Impact of Obesity on the Reparative Potency of Adipose-Derived Mesenchymal Stem Cells in Hypertensive Cardiomyopathy

Li YING[1], Li YAN[1], Jian WANG[2], Shasha YU[1]

[1]Department of Cardiology, First Hospital of China Medical University, Shenyang, Liaoning Province, China, [2]Department of Cardiology, First Affiliated Hospital of Liaoning University of Traditional Chinese Medicine, Shenyang, Liaoning Province, China

Received April 11, 2026
Accepted June 30, 2026

Summary

Obesity constitutes a formidable risk factor for cardiovascular diseases; however, its implications for adipose tissue-derived mesenchymal stem cells (ADMSCs) in the context of hypertensive cardiomyopathy remain insufficiently elucidated. This investigation seeks to illuminate the effects of obesity on the reparative potential of ADMSCs extracted from both obese (O) and normal control (NC) mice within a hypertensive model, thereby addressing a critical void in current research. A model of hypertension (HT) was developed in C57BL/6J mice through the administration of angiotensin II (Ang II). In groups of Non-HT and HT animals, vehicles, NC or obese ADMSCs were injected intravenously. Left ventricular (LV) function *in vivo* was estimated by echocardiogram. Hypertensive cardiomyopathy was meticulously scrutinized by serum biochemical assays, histology, immunohistochemistry, and reverse transcription polymerase chain reaction (RT-PCR). The serum concentrations of pro-inflammatory and pro-fibrotic cytokines were quantified utilizing enzyme-linked immunosorbent assay (ELISA). The expression of autophagy-related and PI3K/AKT pathway related protein was investigated by western blotting. NC-ADMSCs but not O-ADMSCs normalized the Ang II induced elevated blood pressure and myocardial wall thickness. Both NC- and O-ADMSCs alleviated myocardial tissue damage in HT, but NC ADMSCs decreased oxidative stress and blunted myocardial microvascular rarefaction more effectively. Obese ADMSCs exhibited increased inflammation and pro-fibrosis level *in vitro*. The heart tissue of vehicle-injected HT mice had decreased ratio of p-mTOR to mTOR, P-PI3K to PI3K, and P-AKT to AKT, lower abundance of p62, higher level of ULK1 and Beclin 1, and elevated ratio of LC3II to LC3I compared to Non-HT animals, consistent with HT-associated promotion of autophagy. The changes were largely reversed in heart of NC- ADMSCs injected mice but partially alleviated in O-ADMSCs treating. Obese ADMSCs are less effective in protecting against Ang II induced myocardial hypertrophy in mice which might be partially relevant to its impaired regulation of autophagy through the PI3K/AKT axis.

Key words

Adipose tissue-derived mesenchymal stem cell • Obesity • Hypertension • Oxidative stress • Autophagy • PI3K • AKT

Corresponding author

S. Yu, Department of Cardiology, First Hospital of China Medical University, 155 Nanjing North Street, Heping District, Shenyang, 110001, China. E-mail: yuss@cmu1h.com

Introduction

The global prevalence of obesity increased dramatically in recent years, representing a significant hazard to public health and contributing to a heightened prevalence of various chronic diseases, particularly cardiovascular disorders [1]. The World Health Organization (WHO) reports that approximately 39 % of individuals aged 18 years and older were classified as overweight in 2021, with the prevalence of obesity reflecting a significant upward trend [2]. Obesity, characterized by excessive fat accumulation, is closely related to many metabolic dysfunctions, like hypertension, insulin resistance, and dyslipidemia. These remarkable statistics underscore the urgent need to further understanding of the underlying mechanisms linking obesity to cardiovascular pathologies.

 An open access article under the CC BY 4.0 license https://creativecommons.org/licenses/by/4.0/ © 2026 by the authors. Published by the Institute of Physiology, Czech Academy of Sciences, Prague, Czech Republic. E-mail: physres@fgu.cas.cz, www.biomed.cas.cz/physiolres

In recent years, growing considerable attention has been emphasized on the role of adipose tissue-derived mesenchymal stem cells (ADMSCs) on cardiovascular diseases [3]. Previous studies have indicated that ADMSCs possess immunomodulatory properties and can differentiate into various cell types, contributing to tissue regeneration [4]. ADMSCs are characterized by their regenerative potential, particularly in the restoration of cardiac dysfunctions following injury [5]. Despite these promising attributes, emerging evidence suggests that obesity may impair the reparative functions of ADMSCs, leading to diminished cardiac repair mechanisms in obese [6]. For example, obesity, characterized by chronic and low-grade inflammation could induce senescence in ADMSCs, which might decrease the efficacy of this endogenous repair system [7]. Furthermore, Obese adipose tissue is characterized by hypoxia, and metabolic disturbance which may lead to dysfunctions of ADMSCs including multipotent differentiation ability, metabolism, and immunomodulation [8]. All these will result in the reduction of ADSCs's curative effect [9,10]. This paradox posed important challenges about their effectiveness in therapeutic applications and emphasizes the necessity to explore how obesity affects the intrinsic characteristics and regenerative potential of ADMSCs in the context of hypertensive cardiomyopathy.

Despite extensive literature on stem cells' regenerative properties, substantial gaps remain in exploration of how obesity specifically affects the functionality of ADMSCs. There is lack of study intended to figure out the possible effects of metabolic derangements, which are associated with obesity, on the reparative abilities of ADMSCs especially in hypertensive conditions [11-13]. This critical gap in knowledge presents an opportunity to elucidate the mechanisms by which obesity alters the therapeutical effect of ADMSCs, potentially leading to novel strategies for managing hypertensive heart disease.

This study aims to investigate the impact of obesity on the cardioprotective effects of ADMSCs in the context of hypertensive cardiomyopathy. We intend to compare the treating effects of ADMSCs derived from both obese and normal control (NC) mice in a hypertensive model induced by Angiotensin II (Ang II). By elucidating the differences in the reparative capabilities of ADMSCs from obese versus NC sources, this study aims to provide insights into potential therapeutic strategies for enhancing cardiac protective mechanisms in obese individuals suffering from hypertension. The findings may further advance the field of regenerative medicine by strengthening the possible influence of efficacy of stem cell therapies originated from donors. Consequently, this research could pave the way for more effective interventions aimed at improving cardiovascular health in obese populations.

Material and Methods

Animals and experimental design

A total of 36 specific pathogen-free male C57BL/6J mice (age, 8 weeks; weight, 20±2 g) were obtained from the Labs & Centers of China Medical University. All mice were fed in cages with a 12 h light/ 12 h dark cycle, a constant room temperature (22-25 ℃), were free to drink water, and had a standard diet during the study period. All animal experiments were conducted in compliance with the standards outlined in the Guide for the Care and Use of Laboratory Animals (1985) published by the NIH, Bethesda, USA. These experiments received approval from the Ethics Committee of the affiliated hospital of Liaoning University of TCM (Shenyang, China) (No.2023CS(DW)-069-01).

