney injury. EVs from human placenta-derived MSCs (HP-MSC-EVs) were able to reduce BUN and creatinine levels, as well as tubular cast protein, tubular necrosis, and kidney injury molecule-1 (Kim-1) expression[14]. Similar findings were confirmed that injection of HP-MSC-EVs into the renal cortex could reduce fibrosis and tubular necrosis[15]. Human Wharton's jelly MSC-derived microvesicles (HWJMSC-MVs) is reported to reduced Cr, BUN, and inflammatory cell infiltration[16]. Meanwhile, another study demonstrated that human umbilical cord MSC-EVs were able to deliver VEGF to renal tubular epithelial cells, thereby improving angiogenesis in an ischemia-hypoxia model[17]. Furthermore, MSC-EVs can target macrophages and induce M1 to M2 polarization, which contributes to reduced inflammation through modulation of CX3CL1 and TLR-2[18].

The molecular effects of MSCs and EVs also involve several other important mechanisms. In terms of anti-fibrosis, MSCs can suppress myofibroblast activation and reduce the production of TGF-β, a key mediator of fibrosis, thereby slowing the progression of chronic kidney disease [19].

MSCs and EVs decrease pro-inflammatory cytokines such as IL-6, TNF-α, and IFN-γ, and increase anti-inflammatory cytokines such as IL-10[20]. Furthermore, MSC exosomes contain various miRNAs with specific biological functions: miR-122, which plays a role in cholesterol metabolism; miR-126 and miR-210, which support angiogenesis; and miR-125b-5p and miR-93, which have anti-apoptotic properties[21].

In addition to structural damage and inflammation, decreased kidney function is also closely associated with dyslipidemia. Hyperlipidemia, particularly hypercholesterolemia, is a driving factor in atherosclerosis, which can lead to renal artery narrowing and reduced renal perfusion. Oxidized LDL cholesterol (ox-LDL) can be captured by macrophages in the glomerulus, forming foam cells, and triggering inflammation and glomerulosclerosis[22]. Mesangial cells themselves express LDL and ox-LDL receptors, and activation of these receptors triggers cell proliferation, extracellular matrix accumulation, and the release of inflammatory mediators such as IL-6 and MCP-1. MCP-1 plays a role in recruiting macrophages to the glomerulus and exacerbating inflammation. Ox-LDL can also damage podocytes, trigger apoptosis, decrease the expression of nephrin, a key protein in the glomerular filtration barrier, and increase albumin permeability[22]. Interestingly, some miRNAs released by MSC-EVs, including miR-122, also play a role in the regulation of lipid metabolism, thus potentially not only repairing kidney damage due to inflammation and fibrosis, but also addressing dyslipidemia-related damage[23] including miR-122, also play a role in the regulation of lipid metabolism, thus potentially not only repairing kidney damage due to inflammation and fibrosis, but also addressing dyslipidemia-related damage[23].

This suggests that MSCs and their derivatives, particularly EVs, act through multifactorial mechanisms including immunomodulation, anti-fibrosis, angiogenesis, podocyte protection, and lipid regulation, thus providing comprehensive therapeutic potential in preventing the progression of chronic kidney disease.