After 1 week acclimatization, the thirty-six C57BL/6J mice were implanted with osmotic mini-pumps (MINI-OSMOTIC PUMP MODEL 2004; Alzet, CA, USA). The min-pumps constantly infused Ang II (750 ng/kg per minute) dissolved in saline or vehicle (saline) for 14 days. After 14 days, the mice were randomized into six groups. All the mice had comparable body weights at the time of ADMSCs or vehicle administration. Each group received a tail vein injection of ADMSCs on days 0, 4, and 9. Non-HT + phosphate buffered solution (PBS), mice received a tail vein injection of PBS vehicle (n=6); Non-HT + N-ADMSCs, received 5×10^5 ADMSCs from normal control mice (N-ADMSCs) (n=6); Non-HT + obese ADMSCs received 5×10^5 ADMSCs from obese mice (n=6); HT + PBS, HT mice received a tail vein injection of PBS vehicle (n=6); HT + N-ADMSCs, HT mice received 5×10^5 ADMSCs from normal control mice (N-ADMSCs) (n=6); HT + obese ADMSCs, HT mice received 5×10^5 ADMSCs from obese mice (n=6); Body weight and blood pressure were monitored on a continuous basis throughout the study. The duration of the experiment spanned 8 weeks.

ADSC isolation and culture

Four-week-old male C57BL/6J mice was used as donors of adipose tissue for ADMSCs isolation. The normal control group was fed a standard diet, 3.85 kcal/g, with a fat-to-energy ratio of 12 % for ten weeks. The obese mice group was fed with high-fat diet for ten weeks (5.24 kcal/g, 60 % fat, 20 % carbohydrate, 20 % protein, fat-to-energy ratio of 60 %). Fresh inguinal fat was obtained from both normal control and obese mice, followed by washing with Dulbecco's phosphate-buffered saline (DPBS, Gibco). The adipose samples were minced into smaller fragments and digested using 2 mg/ml type I collagenase (Sigma-Aldrich) for 30 min at 37 °C on a shaker. Following digestion, cells were resuspended to centrifugation at 1500 rpm for 5 min; the resulting cells were then filtered through a 40-μm nylon mesh (BD Falcon) to eliminate any remaining tissue debris. The cells were washed twice with DPBS before being resuspended in α-MEM (Gibco) supplemented with 10 % fetal bovine serum (Gibco) and plated in T75 tissue culture flasks (BD Falcon). The cultures were maintained in a humidified incubator with 5 % CO_2 at 37 °C. After 24 h, floating cells were discarded, and the culture medium was refreshed on the third day. Once the cells reached approximately 90 % confluence, they were detached using 0.25 % trypsin, EDTA and passaged accordingly.

Blood pressure measurement and echocardiography

All experimental Mice received Angiotensin II (Ang II) administration for two weeks. Systolic and diastolic blood pressure in conscious mice was measured using a non-invasive tail-cuff technique (Hatteras Instruments). Left ventricular function was evaluated by transthoracic echocardiography with a Vevo® 2100 high-resolution Preclinical Imaging System (FUJIFILM VisualSonics, Toronto, Canada) and a 40-MHz linear ultrasound transducer [14]. Echocardiographic parameters were averaged over three to four cardiac cycles. Interventricular septal dimension, left ventricular posterior wall dimension, left ventricular internal diameter in systole (LVIDs), left ventricular internal diameter in diastole (LVIDd), and left ventricular mass was evaluated and the left ventricular ejection fraction (EF) and left ventricular mass index (LVMI) were calculated. Myocardial hypertrophy and fibrosis were indexed BNP, αMHC, collagen 1 (Col1), Col3 gene expression determined using standard PCR protocols.

Cardiac histopathology

The myocardial tissues were subjected to fixation using 4 % formalin for a duration of four hours, followed by paraffin embedding and sectioning to a thickness of 5 μm. Subsequent to dewaxing with xylene and rehydration through a series of graded ethanol solutions, the specimens were stained using hematoxylin and eosin (H&E). Additionally, the specimens were stained with Masson's Trichrome Stain Kit (G1340; Solarbio, China). The density of cardiac capillaries was assessed by quantifying the area fraction that was positive for CD31 staining (Cat#c77699s, Cell Signaling) across at least ten fields at a magnification of 10×. Furthermore, the evaluation of oxidative stress was conducted by 8-OHDG (ab62623, Abcam) staining. Additionally, microvascular rarefaction was assessed by analyzing the gene expression of Angiopoietin-1 and VEGF using standard PCR protocols, as changes in these gene expressions reflect alterations in microvascular density. The assessment of oxidative stress was based on the measurement of reactive oxygen species (ROS) levels and malondialdehyde (MDA) levels [15].

Enzyme-linked immunosorbent assay (ELISA)

Serum levels of interleukin-6 (IL-6; Abclonal, Wuhan, China, catalog number RK00008), tumor necrosis factor-alpha (TNF-α; Abclonal, Wuhan, China, catalog number RK00027), and transforming growth factor-beta 1 (TGF-β1; Abclonal, Wuhan, China, catalog number RK00057) were measured using ELISA kits following the manufacturer's instructions. After completing the ELISA procedures, the absorbance of each well was measured at 450 nm using a microplate reader, and serum concentrations were determined based on a standard curve.

Flow cytometry

Cell suspensions comprising 1×10^6 cells were incubated with 100 μl of diluted FITC-conjugated rat anti-mouse antibodies targeting CD44, CD90, CD34, CD29, and CD45 (BD Biosciences) for 30 min at 4 °C. Following the surface staining procedure, the cells were washed with PBS and then analyzed using flow cytometry (BD Biosciences). Control experiments were performed using the corresponding isotype antibodies.

Western blot analysis

Total protein was isolated from cardiac tissue for Western blot analysis following a standardized protocol.

An aliquot of thirty micrograms of protein was subjected to SDS-PAGE for separation. The proteins were then transferred onto a polyvinylidene fluoride (PVDF) membrane (Millipore Corp). Following a blocking step, the membranes were incubated overnight at 4 °C with primary antibodies targeting p-mTOR (1:1000, Cell Signaling Technology, USA), mTOR (1:1000, Cell Signaling Technology, USA), ULK-1 (1:1000, Abcam), p62 (1:2000, Abcam), Beclin 1 (1:2000, Cell Signaling Technology, USA), LC3I/II (1:1000, Abcam), p-PI3K (1:2000, Abcam), PI3K (1:2000, Abcam), p-AKT (1:2000, Abcam), AKT (1:2000, Abcam), and β-actin (1:2000, Servicebio, China). Subsequently, the membranes were treated with a horseradish peroxidase-conjugated secondary antibody (Cell Signaling Technology, USA). The protein bands were visualized using ECL Prime Western Blotting Detection Reagent (GE Healthcare). This assay was performed a minimum of three times. A representative Western blot was selected for inclusion in the figures.

Statistical analysis

Statistical analyses were conducted using SPSS statistical software (Chicago, IL). The Shapiro-Wilk test was employed to assess data distribution. Variables with a normal distribution are reported as mean ± standard deviation, while those not normally distributed are expressed as median (interquartile range). Statistical significance for parametric variables was assessed by two-way analysis of variance (ANOVA) followed by Student's *t*-tests; nonparametric variables were analyzed using the Kruskal-Wallis test followed by the Wilcoxon test. A P-value of less than 0.05 was considered statistically significant.

Results

Isolation and characterization of mice ADMSCs

The ADMSCs isolated from mice adipose tissues showed a positive staining with Alizarin Red, which signifies their potential for osteogenic differentiation (Fig. 1A). Furthermore, these cells exhibited a positive reaction to Oil Red O staining, thereby validating their capacity for adipogenic differentiation (Fig. 1B). The stem cell properties of these ADMSCs were evaluated using flow cytometry. At the third passage, the cells displayed positive expressions of specific surface markers such as CD29, CD44 and CD90, while showing no expression of CD34 and CD45 (CD29+, CD44+, CD90+, CD34-, CD45-) (Fig. 1C). This evidence substantiates the successful establishment of mice ADMSCs in the present study.

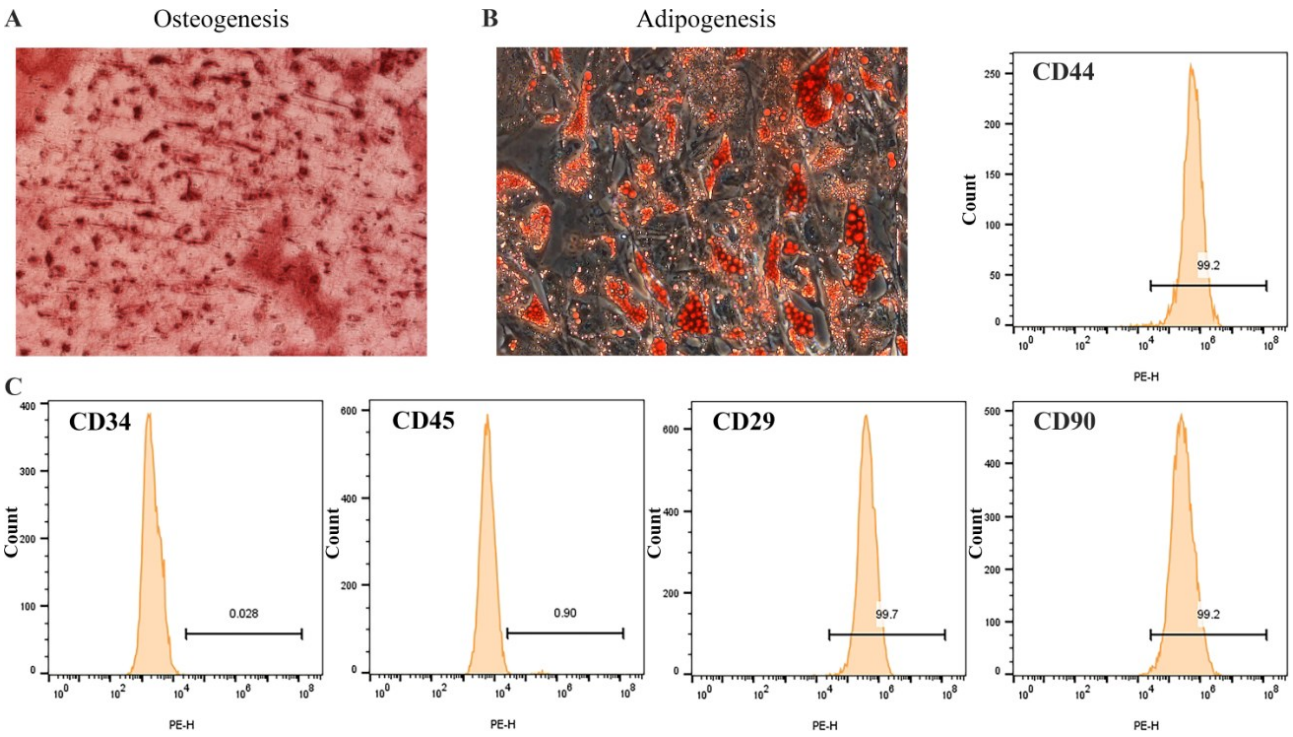


Fig. 1. Differentiation and Surface Marker Profile of ADMSCs. (**A**) Alizarin red assay results show the osteogenic differentiation of mice ADMSCs. (**B**) Oil red O assay results show the adipogenic differentiation potential of the mice ADMSCs. (**C**) FACS analysis results show the cell surface expression levels of CD44, CD34, CD45, CD29, and CD90 in mice ADMSCs.

Effect of ADMSCs on systemic parameters in HT mice

Blood pressure, heart rate and echocardiogram parameters of the mice are shown in Figure 2. There were no BP changes in the Non-HT groups, whereas in HT + PBS, systolic, but not diastolic BP was significantly higher than those three Non-HT groups (Fig. 2A, B). In HT + N-ADMSCs, SBP showed significantly lower compared to HT + PBS groups, whereas obese ADMSCs contrarily failed to reverse the elevated BP compared to Non-HT groups and HT + PBS (Fig. 2A). There were no significant differences in heart rate (P=0.211) among groups (Fig. 2C). HT-induced cardiac hypertrophy and cardiac dysfunction was shown in Figure 2D, E, F. LVMI and wall thickness significantly increased in HT+ PBS but decreased in HT + N-ADMSCs. However, HT increased LVMI and wall thickness failed to be normalized by obese ADMSCs (Fig. 2D, E). Besides, Cardiac dysfunction evaluated by EF decreased in HT + PBS and significantly alleviated by N-ADMSCs but not O-ADMSCs (Fig. 2F).

Effect of ADMSCs on cardiomyocyte hypertrophy and myocardial fibrosis

H&E staining showed that HT induced cardiomyocyte hypertrophy, which was improved significantly by ADMSCs (Fig. 3). Ang II induced myocardial hypertrophy was reversed by N-ADMSCs and O-ADMSCs. However, O-ADMSCs seemed less effective compared to N-ADMSCs (Fig. 3A, B). Compared with Non-HT groups, gene expressions of myocardial hypertrophy parameters (BNP, and αMHC) were significantly increased in HT+ PBS groups but restored in HT + N-ADMSCs but not HT + O-ADMSCs (Fig. 3C, D).

Cardiac fibrosis were markedly elevated in HT + PBS, whereas N-ADMSCs treatment reversed fibrosis and obese ADMSCs improved fibrosis in HT mice (Fig. 3E, F). Compared with Non-HT groups, gene expressions of myocardial fibrotic parameters (Col1 and Col3) were significantly increased in HT+ PBS groups but restored in HT + N-ADMSCs but not HT + O-ADMSCs (Fig. 3G, H).