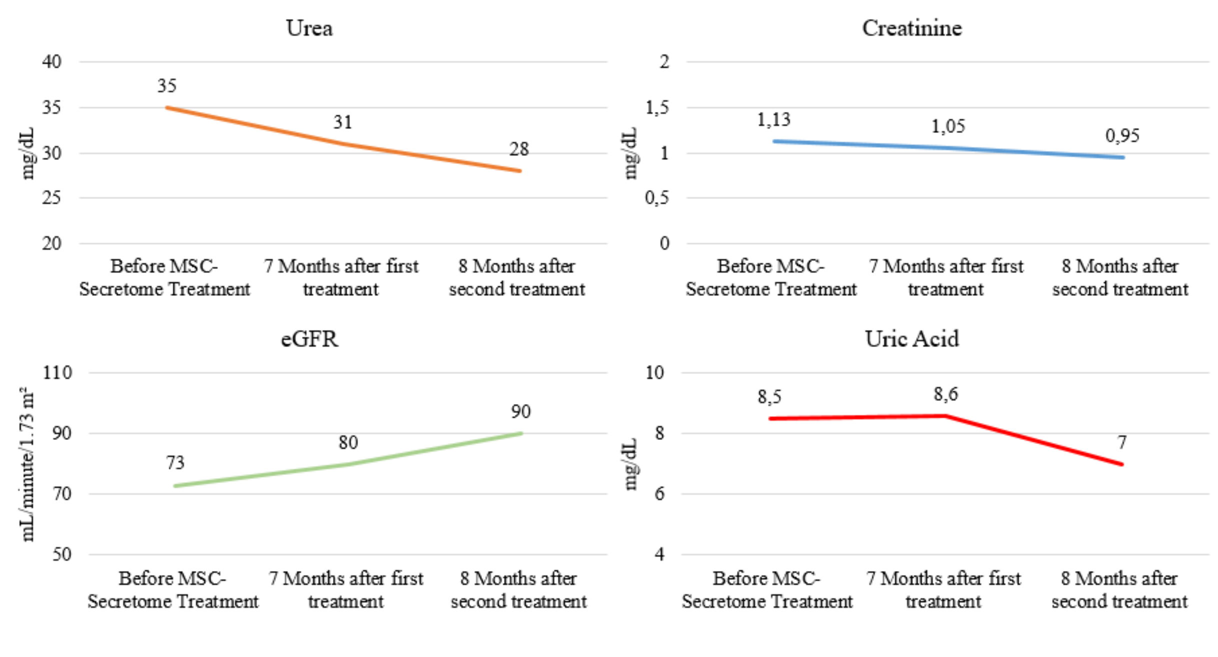

Figure 1. Changes in kidney function parameters following MSC and secretome treatment in the patient. The figure presents pre and post-treatment laboratory results, including urea, creatinine, estimated glomerular filtration rate (eGFR), and uric acid levels. The observed improvements suggest a positive response of renal function to mesenchymal stem cell (MSC) and secretome therapy in this case.

The changes in kidney function parameters observed in this case indicate a progressive improvement following mesenchymal stem cell (MSC) and secretome therapy. Prior to treatment, the patient showed mildly impaired renal function, as reflected by elevated urea (35 mg/dL) and creatinine (1.13 mg/dL) levels, along with a moderately reduced estimated glomerular filtration rate (eGFR) of 73 mL/min. After the first MSC-secretome administration, improvements were observed across most parameters, with urea decreasing to 31 mg/dL, creatinine to 1.05 mg/dL, and eGFR increasing to 80 mL/min, suggesting enhanced glomerular filtration efficiency.

At eight months post-treatment—following the second MSC-secretome administration—these positive trends continued. Urea further decreased to 28 mg/dL, creatinine to 0.95 mg/dL, and eGFR rose to 90 mL/min, approaching the normal range for renal function. Although uric acid levels initially increased slightly from 8.5 mg/dL to 8.6 mg/dL after the first treatment, they subsequently decreased to 7.0 mg/dL after the second treatment, suggesting a delayed but favorable metabolic adjustment.

These findings suggest that MSC and secretome therapy may contribute to renal function recovery, possibly through mechanisms involving anti-inflammatory, anti-apoptotic, and paracrine regenerative effects that promote tubular repair and improve glomerular filtration. Previous studies have demonstrated that MSCs exert renoprotective effects by modulating immune responses, reducing oxidative stress, and enhancing tissue regeneration through their secretome, which contains cytokines, growth factors, and extracellular vesicles[24]. The gradual improvement over time, particularly following repeated administrations, aligns with existing evidence that MSC-derived secretome exerts sustained biological effects by regulating inflammation and promoting renal tissue recovery[24].