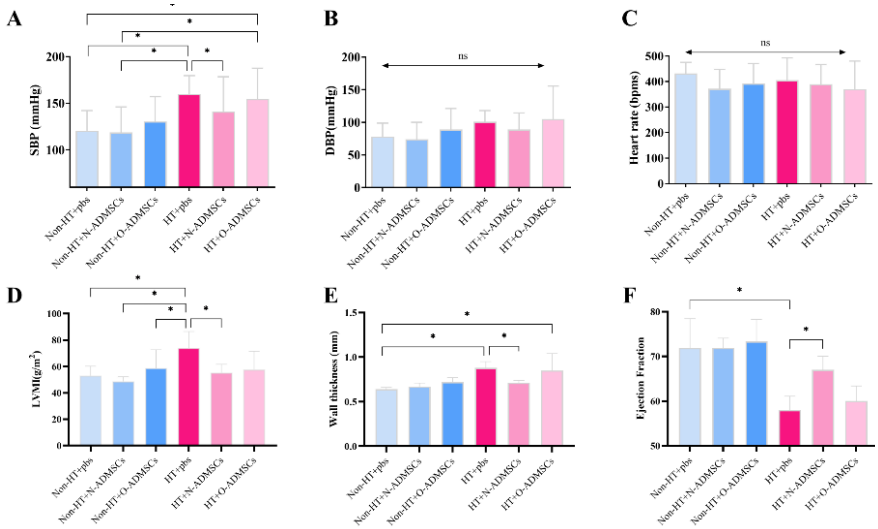


Fig. 2. Monitoring hypertensive and non-hypertensive mice blood pressure by non-invasive tail-cuff method and myocardial hypertrophy using M-mode echocardiograms *in vivo* (n=6 per group). Data means standard deviation. HT: hypertension; N-ADMSCs: normal control adipose tissue-derived mesenchymal stem cells; O-ADMSCs: obese-adipose tissue-derived mesenchymal stem cells; LVMI: left ventricular mass index. * means P<0.05.

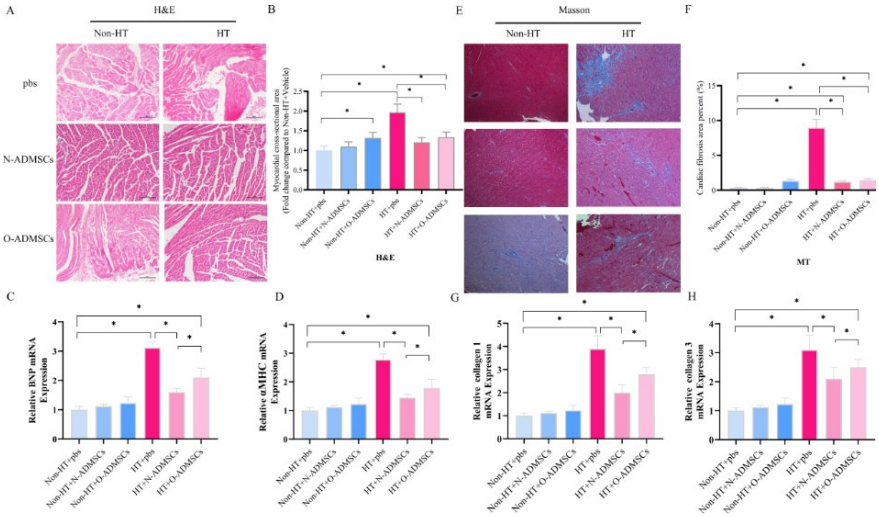


Fig. 3. Adipose tissue-derived mesenchymal stem cells exhibited attenuated myocytes hypertrophy and fibrotic remodelling in response to angiotensin II (Ang II) infusion. Representative histological sections of hematoxylin-eosin (HE) (**A, B**) staining and gene expression of BNP, and α MHC (**C, D**) show cardiomyocyte hypertrophy. Masson's trichrome staining (**E, F**) and gene expression of collagen 1, collagen 3 (**G, H**) suggests cardiac fibrosis. Data means standard deviation. HT: hypertension; N-ADMSCs: normal control adipose tissue-derived mesenchymal stem cells; O-ADMSCs: obese-adipose tissue-derived mesenchymal stem cells. * means P<0.05.

ADMSCs attenuate the levels of pro-inflammatory and pro-fibrotic cytokines

Myocardial inflammation is characteristic features of cardiac hypertrophy and fibrosis. The serum levels of the pro-inflammatory cytokines IL-6 and TNF-α, along with the pro-fibrotic cytokine TGF-β1, were analyzed across various groups (Fig. 4). As shown, the serum concentrations of IL-6 and TGF-β1 were higher in HT + PBS mice. There were no significant changes of TNF-α between different groups. Administration of both N- and O-ADMSCs were able to partially alleviate the increased IL-6 level. However, O-ADMSCs treatment showed significantly higher level of IL-6 compared with N-ADMSCs treatment. Furthermore, elevation of TGF-β1 in HT mice was alleviated by N-ADMSCs treatment but not O-ADMSCs treatment. pro-inflammatory cytokines and the pro-fibrotic cytokine significantly. This demonstrated that ADMSCs suppressed inflammation in the heart tissues of HT mice. This also demonstrated the anti-fibrotic effects of the ADMSCs.

ADMSCs alleviated cardiac damage in HT mice

Oxidative stress denoted by 8-OHDG staining was significantly increased in both Non-HT + O-ADMSCs and HT + PBS compared with Non-HT + PBS and Non-HT + N-ADMSCs. Both N- and O-ADMSCs decreased oxidative stress in HT, yet it remained higher than in Non-HT + PBS and Non-HT + N-ADMSCs. Furthermore, HT + O-ADMSCs showed higher oxidative stress than HT + N-ADMSCs (Fig. 5A, B). Expression of ROS and MDA also significantly changes in HT + PBS group and alleviated when administration ADMSCs. HT also induced myocardial microvascular rarefaction detected by CD31 staining (Fig. 5E, F), which both N- and obese-ADMSCs successfully reversed. Interestingly, obese AMSC also elicited microvascular rarefaction in Non-HT mice. Gene expressions of angiopoietin and VEGF in HT + PBS appeared significantly higher compared to Non-HT groups (Fig. 5G, H). Both NC and obese ADMSCs could successfully decrease them.

ADMSCs modulated autophagy and inhibited the PI3K/AKT signaling pathway in HT mice

Previous study confirmed that autophagy was dysregulated in HT [16], we performed a quantitative assessment of specific autophagy-related proteins. As shown in Figure 6, the heart tissues of the HT + PBS showed significantly lower levels of p-mTOR, p62, P-PI3K, P-AKT level and higher levels of ULK-1, Beclin1, LC3I/II compared to Non-HT groups. This indicated action of the autophagy and PI3K/AKT signaling pathway in the heart of the HT groups. However, the HT + N-ADMSCs and HT + obese ADMSCs showed higher levels of p-mTOR, p62, P-PI3K, P-AKT level and lower levels of ULK-1, Beclin1, LC3I/II compared to HT+ vehicle group. This data further confirmed that the ADMSCs suppressed hypertrophy and fibrosis in the heart of the HT model mice through modulation of autophagy *via* the PI3K/AKT/mTOR axis.

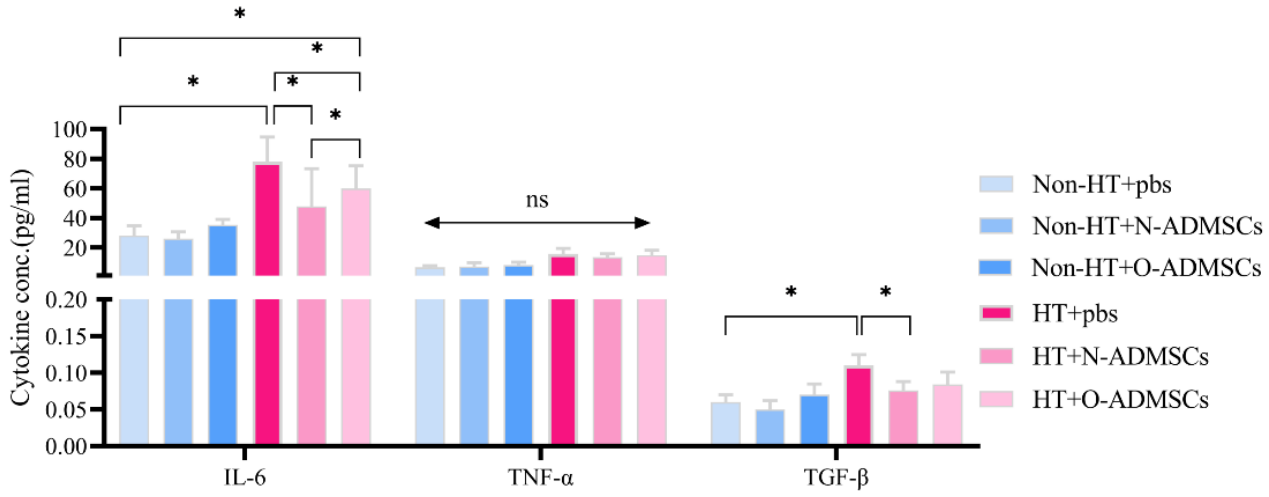


Fig. 4. Serum concentrations of pro-inflammatory and pro-fibrotic cytokines *in vivo* experiments: Graphical representations of the concentrations of IL-6, TNF-α and TNF-β measured by ELISA in serum samples from different groups. Data means standard deviation, n=6 per group. HT: hypertension; N-ADMSCs: normal control adipose tissue-derived mesenchymal stem cells; O-ADMSCs: obese-adipose tissue-derived mesenchymal stem cells. * means P<0.05.

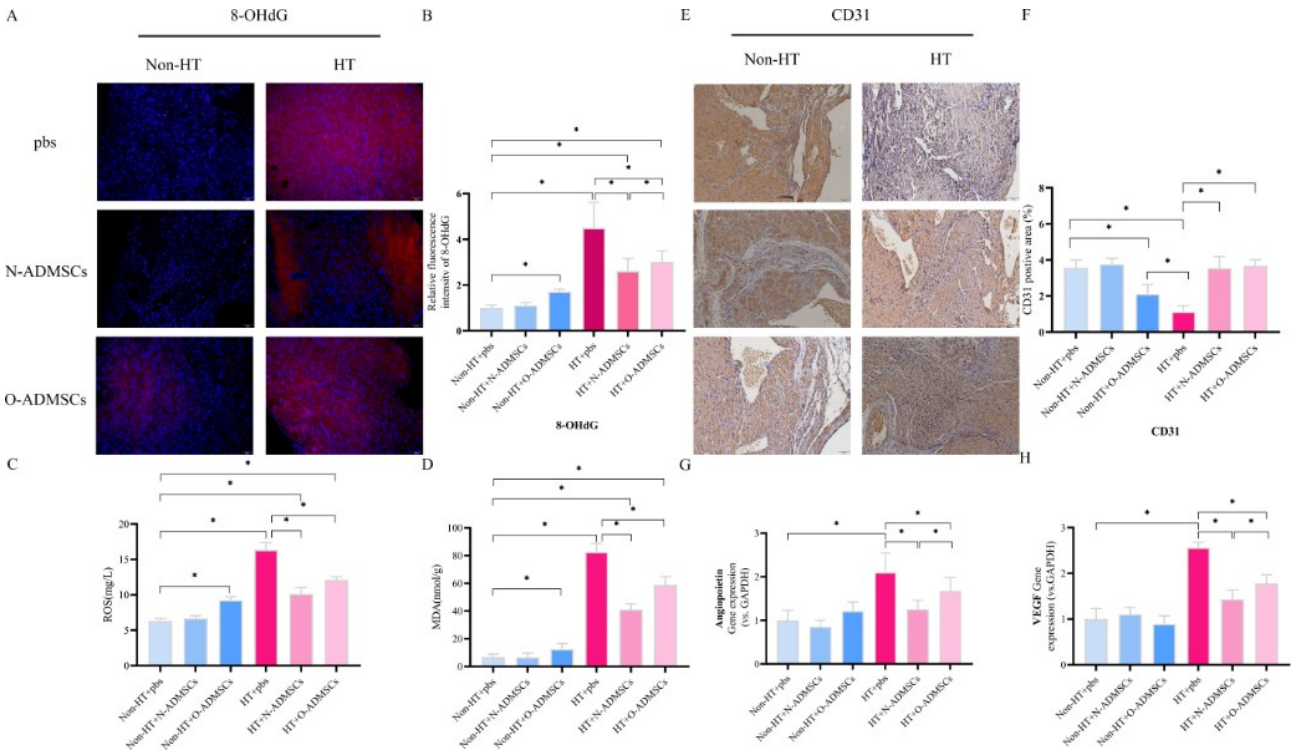


Fig. 5. Hypertension increases oxidative stress and microvascular rarefaction in mice, whereas ADMSCs alleviate them. (**A, B**) Representative immunofluorescence images labels with 8-OHdG in the heart. (**C, D**) Detection of oxidative stress levels in mice of each group. (**E, F**) CD-31-stained myocardial sections and quantification shows cardiac oxidative stress and microvascular density. (**G, H**) Expression of angiopoietin and VEGF increased in myocardium. Data means standard deviation, n=6 per group. HT: hypertension; N-ADMSCs: normal control adipose tissue-derived mesenchymal stem cells; O-ADMSCs: obese-adipose tissue-derived mesenchymal stem cells. * means P<0.05.