Overall, the observed laboratory improvements support the therapeutic potential of MSC-secretome intervention in ameliorating kidney dysfunction, especially in chronic or degenerative renal conditions where conventional treatments provide limited recovery potential.

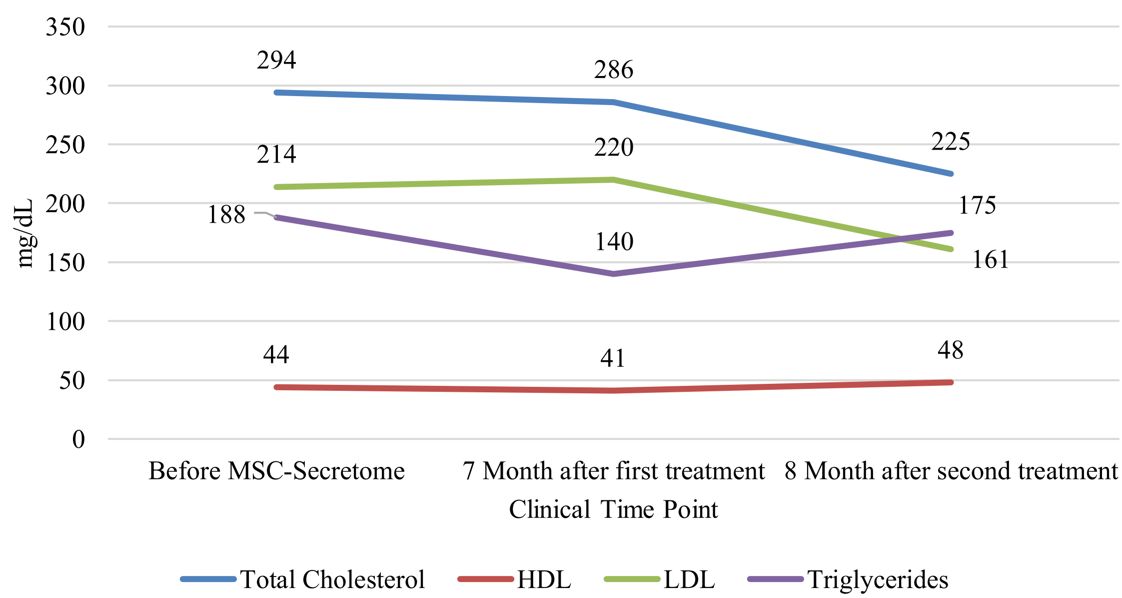

Figure 2. Lipid profile changes in the patient after mesenchymal stem cell (MSC) and secretome treatment. The graph shows pre and post-treatment levels of total cholesterol, high-density lipoprotein (HDL), low-density lipoprotein (LDL), and triglycerides, indicating the patient's lipid metabolism response following therapy.

The patient showed significant improvement in their serum lipid profile after receiving human umbilical cord-derived mesenchymal stem cells (hUC-MSCs) and their secretome. Total cholesterol decreased from 294 mg/dL at baseline to 286 mg/dL seven months after the first treatment and to 225 mg/dL eight months after the second treatment, indicating a sustained hypolipidemic effect. This reduction suggests long-term modulation of lipid metabolism, which is potentially mediated by the paracrine signaling mechanisms of the MSCs that influence hepatic lipid homeostasis[25].