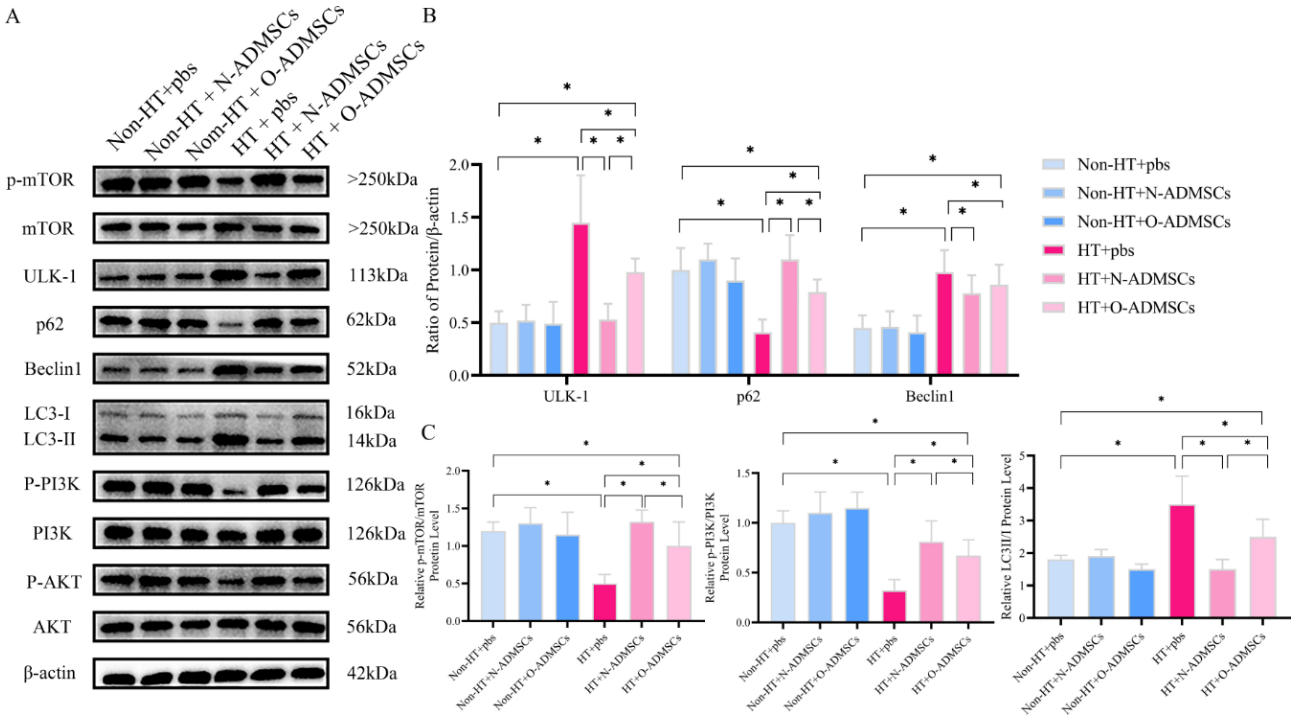


Fig. 6. Effect of ADMSCs on the expression level of autophagy related protein and the activity of the PI3K/AKT pathway in cardiac tissue from mice. Representative images of the Western blots (**A**) and the corresponding statistical analyses show the levels of ULK1, Beclin1, p62 (**B**), mTOR, p-mTOR, p-PI3K, PI3K, LC3I/II (**C**) and a housekeeping protein (β-actin) in the cardiac tissue in different groups. Data means standard deviation, n=6 per group. HT: hypertension; N-ADMSCs: normal control adipose tissue-derived mesenchymal stem cells; O-ADMSCs: obese-adipose tissue-derived mesenchymal stem cells. * means P<0.05.

Discussion

This study revealed, for the first time, that ADMSCs is effective cell-based therapy for alleviating myocardial hypertrophy in Ang II induced HT mice whereas obese ADMSCs seemed less effective when compared to N-ADMSCs. Furthermore, an improvement in myocardial oxidative stress, microvascular rarefaction accompanied by decreased systemic pro-inflammation and pro-fibrosis were more dramatic in NC rather than obese ADMSCs treatment. In all, this discrepance might be relevant to the weaker modulation of autophagy through PI3K/AKT/mTOR axis with obese ADMSCs treatment.

Changes in myocardial architecture associated with hypertension include both structural and functional dysfunctions within cardiac muscle tissue. These changes involve myocardial hypertrophy, fibrosis, and inflammation. While myocardial hypertrophy arises directly from hypertension, fibrosis and inflammation may result from subsequent pathological processes [17]. These alterations not only affect the systolic and diastolic functions of the heart but are also associated with a myriad of adverse cardiovascular events that can severely impact a patient's quality of life, including, but not limited to, heart failure and markedly increased morbidity and mortality rates [18]. Pathological remodeling of the heart is frequently related to inflammation, fibrosis, and cellular dysfunction affecting cardiomyocytes and other cell types such as fibroblasts and endothelial cells. This dysfunction may manifest irregular interactions between cardiomyocytes and these non-cardiomyocytes; oxidative stress; endoplasmic reticulum stress; disturbances in autophagy; and disruptions in metabolic and signaling pathways [19]. Even when blood pressure is well controlled, cardiac remodeling caused by hypertension might not be completely reverse, emphasizing the importance of other interventions besides antihypertensive drugs [20]. As the global prevalence of obesity continues to rise at an alarming rate, understanding its multifaceted impact on cardiovascular health, particularly in the context of hypertensive heart disease, has become increasingly pertinent and urgent [21]. Obesity is a major risk factor for CVD, causing systemic inflammation, insulin resistance, and neurohormonal activation [22]. Obesity is a chronic condition. It is characterized by an excessive accumulation of adipose tissue. This excess adiposity can impair health by disrupting the normal functioning of multiple organs, including the lungs, heart, and liver, leading to complications such as respiratory difficulties, cardiovascular diseases, and liver dysfunction [23]. An accumulation of surplus fat and its abnormal storage in visceral adipose tissue can impair its function. This impairment promotes the development of metabolic disorders [23]. The alterations in adipose tissue, which serve not only as a fat reservoir but also function as a crucial endocrine organ, may further exacerbate the numerous challenges posed by hypertension, thereby complicating the treatment and management of this condition.

In this study, we rigorously investigate the influence of obesity on the reparative capabilities of ADMSCs specifically within the setting of hypertensive cardiomyopathy. By meticulously comparing the functional outcomes of ADMSCs derived from obese versus non-obese murine models, we aim to elucidate the inherent differences in their therapeutic effectiveness and regenerative potential. Initial findings indicate a concerning trend: ADMSCs obtained from obese subjects demonstrate a significantly diminished reparative potential when injected into hypertensive models, which underscores a potential mechanistic link between the inflammation related to obesity and impaired cardiac recovery. Furthermore, the observation that ADMSCs sourced from obese mice exhibit heightened levels of inflammation, which consequently impair their reparative capabilities, suggests a critical and complex role of the inflammatory microenvironment in modulating stem cell function. This phenomenon is consistent with existing findings in previous literature, where obesity has been shown to induce a pro-inflammatory state that adversely affects the functional properties of stem cells, primarily through the upregulation of inflammatory cytokines such as IL-6 and TNF-α [7,24]. The increased concentrations of these cytokines can lead to cellular senescence, thereby diminishing stem cell plasticity-a detail that has been well-documented in various studies investigating the effects of obesity on mesenchymal stem cells [25]. Notably, the activation of NF-κB signaling pathways in obese ADMSCs may further exacerbate the inflammatory response, resulting in an autocrine loop that perpetuates their impaired function [26]. Thus, while ADMSCs derived from non-obese subjects retain their regenerative potential due to lower inflammatory markers, their obese-derived counterparts are severely hindered by an adverse microenvironment that promotes inflammation rather than the necessary repair processes.

In terms of the underlying molecular mechanisms, the study identified the significant

involvement of the PI3K/AKT signaling pathway in the repair processes mediated by ADMSCs. We demonstrated that ADMSCs regulate autophagy induced by Ang II in mice, and the direct regulation of the PI3K/AKT/mTOR signaling pathway in this process. This pathway is pivotal for essential cellular functions such as survival, proliferation, and autophagy, all of which are crucial for effective tissue regeneration [26]. Our data indicated that N-ADMSCs exert a markedly stronger activation of this critical signaling cascade compared to their obese counterparts, suggesting a potential mechanism by which obesity leads to a diminished regenerative capacity through impaired PI3K/AKT signaling [25,27]. Furthermore, the dysregulation of autophagy in obese ADMSCs, as highlighted by the decreased expression of autophagy-related proteins, may also contribute significantly to their reduced functionality, complicating the already intricate relationship between obesity, inflammation, and stem cell efficacy in the context of hypertensive cardiomyopathy. Corroborating findings from other studies serves to reinforce the understanding that the impairment of the PI3K/AKT signaling pathway associated with obesity does not merely hinder cellular survival; it also significantly disrupts the autophagic processes that are essential for the proper functioning of stem cells [28]. Lakhan Km and colleagues confirmed that PI3K pathway plays an important role in regulating the autophagic response of cells in response to changing reactive oxygen species (ROS) levels [29]. Our study also found that Ang II resulted in higher levels of ROS in mice heart whereas both ADMSCs significantly decreased it. This impairment has profound implications for the overall health and regenerative abilities of these cells. Moreover, the differential expression of genes that are intricately linked to the mTOR signaling pathway within ADMSCs emerged as a pivotal focus of this comprehensive study. The results compellingly demonstrated that N-ADMSCs exhibited markedly higher activation levels of mTOR, a key regulator that promotes anabolic processes and cellular growth, when compared to their obese counterparts, which displayed a concerning reduction in mTOR signaling [30]. This significant discrepancy is crucial, as mTOR signaling is known to play an integral role in modulating cellular responses to nutrient availability and stressors. The dysregulation of this pathway in the context of obesity could ultimately lead to compromised cellular functions and diminished repair capabilities [25,31]. The current findings robustly support the notion that the impairment of PI3K/AKT/mTOR signaling pathways in obese ADMSCs is a critical factor that underpins their reduced efficacy in tissue repair contexts, thereby contributing to the broader implications of obesity on regenerative medicine.

Overall, the findings from this study significantly advance our understanding of the intricate molecular underpinnings that illustrate how obesity adversely impacts AMSC function. They also underscore the potential for targeting these pathways in therapeutic strategies aimed at ameliorating the negative effects of obesity on stem cell functionality and overall health.

It is important to acknowledge several notable limitations inherent in this study that warrant careful consideration. Firstly, the relatively small sample size employed in our experiments may considerably restrict the generalizability of our findings, as larger cohorts are often necessary to adequately account for biological variability and ensure the robustness of the results. Furthermore, the absence of clinical validation poses a significant limitation to the applicability of our results to human subjects, potentially undermining the translational relevance of our observations. Additionally, while our *in vitro* analyses yielded valuable insights into the behavior and characteristics of ADMSCs, the lack of corresponding *in vivo* experiments to corroborate these findings raises pertinent questions regarding the robustness and applicability of our conclusions to real-world scenarios.

Conclusions

In summary, our results, for the first time, have provided evidence that N-ADMSCs better reduce HT related cardiomyocyte hypertrophy than obese ADMSCs. Further, these protective effects may be that ADMSCs regulated oxidative stress, improved microvascular rarefaction, decreased pro-inflammatory and pro-fibrotic levels. The possible mechanism might be relevant to the modulation of autophagy through PI3K/AKT/mTOR axis. These findings demonstrate that both N- and obese ADMSCs infusion may be used for the alleviation of HT related cardiomyocyte hypertrophy but N-ADMSCs might be a better choice.

Conflict of Interest

There is no conflict of interest.

Acknowledgements

This research was supported by the High-Quality Development Technology Fund Project of China Medical University (Project Number: 2023JH2/20200024). We are grateful to Prof Lilach O. Lerman, Principal of Division of Nephrology and Hypertension, Mayo Clinic, whose facilitation was instrumental in the smooth conduct of this research.