Interestingly, HDL cholesterol levels were initially elevated at 214 mg/dL and increased modestly after the first treatment to 220 mg/dL, before decreasing to 175 mg/dL after the second treatment. This reduction may indicate the normalization of an initially dysregulated lipid transport system because excessively high HDL levels have been linked to dysfunctional HDL particles that exhibit pro-inflammatory and pro-oxidant activity rather than cardioprotective effects[26]. MSC-derived secretome components, including extracellular vesicles (EVs) and cytokines, may restore HDL functionality by reducing systemic inflammation and oxidative stress[27]. The LDL cholesterol concentration improved substantially, decreasing from 188 mg/dL at baseline to 140 mg/dL after the first treatment. However, a partial rebound to 175 mg/dL was observed after the second treatment. This dynamic response may represent physiological adaptation during metabolic recovery. Several studies have reported that mesenchymal stem cell (MSC) therapy exerts lipid-lowering effects via suppression of hepatic lipid synthesis, promotion of LDL receptor expression, and attenuation of macrophage foam cell formation[28]. The modest increase observed after the second treatment may also be due to variations in diet or lifestyle during the follow-up period. Concurrently, triglyceride (TG) levels remained within the normal range during the observation period (44 mg/dL at baseline; 51 mg/dL at 7 months; 48 mg/dL at 8 months), suggesting that hUC-MSC and secretome therapy did not induce lipid dysregulation or metabolic stress. The maintenance of stable TG levels is indicative of a preserved lipolytic balance and a normal very-low-density lipoprotein (VLDL) metabolism[27].

The collective findings underscore the multifactorial impact of hUC-MSC and secretome therapy on lipid metabolism. The observed lipid normalization may result from the combined anti-inflammatory, anti-oxidative, and hepatoprotective activities of MSC-secreted bioactive molecules, such as hepatocyte growth factor (HGF), transforming growth factor-β (TGF-β), and vascular endothelial growth factor (VEGF)[29]. Such paracrine mechanisms may contribute to improved endothelial function, lipid utilization, and cholesterol clearance.

These findings are consistent with emerging evidence that MSC-derived secretome exerts systemic metabolic regulation and may serve as a promising adjunctive strategy for managing hypercholesterolemia and early-stage chronic kidney disease[30]. Further mechanistic studies and controlled clinical trials are required to delineate the molecular pathways underlying MSC-mediated lipid modulation and to determine the optimal therapeutic regimen for sustained lipid homeostasis.

CONCLUSION

This study demonstrates that hypoxia exerts a biphasic effect on mesenchymal stem cells (MSCs), enhancing stemness-related gene expression during short-term exposure while inducing stress responses with prolonged treatment. Specifically, a 12-hour hypoxic exposure (5% O_2) significantly upregulated OCT-4, SOX-2, and NANOG expression, indicating optimal activation of the pluripotency network. However, beyond this duration, sustained hypoxia led to morphological alterations and decreased gene expression, suggesting the onset of cellular stress and reduced viability. These findings underscore the importance of precisely controlling hypoxic duration to harness its beneficial effects while avoiding cytotoxic consequences. Establishing an optimal hypoxic preconditioning window can improve MSC-based therapeutic strategies by preserving stemness, enhancing paracrine activity, and promoting overall regenerative potential.

Competing interests

The authors report no conflicts of interest.

Funding

This research and its publication did not receive any financial support.

Authors' contributions

All authors equally participated in the study, including conceptualization, data collection and analysis, literature review, manuscript drafting, and editing.