References

1. Piqueras P, Ballester A, Durá-Gil JV, Martinez-Hervas S, Redón J, Real JT. Anthropometric Indicators as a Tool for Diagnosis of Obesity and Other Health Risk Factors: A Literature Review. Front Psychol 2021;12:631179. https://doi.org/10.3389/fpsyg.2021.631179
2. Limcharoen T, Pouyfung P, Ngamdokmai N, Prasopthum A, Ahmad AR, Wisdawati W, et al. Inhibition of α-Glucosidase and Pancreatic Lipase Properties of Mitragyna speciosa (Korth.) Havil. (Kratom) Leaves. Nutrients 2022;14:3909. https://doi.org/10.3390/nu14193909
3. Hoang DM, Pham PT, Bach TQ, Ngo ATL, Nguyen QT, Phan TTK, et al. Stem cell-based therapy for human diseases. Signal Transduct Target Ther 2022;7:272. https://doi.org/10.1038/s41392-022-01134-4
4. Keriquel V, Oliveira H, Rémy M, Ziane S, Delmond S, Rousseau B, et al. In situ printing of mesenchymal stromal cells, by laser-assisted bioprinting, for in vivo bone regeneration applications. Sci Rep 2017;7:1778. https://doi.org/10.1038/s41598-017-01914-x
5. Al-Ghadban S, Bunnell BA. Adipose Tissue-Derived Stem Cells: Immunomodulatory Effects and Therapeutic Potential. Physiology (Bethesda) 2020;35:125-133. https://doi.org/10.1152/physiol.00021.2019
6. Foti R, Storti G, Palmesano M, Scioli MG, Fiorelli E, Terriaca S, et al. Senescence in Adipose-Derived Stem Cells: Biological Mechanisms and Therapeutic Challenges. Int J Mol Sci 2024;25:8390. https://doi.org/10.3390/ijms25158390
7. Conley SM, Hickson LJ, Kellogg TA, McKenzie T, Heimbach JK, Taner T, et al. Human Obesity Induces Dysfunction and Early Senescence in Adipose Tissue-Derived Mesenchymal Stromal/Stem Cells. Front Cell Dev Biol 2020;8:197. https://doi.org/10.3389/fcell.2020.00197
8. Blüher M. Adipose tissue dysfunction in obesity. Exp Clin Endocrinol Diabetes 2009;117:241-250. https://doi.org/10.1055/s-0029-1192044
9. Louwen F, Ritter A, Kreis NN, Yuan J. Insight into the development of obesity: functional alterations of adipose-derived mesenchymal stem cells. Obes Rev 2018;19:888-904. https://doi.org/10.1111/obr.12679
10. Ritter A, Friemel A, Kreis NN, Hoock SC, Roth S, Kielland-Kaisen U, et al. Stem Cell Reports 2018;10:583-599. https://doi.org/10.1016/j.stemcr.2017.12.022
11. Todorova VB, Baxan N, Delahaye M, Harding SE, Rankin SM. Drug-based mobilisation of mesenchymal stem/stromal cells improves cardiac function post myocardial infarction. Dis Model Mech 2023;16:dmm049630. https://doi.org/10.1242/dmm.049630
12. Lin X, Peng P, Cheng L, Chen S, Li K, Li ZY, et al. A natural compound induced cardiogenic differentiation of endogenous MSCs for repair of infarcted heart. Differentiation 2012;83:1-9. https://doi.org/10.1016/j.diff.2011.09.001
13. Rahbarghazi R, Nassiri SM, Ahmadi SH, Mohammadi E, Rabbani S, Araghi A, Hosseinkhani H. Dynamic induction of pro-angiogenic milieu after transplantation of marrow-derived mesenchymal stem cells in experimental myocardial infarction. Int J Cardiol 2014;173:453-466. https://doi.org/10.1016/j.ijcard.2014.03.008
14. Zhang N, Zhang Y, Qian H, Wu S, Cao L, Sun Y. Selective targeting of ubiquitination and degradation of PARP1 by E3 ubiquitin ligase WWP2 regulates isoproterenol-induced cardiac remodelling. Cell Death Differ 2020;27:2605-2619. https://doi.org/10.1038/s41418-020-0523-2
15. Meng S, Wang B, Li W. CircAXL Knockdown Alleviates Aβ1-42-Induced Neurotoxicity in Alzheimer's Disease via Repressing PDE4A by Releasing miR-1306-5p. Neurochem Res 2022;47:1707-1720. https://doi.org/10.1007/s11064-022-03563-7
16. Du J, Zhang C, Zhao W. Autophagy and Hypertension. Adv Exp Med Biol 2020;1207:213-216. https://doi.org/10.1007/978-981-15-4272-5_14

17. Hu Y, Lin L, Zhang L, Li Y, Cui X, Lu M, et al. Identification of Circulating Plasma Proteins as a Mediator of Hypertension-Driven Cardiac Remodeling: A Mediation Mendelian Randomization Study. Hypertension 2024;81:1132-1144. https://doi.org/10.1161/HYPERTENSIONAHA.123.22504
18. Qu Y, Ma D, Wu T, Wang H, Tian Z, Liu X, Wang Y. A multi-omics approach identifies the key role of disorders of sphingolipid metabolism in Ang II-induced hypertensive cardiomyopathy myocardial remodeling. Sci Rep 2024;14:30379. https://doi.org/10.1038/s41598-024-81611-8
19. Wu QQ, Xiao Y, Yuan Y, Ma ZG, Liao HH, Liu C, et al. Mechanisms contributing to cardiac remodelling. Clin Sci (Lond) 2017;131:2319-2345. https://doi.org/10.1042/CS20171167
20. Liu A, Xie H, Tian F, Bai P, Weng H, Liu Y, et al. ESCRT-III Component CHMP4C Attenuates Cardiac Hypertrophy by Targeting the Endo-Lysosomal Degradation of EGFR. Hypertension 2023;80:2674-2686. https://doi.org/10.1161/HYPERTENSIONAHA.123.21427
21. Al Ta'ani O, Al-Ajlouni YA, Aleyadeh W, Al-Bitar F, Alsakarneh S, Saadeh A, et al. The impact of overweight and obesity on health outcomes in the United States from 1990 to 2021. Diabetes Obes Metab 2024;26:5455-5465. https://doi.org/10.1111/dom.15924
22. Seth C, Schmid V, Mueller S, Haykowsky M, Foulkes SJ, Halle M, Wernhart S. Diabetes, obesity, and cardiovascular disease-what is the impact of lifestyle modification? Herz 2025;50:240-245. https://doi.org/10.1007/s00059-025-05309-x
23. Palma G, Sorice GP, Genchi VA, Giordano F, Caccioppoli C, D'Oria R, et al. Adipose Tissue Inflammation and Pulmonary Dysfunction in Obesity. Int J Mol Sci 2022;3:7349. https://doi.org/10.3390/ijms23137349
24. Pestel J, Blangero F, Eljaafari A. Pathogenic Role of Adipose Tissue-Derived Mesenchymal Stem Cells in Obesity and Obesity-Related Inflammatory Diseases. Cells 2023;12:348. https://doi.org/10.3390/cells12030348
25. Eirin A, Thaler R, Glasstetter LM, Xing L, Zhu XY, Osborne AC, et al. Obesity-driven mitochondrial dysfunction in human adipose tissue-derived mesenchymal stem/stromal cells involves epigenetic changes. Cell Death Dis 2024;15:387. https://doi.org/10.1038/s41419-024-06774-8
26. Hong S, Huang W, Zhu X, Tang H, Krier JD, Xing L, et al. Obesity blunts amelioration of cardiac hypertrophy and fibrosis by human mesenchymal stem/stromal cell-derived extracellular vesicles. Am J Physiol Heart Circ Physiol 2023;325:H163-H171. https://doi.org/10.1152/ajpheart.00676.2022
27. Lau DH, Shenasa HA, Shenasa M. Hypertension, Prehypertension, Hypertensive Heart Disease, and Atrial Fibrillation. Card Electrophysiol Clin 2021;13:37-45. https://doi.org/10.1016/j.ccep.2020.11.009
28. Yu S, Klomjit N, Jiang K, Zhu XY, Ferguson CM, Conley SM, et al. Human Obesity Attenuates Cardioprotection Conferred by Adipose Tissue-Derived Mesenchymal Stem/Stromal Cells. J Cardiovasc Transl Res 2023;16:221-232. https://doi.org/10.1007/s12265-022-10279-0
29. Kma L, Baruah TJ. The interplay of ROS and the PI3K/Akt pathway in autophagy regulation. Biotechnol Appl Biochem 2022;69:248-264. https://doi.org/10.1002/bab.2104
30. Rosenzweig EB, Krishnan U. Congenital Heart Disease-Associated Pulmonary Hypertension. Clin Chest Med 2021;42:9-18. https://doi.org/10.1016/j.ccm.2020.11.005
31. Rippe JM. Lifestyle Medicine and Cardiovascular Health. Am J Lifestyle Med 2025;20:15598276251365194. https://doi.org/10.1177/15598276251365194