REFERENCES

1. Antebi B, Rodriguez LA II, Walker KP III, Asher AM, Kamucheka RM, Alvarado L, Mohammadipoor A, Cancio LC. Short-term physiological hypoxia potentiates the therapeutic function of mesenchymal stem cells. *Stem Cell Res Ther.* 2018;9:265. doi:10.1186/s13287-018-1007-x
2. Ejtehadifar M, Shamsasenjan K, Movassaghpour A, Akbarzadehlaleh P, Dehdilani N, Abbasi P, Molaeipour Z, Saleh M. The effect of hypoxia on mesenchymal stem cell biology. *Adv Pharm Bull.* 2015;5(2):141–149. doi:10.15171/apb.2015.021
3. Ahmed NM, Murakami M, Kaneko S, et al. The effects of hypoxia on the stemness properties of human dental pulp stem cells (DPSCs). *Sci Rep.* 2016;6:35476. doi:10.1038/srep35476
4. Yustianingsih V, Sumarawati T, Putra A. Hypoxia enhances self-renewal properties and markers of mesenchymal stem cells. *Univ Med.* 2019;38(3):164–171. doi:10.18051/UnivMed.2019.v38.164-171
5. Ma M. Role of hypoxia in mesenchymal stem cells from dental pulp: influence, mechanism and application. *Cell Biochem Biophys.* 2024;82:535–547. doi:10.1007/s12013-024-01274-0
6. Alwohoush E, Ismail MA, Al-Kurdi B, Barham R, Al Hadidi S, Awidi A, Ababneh NA. Effect of hypoxia on proliferation and differentiation of induced pluripotent stem cell-derived mesenchymal stem cells. *Heliyon.* 2024;10(19):e38857. doi:10.1016/j.heliyon.2024.e38857
7. Huang Q, Zhuo Y, Duan Z, Long Y, Wang J, Zhang Z, et al. Long-term hypoxic atmosphere enhances the stemness, immunoregulatory functions, and therapeutic application of human umbilical cord mesenchymal stem cells. *Bone Joint Res.* 2024;13(12):764–778. doi:10.1302/2046-3758.1312.BJR-2024-0136.R2
8. Silvestro S, Diomede F, Chiricosta L, Zingale VD, Marconi GD, Pizzicannella J, Valeri A, Avanzini MA, Calcaterra V, Pelizzo G, Mazzon E. The role of hypoxia in improving the therapeutic potential of mesenchymal stromal cells: a comparative study from healthy lung and congenital pulmonary airway malformations in infants. *Front Bioeng Biotechnol.* 2022;10:868486. doi:10.3389/fbioe.2022.868486
9. Mazini L, Rochette L, Admou B, Malka G. Molecular mechanisms of hypoxia in mesenchymal stem cell biology. *Stem Cells Int.* 2020;2020:1059502. doi:10.1155/2020/1059502
10. Ding H, Chen S, Yin J, Xie X, Zhu Z, Gao Y, Zhang C. Continuous hypoxia regulates the osteogenic potential of mesenchymal stem cells in a time-dependent manner. *Mol Med Rep.* 2014;10(4):2184–2190. doi:10.3892/mmr.2014.2451

11. Zhi X, Xiong J, Wang M, Zhang H, Huang G, Zhao J, Zi X, Hu YP. Physiological hypoxia enhances stemness preservation, proliferation, and bidifferentiation of induced hepatic stem cells. *Stem Cells Int.* 2018;2018:7618704. doi:10.1155/2018/7618704
12. Burzi IS, Parchi PD, Barachini S, Pardini E, Sardo Infirri G, Montali M, Petrini I. Hypoxia promotes the stemness of mesangiogenic progenitor cells and prevents osteogenic but not angiogenic differentiation. *Stem Cell Rev Rep.* 2024;20:1830–1842. doi:10.1007/s12015-024-10749-9
13. Kim Y, Jin HJ, Heo J, Ju H, Lee HY, Kim S, et al. Small hypoxia-primed mesenchymal stem cells attenuate graft-versus-host disease. *Leukemia.* 2018;32:2672–2684. doi:10.1038/s41375-018-0114-5
14. Bahir B, Choudhery MS, Hussain I. Hypoxic preconditioning as a strategy to maintain the regenerative potential of mesenchymal stem cells. In: *Regenerative Medicine.* London: IntechOpen; 2020. doi:10.5772/intechopen.93217
15. Di Mattia M, Mauro A, Citeroni MR, Dufrusine B, Peserico A, Russo V, et al. Insight into hypoxia stemness control. *Cells.* 2021;10(8):2161. doi:10.3390/cells10082161
16. Tsai CC, Chen YJ, Yew TL, Chen LL, Wang JY, Chiu CH, Hung SC. Hypoxia inhibits senescence and maintains mesenchymal stem cell properties through down-regulation of E2A-p21 by HIF-TWIST. *Blood.* 2011;117(2):459–469. doi:10.1182/blood-2010-05-287508
17. Li G, Kitada M, Dezawa M. Hypoxia boosts pluripotent-like Muse cell ratio in mesenchymal stromal cells and upregulates the pluripotency gene expression. *Sci Rep.* 2025;15:31183. doi:10.1038/s41598-025-31183-0
18. Tomecka E, Lech W, Zychowicz M, Sarnowska A, Murzyn M, Oldak T, et al. Assessment of the neuroprotective and stemness properties of human Wharton's jelly-derived mesenchymal stem cells under variable (5% vs. 21%) aerobic conditions. *Cells.* 2021;10(4):717. doi:10.3390/cells10040717
19. Shimasaki M, Ichiseki T, Ueda S, Hirata H, Kawahara N, Ueda Y. Mesenchymal stem cells preconditioned with hypoxia and dexamethasone promote osteoblast differentiation under stress conditions. *Int J Med Sci.* 2024;21(8):1511–1517. doi:10.7150/ijms.91222
20. Ohori-Morita Y, Ashry A, Niibe K, Egusa H. Current perspectives on the dynamic culture of mesenchymal stromal/stem cell spheroids. *Stem Cells Transl Med.* 2025;14:szae093. doi:10.1093/stcltm/szae093
21. Mendiratta M, Mendiratta M, Malhotra L, Rai S, Sarangathem V, Dahiya P, et al. Hypoxia-mediated molecular interactions of tissue-specific mesenchymal stem cells drive metabolic reprogramming and immunomodulation in acute graft-versus-host disease. *bioRxiv.* 2025 Jan 6. doi:10.1101/2025.01.06.630457
22. Ye Y, Zhao X, Xu Y, Yu J. Hypoxia-inducible non-coding RNAs in mesenchymal stem cell fate and regeneration. *Front Dent Med.* 2021;2:799716. doi:10.3389/fdmed.2021.799716
23. He X, An W, Liu J. Effects of hypoxia on stemness, survival and angiogenic capacity of muscle-derived stem/progenitor cells. *Biochem Cell Mol Biol.* 2021;3(4):855–868. doi:10.1080/26895293.2021.1977725
24. Wang H, Huang N, Tan M, Zhang X, Chen J, Wei Q. Characteristics of cell adhesion molecules expression and environmental adaptation in yak lung tissue. *Sci Rep.* 2025;15:10914. doi:10.1038/s41598-025-95882-2
25. Obradović H, Krstic J, Trivanović D, Mojsilović S, Okić I, Kukolj T, Ilić V, Krstic A, Terzic M, Bugarski D. Improving stemness and functional features of mesenchymal stem cells from Wharton's jelly of a human umbilical cord by mimicking the native, low oxygen stem cell niche. *Placenta.* 2019;82:50–60. doi:10.1016/j.placenta.2019.05.005
26. Semenza GL. HIF-1 mediates metabolic responses to intratumoral hypoxia and oncogenic mutations. *J Clin Invest.* 2013;123(9):3664–3671. doi:10.1172/JCI67230

27. Wan Kamarul Zaman WS, Wong CW, Yong K, Choi JR, Mat Adenan NA, Omar SZ, Wan Abas WAB, Pingguan-Murphy B. The effects of hypoxia and serum-free conditions on the stemness properties of human adipose-derived stem cells. *Cytotechnology.* 2016;68(5):1859–1872. doi:10.1007/s10616-015-9939-9
28. Otero-Albiol D, Carnero A. Cellular senescence or stemness: hypoxia flips the coin. *J Exp Clin Cancer Res.* 2021;40:243. doi:10.1186/s13046-021-02021-3